29, 30
Ιανουαρίου 2021

Digital Edition

ενδοράμα

Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

Toujeo®

insulin glargine 300U/mL

Νέα Πένα

MAT-GR-2100006 / V. 0.1 / January 2021

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

Πριν τη συνταγογράφηση συμβουλευθείτε την Π.Χ.Π. που θα βρείτε πατώντας στο λογότυπο της εταιρείας στο link των χορηγών
Toujeo Solostar (συσκευασία 3 προγεμισμένων πενών): Λ.Τ. 46.08€ | Toujeo Doublestar (συσκευασία 3 προγεμισμένων πενών): Λ.Τ. 85.08€. Χορήγηση με ιατρική συνταγή

Για αναφορά πιθανής Ανεπιθύμητης Ενέργειας (ΑΕ), παρακαλείσθε όπως επικοινωνήσετε με το τμήμα Φαρμακοεπαγρύπνησης:
Ελλάδα: Τηλέφωνο: 210 9001 600 | Email: PV-Greece@sanofi.com | **Κύπρος:** Τηλέφωνο: 22871600 | Email: Pharmacovigilance.Cyprus@Sanofi.com

SANOFI

Λ. Συγγρού 348, Κτήριο Α, 17674 Καλλιθέα
Τηλ.: 210-9001600, Fax: 210-9249129 | www.sanofi.gr

Αγαπητές -οι συνάδελφοι

Η γνωστή φράση των Λατίνων Dum spiro spero (Όσο ζω ελπίζω) ανταποκρίνεται απόλυτα στην αντίληψη που οφείλει να διακατέχει τις μέρες μας. Ποιος από μας φανταζόταν ότι ένα μόλις μήνα μετά τη συνάντηση μας τον Ιανουάριο 2020 στο ΕΝΔΟΡΑΜΑ θα βιώναμε μια πρωτοφανή δοκιμασία τόσο ως κοινωνία, όσο και ως επιστημονικός κλάδος. Οι πρωτόγνωρες συνθήκες και κίνδυνοι ενώπιον των οποίων κληθήκαμε να ανταποκριθούμε και βεβαίως εξακολουθούμε να ζούμε, ατομικά και συλλογικά, δημιούργησαν νέες καταστάσεις και νέες πραγματικότητες που δεν τις φανταζόμασταν ποτέ. Διατηρώντας την αισιοδοξία μας διατηρούμε τη βεβαιότητα ότι θα βγούμε νικητές.

Υπό το πνεύμα αυτό σας ανακοινώνουμε τη διοργάνωση του προσεχούς ΕΝΔΟΡΑΜΑΤΟΣ που θα γίνει όπως πάντα στο Συνεδριακό Κέντρο του Πανεπιστημίου Πατρών την Παρασκευή και Σάββατο, στις 29 και 30 Ιανουαρίου 2021, ενώ δίνεται παράλληλα δυνατότητα ψηφιακής συμμετοχής των συνέδρων μέσω χρήσης κατάλληλης πλατφόρμας. Η λειτουργικότητα και οι χώροι του Συνεδριακού Κέντρου, όπως έχετε διαπιστώσει, παρέχουν τη δυνατότητα διενέργειας του συνεδρίου μας τηρώντας τους κανόνες υγειονομικής προστασίας. Αν, ο μη γένοιτο, τον Ιανουάριο 2021 υπάρχει πλήρης απαγόρευση συνεδριακών επιστημονικών δραστηριοτήτων θα υπάρχει πρόβλεψη για εξολοκλήρου διαδικτυακή διεξαγωγή του συνεδρίου.

Όπως πάντα θα καλυφθούν όλα τα γνωστικά πεδία της Ενδοκρινολογίας από έγκριτους συναδέλφους από την Ελλάδα και το εξωτερικό, παλαιότερους και νέους, που θα παρουσιάσουν όλες τις τελευταίες εξελίξεις της επιστήμης μας. Ταυτόχρονα, θα υπάρξει και νέα ενότητα που θα αφορά την ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ ΤΗΝ ΕΠΟΧΗ ΤΟΥ COVID-19.

Έχοντας την πεποίθηση ότι θα συναντηθούμε δια ζώσης σας περιμένουμε στην Πάτρα τον προσεχή Ιανουάριο.

Απόστολος Γ. Βαγενάκης

Νεοκλής Α. Γεωργόπουλος

Κώστας Β. Μάρκου


ενδόραμα
Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

ενδοραμα

Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

https://www.endorama.gr/

EndoramaCongress/

Διοργάνωση:
Ιατρική Εταιρεία Δυτικής Ελλάδος και Πελοποννήσου

Αιγίδα:
Ελληνική Ενδοκρινολογική Εταιρεία
Πανελλήνια Ένωση Ενδοκρινολόγων

Γραμματεία Συνεδρίου

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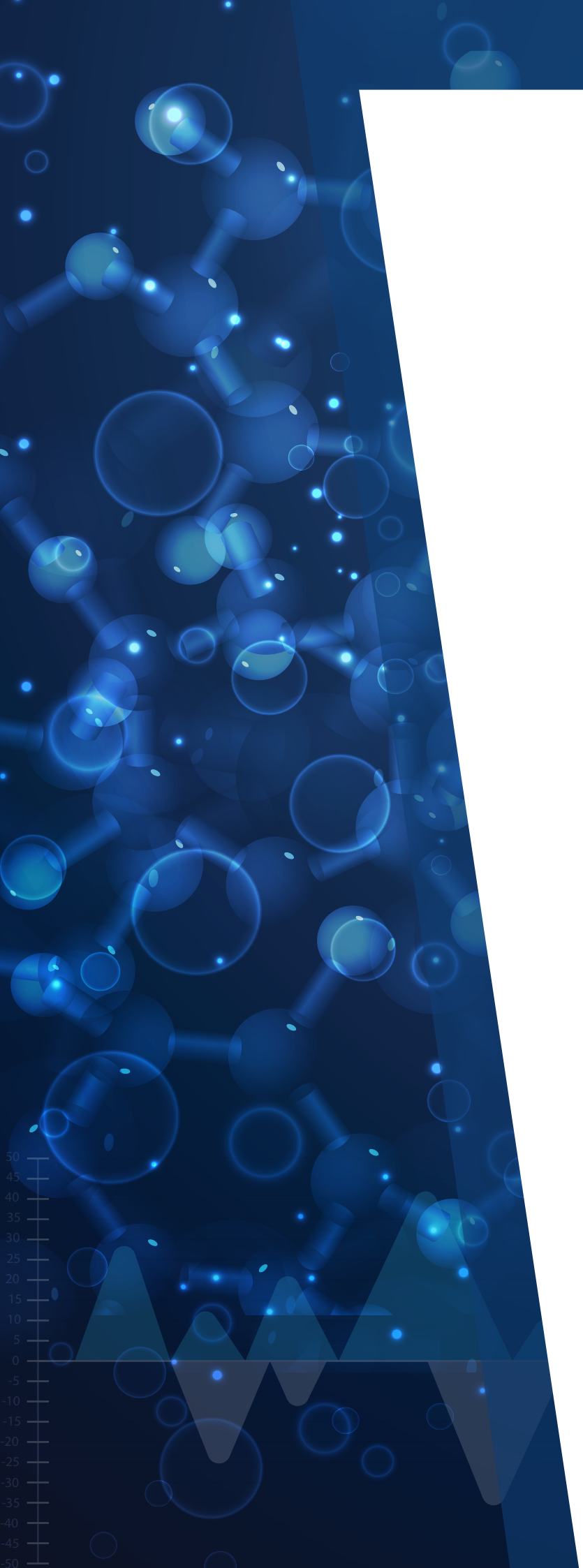


ενδοραμα
Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

Το Ιατρικό Συνέδριο ΕΝΔΟΡΑΜΑ είναι μια πρωτότυπη ετήσια ιατρική διημερίδα που διεξάγεται στο Πανεπιστήμιο Πατρών σε ετήσια βάση. Στα πλαίσια αυτού παρουσιάζονται κλινικά περιστατικά και ιατρικά δεδομένα, γίνεται ανασκόπηση των πλέον ενδιαφερόντων άρθρων που δημοσιεύτηκαν στη διεθνή βιβλιογραφία τη χρονιά που πέρασε σε όλα τα γνωστικά πεδία της Ενδοκρινολογίας.

Επίσης παρουσιάζονται και συζητούνται τα τελευταία ερευνητικά αποτελέσματα, ιδέες, εξελίξεις και εφαρμογές στον τομέα της ενδοκρινολογίας καθώς παρουσιάζονται όλα τα αντίστοιχα νέα φάρμακα που κυκλοφόρησαν την ίδια περίοδο.

Σε συνέχεια των προηγούμενων 12 συνεδρίων και ακολουθώντας τις εξελίξεις το ΕΝΔΟΡΑΜΑ '20 θα πραγματοποιηθεί Υβριδικά, με διαζώσης συμμετοχές αλλά και απομακρυσμένα μέσω του επίσημου site του συνεδρίου (**www.endorama.gr**).

Οι ψηφιακές υπηρεσίες δεν αφορούν μόνο την συμμετοχή των συνέδρων αλλά και των χορηγών καθώς στο site το συνεδρίου θα λειτουργεί virtual έκθεση χορηγών με πολλές νέες ψηφιακές παροχές.

ΟΜΙΛΗΤΕΣ - ΠΡΟΕΔΡΟΙ

Ανδρέου Λίλλη, Ενδοκρινολόγος, Κλινικός Ανδρολόγος με εξειδίκευση στην Ανδρική Αναπαραγωγή στη Γάνδη Βελγίου

Ανδρίκουλα Μαρία, Ενδοκρινολόγος, Διδάκτωρ Ιατρικής Σχολής Πανεπιστημίου Ιωαννίνων

Βασιλείου Βασιλική, Διευθύντρια ΕΣΥ, Ενδοκρινολογικό Τμήμα- Διαβητολογικό Κέντρο, ΓΝΑ "Ο Ευαγγελισμος"

Βλασσοπούλου Βαρβάρα, Ενδοκρινολόγος - Διαβητολόγος, τέως Διευθύντρια ΕΣΥ, Τμήμα Ενδοκρινολογίας - Διαβήτη - Μεταβολισμού, ΓΝΑ "Ο Ευαγγελισμός"

Γαλλή – Τσινοπούλου Ασημίνα, Καθηγήτρια Παιδιατρικής – Παιδιατρικής Ενδοκρινολογίας, Διευθύντρια Β΄ Παιδιατρικής Κλινικής Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης, ΠΓΝΘ ΑΧΕΠΑ Θεσσαλονίκης

Γιαβροπούλου Μαρία, Ενδοκρινολόγος Διευθύντρια ΕΣΥ, Ενδοκρινολογική Μονάδα, Α΄Προπαιδευτική Παθολογική Κλινική, Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Δουζδαμπάνης Περικλής, Ιατρός Νεφρολόγος, Διδάκτορας Ιατρικής Σχολής Πανεπιστημίου Πατρών, Πρόεδρος Ιατρικής Εταιρείας Δυτικής Ελλάδος – Πελοποννήσου (ΙΕΔΕΠ)

Ηλίας Ιωάννης, Ιατρός Ενδοκρινολόγος, Επιμελητής Α', Τμήμα Ενδοκρινολογίας, Διαβήτη και Μεταβολισμού, Νοσοκομείο «Έλενα Βενιζέλου»

Θεοδωροπούλου Αναστασία, Ενδοκρινολόγος, Διευθύντρια ΕΣΥ ΠΓΝΠ "ΠΑΝΑΓΙΑ Η ΒΟΗΘΕΙΑ"

Καλανταρίδου Σοφία, Καθηγήτρια Μαιευτικής-Γυναικολογίας και Στείρωσης της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών, Διευθύντρια Γ' Μαιευτικής και Γυναικολογικής Κλινικής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών, ΠΓΝ «Αττικόν» Διευθύντρια του Προγράμματος Μεταπτυχιακών Σπουδών «Παθολογία της Κύησης» της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

Κούκκου Ευτυχία, Ενδοκρινολόγος, Διδάκτωρ Ιατρικής του ΕΚΠΑ, Διευθύντρια ΕΣΥ, Τμήματος Ενδοκρινολογίας, Διαβήτη & Μεταβολισμού, Περιφερειακού Γενικού Νοσοκομείου- Μαιευτηρίου «Έλενα Βενιζέλου»

Κουτσιλιέρης Μιχάλης, Καθηγητής Πειραματικής Φυσιολογίας –Διευθυντής Εργαστηρίου Φυσιολογίας, Ιατρικής Σχολής -Σχολής Επιστημών Υγείας Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών

Λιπαράκη Μαρία, Ενδοκρινολόγος Διδάκτωρ Πανεπιστημίου Αθηνών. Πτυχίο Ιατρικής του Πανεπιστημίου Αθηνών, Ειδικότητα Ενδοκρινολογίας Διαβήτη και Μεταβολισμού, Έδρα Παθολογικής Φυσιολογίας Πανεπιστημίου Αθηνών- Λαϊκό Νοσοκομείο. Διδακτορική διατριβή Πανεπιστημίου Αθηνών

Μακράκης Ευάγγελος, MD, PhD, Μαιευτήρας - Γυναικολόγος Αναπαραγωγής, Διδάκτωρ Πανεπιστημίου Αθηνών, Εξειδικευμένος στην Υποβοηθούμενη Αναπαραγωγή.- Υπεύθυνος ιατρός Μονάδας Εξωσωματικής 'ΕΜΒΡΥΟ ART – Ακεσώ Μαιευτήρας - Γυναικολόγος εξειδικευμένος στην Ανθρώπινη Αναπαραγωγή Επιστημονικός Υπεύθυνος Μονάδας Υποβοηθούμενης Αναπαραγωγής, Γ' Μαιευτική Γυναικολογική Κλινική ΕΚΠΑ, ΠΓΝ Αττικόν

ΟΜΙΛΗΤΕΣ - ΠΡΟΕΔΡΟΙ

Μεντζελοπούλου Παρασκευή, Ενδροκρινολόγος, Διπλωματούχος των American Board of Internal Medicine και American Board of Endocrinology, Diabetes and Metabolism

Μηλιώνης Χαράλαμπος, Ιατρός Παθολόγος, MD, PhD, Αναπληρωτής Καθηγητής Παθολογίας Σχολής Επιστημών Υγείας, Τμήματος Ιατρικής του Πανεπιστημίου Ιωαννίνων

Μιχαλάκη Μαρίνα, Ιατρός Ενδοκρινολόγος, Διευθύντρια ΕΣΥ, Ενδοκρινολογικό Τμήμα της Πανεπιστημιακής Παθολογικής Κλινικής του Πανεπιστημιακού Γενικού Νοσοκομείου Πατρών

Μπένος Αλέξης, Ομότιμος Καθηγητής Υγιεινής, Κοινωνικής Ιατρικής & Πρωτοβάθμιας Φροντίδας Υγείας ΑΠΘ Εργαστήριο Πρωτοβάθμιας Φροντίδας Υγείας, Γενικής Ιατρικής & Έρευνας Υπηρεσιών Υγείας, Τμήμα Ιατρικής Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

Μπράβη Βασιλική, (FRCP, MBBS, MA Cantab, MRes, PGCE) Consultant in Endocrinology, Diabetes and Internal Medicine Imperial College Healthcare NHS Trust and an Honorary Senior Clinical Lecturer at Imperial College London

Παπαγεωργίου Άννα, Κλινική Διαιτολόγος – Διατροφολόγος και Καθηγήτρια Φυσικής Αγωγής

Παπαλεοντίου Μαρία, MD, Assistant Professor, Division of Metabolism, Endocrinology and Diabetes Institute of Healthcare Policy and Innovation University of Michigan

Σαριδάκη Αικατερίνη, Ιατρός Ενδροκρινολόγος, πρ. Διευθύντρια ΕΣΥ Ηράκλειο Κρήτης, Διευθύντρια Β Ενδοκρινολογικού, σύμβουλος Ενδοκρινολόγος Γενικό Νοσοκομείο Ευρωκλινικής Αθηνών

Τουρνής Συμεών, Ενδοκρινολόγος, Διδάκτωρ Ιατρικής Σχολής Πανεπιστημίου Ιωαννίνων

Τσαμέτης Χρήστος, Ενδοκρινολόγος, Κλινικός Ανδρολόγος Ε.Α.Α, Διδάκτωρ Ιατρικής Α.Π.Θ., Επιστημονικός Συνεργάτης Μονάδας Ενδοκρινολογίας Αναπαραγωγής, Α' Μαιευτική και Γυναικολογική Κλινική Α.Π.Θ., ΓΝΘ "Παπαγεωργίου"

Τσιμιχόδημος Βασίλης, Αναπληρωτής Καθηγητής Παθολογίας, Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων

Φούντας Αθανάσιος, MD, MSc, MHA, Post-CCT Fellow in Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust and Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Χαρμανδάρη Ευαγγελία, MD, MSc, PhD, MRCP(UK), CCT(UK), Καθηγήτρια Παιδιατρικής - Παιδιατρικής Ενδοκρινολογίας, Ιατρική Σχολή Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

Οργανωτική επιτροπή

Α.Γ. Βαγενάκης
Ν.Α. Γεωργόπουλος
Κ.Β. Μάρκου

ενδοραμα
Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

ΠΡΟΓΡΑΜΜΑ 2020

Παρασκευή 29/01/21

15:30-16:30
Εγγραφές

16:30-17:30
Λιπίδια
ΠΡΟΕΔΡΟΣ: Βασίλης Τσιμιχόδημος
ΟΜΙΛΗΤΗΣ: Χαράλαμπος Μηλιώνης

17:30-18:30
Γυναικεία Αναπαραγωγή
ΠΡΟΕΔΡΟΣ: Ευάγγελος Μακράκης
ΟΜΙΛΗΤΗΣ: Μαρία Ανδρίκουλα

18:30-18:45
Διάλειμμα

18:45-19:45
Ανδρική Αναπαραγωγή
ΠΡΟΕΔΡΟΣ: Λίλλη Ανδρέου
ΟΜΙΛΗΤΗΣ: Χρήστος Τσαμέτης

19:45-20:45
Η ενδοκρινολογία στην εποχή του Covid-19
ΠΡΟΕΔΡΟΣ: Περικλής Δουζδαμπάνης
ΟΜΙΛΗΤΗΣ: Ευτυχία Κούκκου

20:45-21:15
Πολιτιστικό Ενδόραμα
ΟΙ ΠΑΝΔΗΜΙΕΣ ΣΤΗ ΡΟΗ ΤΗΣ ΙΣΤΟΡΙΑΣ
ΟΜΙΛΗΤΗΣ: Αλέξης Μπένος,
Ομότιμος Καθηγητής Υγιεινής, Κοιν. Ιατρικής & Πρωτοβάθμιας Φροντίδας Υγείας ΑΠΘ Εργ. Πρωτοβάθμιας Φροντίδας Υγείας, Γεν. Ιατρικής & Έρευνας Υπηρεσιών Υγείας, Τμήμα Ιατρικής Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

ενδόραμα
Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός

Σάββατο 30/01/21

09:00-10:00
Παιδιατρική Ενδοκρινολογία
ΠΡΟΕΔΡΟΣ: Ασημίνα Γαλλή -Τσινοπούλου
ΟΜΙΛΗΤΗΣ: Ευαγγελία Χαρμανδάρη

10:00-11:00
Υπόφυση
ΠΡΟΕΔΡΟΣ: Μαρία Λιπαράκη
ΟΜΙΛΗΤΗΣ: Αθανάσιος Φούντας

11:00-11:30
Διάλειμμα

11:30-12:30
Ινσουλινο-εξαρτώμενος Σακχαρώδης διαβήτης
ΠΡΟΕΔΡΟΣ: Βαρβάρα Βλασσοπούλου
ΟΜΙΛΗΤΗΣ: Βασιλική Μπράβη

12:30-13:30
Μη Ινσουλινο-εξαρτώμενος Σακχαρώδης διαβήτης
ΠΡΟΕΔΡΟΣ: Βαρβάρα Βλασσοπούλου
ΟΜΙΛΗΤΗΣ: Παρασκευή Μεντζελοπούλου

13:30-14:30
Διατροφή
ΠΡΟΕΔΡΟΣ: Μιχαήλ Κουτσιλιέρης
ΟΜΙΛΗΤΗΣ: Άννα Παπαγεωργίου

14:30-16:00
Διάλλειμα

16:00-17:00
Επινεφρίδια
ΠΡΟΕΔΡΟΣ: Αικατερίνη Σαριδάκη
ΟΜΙΛΗΤΗΣ: Γιάννης Ηλίας

17:00-18:45
Νέα Φάρμακα
ΠΡΟΕΔΡΟΣ: Αναστασία Θεοδωροπούλου
ΟΜΙΛΗΤΗΣ: Μαρίνα Μιχαλάκη
Βασιλική Βασιλείου
Σοφία Καλανταρίδου

18:45-19:00
Διάλλειμα

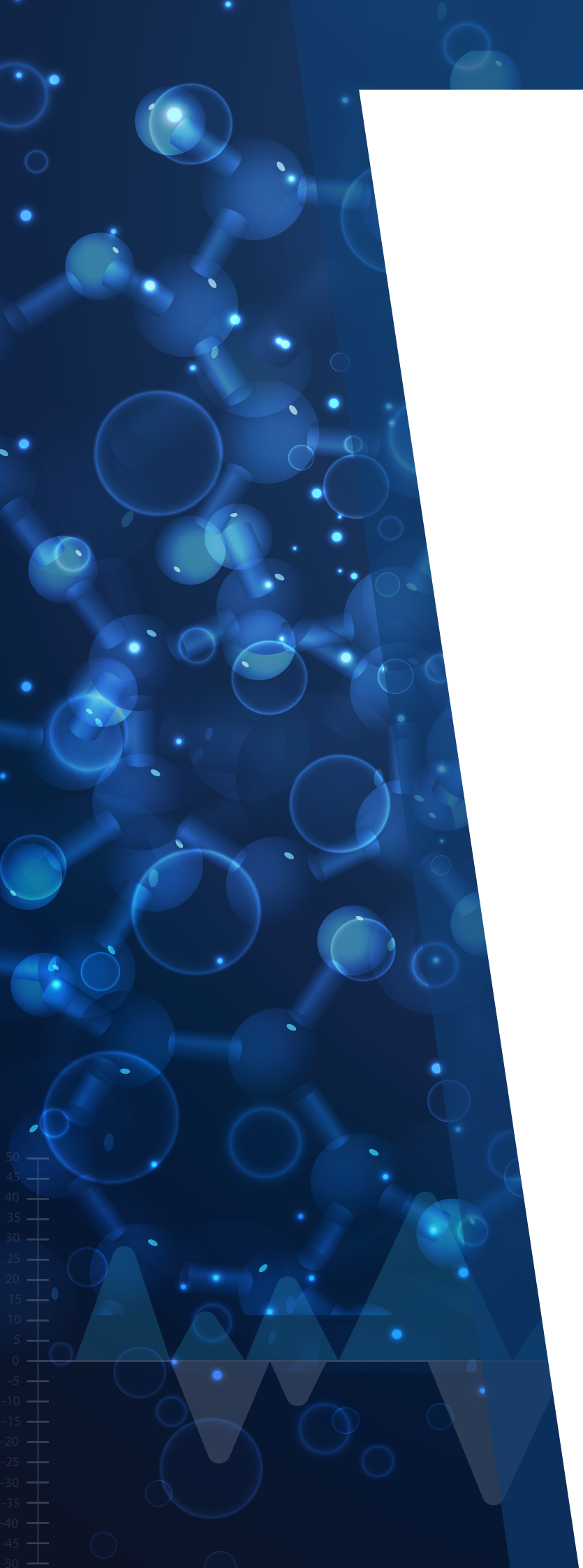
19:00-20:00
Μεταβολισμός Οστών
ΠΡΟΕΔΡΟΣ: Συμεών Τουρνής
ΟΜΙΛΗΤΗΣ: Μαρία Γιαβροπούλου

20:00-21:00
Θυροειδής
ΠΡΟΕΔΡΟΣ: Μαρίνα Μιχαλάκη
ΟΜΙΛΗΤΗΣ: Μαρία Παπαλεοντίου

21:00
Συμπεράσματα -Λήξη

Οργανωτική επιτροπή
Α.Γ. Βαγενάκης
Ν.Α. Γεωργόπουλος
Κ.Β. Μάρκου

ενδοραμα
Ενδοκρινολογία I Διαβητολογία I Μεταβολισμός



ΠΕΡΙΕΧΟΜΕΝΑ

Παιδιατρική Ενδοκρινολογία

ΠΡΟΕΔΡΟΣ: Ασημίνα Γαλλή -Τσινοπούλου
ΟΜΙΛΗΤΗΣ: Ευαγγελία Χαρμανδάρη

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity

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ABSTRACT

BACKGROUND

Obesity is a chronic disease with limited treatment options in pediatric patients. Liraglutide may be useful for weight management in adolescents with obesity.

METHODS

In this randomized, double-blind trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we enrolled adolescents (12 to <18 years of age) with obesity and a poor response to lifestyle therapy alone. Participants were randomly assigned (1:1) to receive either liraglutide (3.0 mg) or placebo subcutaneously once daily, in addition to lifestyle therapy. The primary end point was the change from baseline in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) standard-deviation score at week 56.

RESULTS

A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group. Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard-deviation score at week 56 (estimated difference, −0.22; 95% confidence interval [CI], −0.37 to −0.08; P=0.002). A reduction in BMI of at least 5% was observed in 51 of 113 participants in the liraglutide group and in 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively (estimated percentage, 26.1% vs. 8.1%). A greater reduction was observed with liraglutide than with placebo for BMI (estimated difference, −4.64 percentage points) and for body weight (estimated difference, −4.50 kg [for absolute change] and −5.01 percentage points [for relative change]). After discontinuation, a greater increase in the BMI standard-deviation score was observed with liraglutide than with placebo (estimated difference, 0.15; 95% CI, 0.07 to 0.23). More participants in the liraglutide group than in the placebo group had gastrointestinal adverse events (81 of 125 [64.8%] vs. 46 of 126 [36.5%]) and adverse events that led to discontinuation of the trial treatment (13 [10.4%] vs. 0). Few participants in either group had serious adverse events (3 [2.4%] vs. 5 [4.0%]). One suicide, which occurred in the liraglutide group, was assessed by the investigator as unlikely to be related to the trial treatment.

CONCLUSIONS

In adolescents with obesity, the use of liraglutide (3.0 mg) plus lifestyle therapy led to a significantly greater reduction in the BMI standard-deviation score than placebo plus lifestyle therapy. (Funded by Novo Nordisk; NN8022-4180 ClinicalTrials.gov number, NCT02918279.)

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*A complete list of the NN8022-4180 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CLINICAL RESEARCH ARTICLE

Clinical but Not Histological Outcomes in Males With 45,X/46,XY Mosaicism Vary Depending on Reason for Diagnosis

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Context: Larger studies on outcomes in males with 45,X/46,XY mosaicism are rare.

Objective: To compare health outcomes in males with 45,X/46,XY diagnosed as a result of either genital abnormalities at birth or nongenital reasons later in life.

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Abbreviations: COST, European Cooperation in Science and Technology; DSD, disorders of sex development; EMS, external masculinization score; FSH, follicle-stimulating hormone; GCNIS, germ-cell neoplasia *in situ*; I-DSD, International Disorders of Sex Development; LH, luteinizing hormone; LOD, limit of detection; rhGH, recombinant human GH; SCO, Sertoli cell only; SDS, SD score; T, testosterone; WHO, World Health Organization.

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Design: A retrospective, multicenter study.

Setting: Sixteen tertiary centers.

Patients or Other Participants: Sixty-three males older than 13 years with 45,X/46,XY mosaicism.

Main Outcome Measures: Health outcomes, such as genital phenotype, gonadal function, growth, comorbidities, fertility, and gonadal histology, including risk of neoplasia.

Results: Thirty-five patients were in the genital group and 28 in the nongenital. Eighty percent of all patients experienced spontaneous pubertal onset, significantly more in the nongenital group (P = 0.023). Patients were significantly shorter in the genital group with median adult heights of 156.7 cm and 164.5 cm, respectively (P = 0.016). Twenty-seven percent of patients received recombinant human GH. Forty-four patients had gonadal histology evaluated. Germ cells were detected in 42%. Neoplasia *in situ* was found in five patients. Twenty-five percent had focal spermatogenesis, and another 25.0% had arrested spermatogenesis. Fourteen out of 17 (82%) with semen analyses were azoospermic; three had motile sperm.

Conclusion: Patients diagnosed as a result of genital abnormalities have poorer health outcomes than those diagnosed as a result of nongenital reasons. Most patients, however, have relatively good endocrine gonadal function, but most are also short statured. Patients have a risk of gonadal neoplasia, and most are azoospermic, but almost one-half of patients has germ cells present histologically and up to one-quarter has focal spermatogenesis, providing hope for fertility treatment options. (***J Clin Endocrinol Metab*** **104: 4366–4381, 2019)**

The 45,X/46,XY karyotype and its variants are rare, with a previously reported incidence of one of 15,000 live births (1). The resulting phenotype spans across a wide range of effects, including genital anomalies, impaired growth, altered gonadal function and histology, and infertility. The karyotype is covered by the umbrella term differences (or disorders) of sex development (DSD), referring to diagnoses in which anatomical, gonadal, and/or chromosomal sex are affected (2). The 45,X cell line in these patients probably stems from the loss of a normal or structurally abnormal Y-chromosome in early embryonic mitosis, which produces the mosaicism (3–7).

The phenotypic spectrum of 45,X/46,XY patients varies greatly from females with Turner syndrome to normally androgenized males. Moreover, several studies have reported that 80% to 95% of prenatally diagnosed cases with a 45,X/46,XY karyotype are born as normally androgenized males (3, 5, 8, 9), whereas postnatally diagnosed pediatric cases present more varied phenotypes, including ambiguous genitalia (5, 10, 11). Furthermore, normally androgenized male patients with a 45,X/46,XY karyotype diagnosed in adulthood are now more frequently identified as a result of male infertility work-ups, including genetic screening (12). Thus, severity of the patient's phenotype often appears to be directly related to the age at diagnosis and reason for referral.

The wide spectrum of phenotypes in these patients is also reflected in health outcomes, such as growth, gonadal function, risk of gonadal neoplasia, and comorbidities, which are all reported with varying incidences and severities, both within the same centers and between centers (5, 7, 10, 13–16). It seems intuitive that the severity of the genital phenotype may be considered a read-out for other health outcomes. Nevertheless, even normally androgenized males diagnosed in adulthood have been reported to have short stature and declining testicular function with age and infertility, likely related to histologically dysgenetic testes (5, 6). However, there is a lack of studies with direct comparisons of outcomes in terms of growth, gonadal function, and comorbidities between patients diagnosed at birth as a result of genital abnormalities and those diagnosed later in life as a result of other reasons, such as short stature, pubertal delay, and infertility.

The risk of gonadal neoplasia in patients with 45,X/46,XY mosaicism is reported to be relatively high, at ~10%–15% (5, 16–19). The current practice of early (prepubertal) gonadectomy in girls renders it impossible to evaluate gonadal function and possible fertility potential in women. Moreover, single-center studies on histological outcomes are limited by numbers, thereby making thorough pathohistological evaluations of larger datasets rare.

Thus, we wanted to investigate and compare health outcomes, such as growth, gonadal function, comorbidities, fertility, and histology, including risk of neoplasia in males with 45,X/46,XY mosaicism and variants diagnosed as a result of the following different reasons: (i) genital abnormalities and (ii) other reasons, such as stunted growth, lack of pubertal onset, undervirilization, and infertility, in a large multicenter study with 16

CLINICAL RESEARCH ARTICLE

Combined Gestational Age- and Birth Weight–Adjusted Cutoffs for Newborn Screening of Congenital Adrenal Hyperplasia

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Context: Congenital adrenal hyperplasia (CAH) was among the first genetic disorders included in newborn screening (NBS) programs worldwide, based on 17α-hydroxyprogesterone (17-OHP) levels in dried blood spots. However, the success of NBS for CAH is hampered by high false positive (FP) rates, especially in preterm and low-birthweight infants.

Objective: To establish a set of cutoff values adjusting for both gestational age (GA) and birthweight (BW), with the aim of reducing FP rates.

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Abbreviations: 17-OHP, 17α-hydroxyprogesterone; BW, birthweight; CAH, congenital adrenal hyperplasia; DBS, dried blood spots; FP, false-positive; GA, gestational age; NBS, newborn screening; NICU, neonatal/preterm intensive care unit; PPV, positive predictive value.

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Design: This cross-sectional, population-based study summarizes 10 years of experience of the Israeli NBS program for diagnosis of CAH. Multitiered 17-OHP cutoff values were stratified according to both BW and GA.

Participants: A total of 1,378,132 newborns born between 2008 and 2017 were included in the NBS program.

Results: Eighty-eight newborns were ultimately diagnosed with CAH; in 84 of these, CAH was detected upon NBS. The combined parameters–adjusted approach significantly reduced the recall FP rate (0.03%) and increased the positive predictive value (PPV) (16.5%). Sensitivity among those referred for immediate attention increased significantly (94%). There were four false negative cases (sensitivity, 95.4%), all ultimately diagnosed as simple-virilizing. Sensitivity and specificity were 95.4% and 99.9%, respectively, and the percentage of true-positive cases from all newborns referred for evaluation following a positive NBS result was 96%.

Conclusions: The use of cutoff values adjusted for both GA and BW significantly reduced FP rates (0.03%) and increased overall PPV (16.5%). Based on our 10 years of experience, we recommend the implementation of this two parameter–adjusted approach for NBS of classic CAH in NBS programs worldwide. (***J Clin Endocrinol Metab*** **104: 3172–3180, 2019)**

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by deficiencies of steroidogenic enzymes leading to inborn errors of cortisol biosynthesis. More than 90% of cases are caused by deficiency of 21-hydroxylase, associated with deleterious variants in the *CYP21A2* gene (1). CAH is divided into two groups and three main clinical presentations depending on the type of mutation and the level of enzymatic activity (2, 3). Seventy-five percent of patients with the classic, more severe form have the salt-wasting type, and the remaining are designated as having the simple virilizing type (4). The worldwide incidence of the classic form of CAH is 1 per 10,000 to 1:15,000 live births (3). The classic form leads to prenatal virilization in the female fetus; hence, the diagnosis is made at birth. The other group is nonclassic CAH, defined also as late-onset, and so is less likely to be detected by newborn screening (NBS). Classic salt-wasting CAH is a life-threatening condition, especially in infancy, and early detection and therapeutic intervention can significantly alter the prognosis and reduce the associated morbidity and mortality (5). CAH has a relatively high incidence, and high-throughput screening tests are both sensitive and cost-effective (5). Thus, CAH has long been considered an excellent candidate for NBS and indeed was among the first genetic disorders to be included in NBS programs worldwide; screening is commonly based on the measurement of 17α-hydroxyprogesterone (17-OHP) levels in dried blood spots (DBS) (6–8).

Nevertheless, one of the greatest concerns hampering the success of NBS for CAH has been the high rate, up to 1%, of false-positive (FP) results (1). This caveat is particularly important in preterm and low-birthweight infants (9, 10), in part because of transient elevations in 17-OHP levels affected by birth stress, adrenal immaturity, and early collection of specimens before 24 hours (11).

Subsequently, over the past few decades, NBS worldwide have pursued several different strategies aimed at lowering the FP rates and improving the positive predictive value (PPV), with varying degrees of success.

One such approach has been to adjust the threshold levels of 17-OHP according to birthweight (BW) (12–14). Alternatively, cutoff levels based on gestational age were attempted and described (15, 16). In a study comparing the two determinants, van der Kamp *et al.* (17) used regression analysis and concluded that the latter was associated with greater specificity. Indeed, many countries worldwide chose to implement BW- or gestational age (GA)–adjusted cutoffs.

An additional approach, first implemented in Bavaria and described by Olgemöller *et al.* (18), based cutoff levels on both BW and age at sampling, subsequently improving the PPV and decreasing FP rates to 0.79%. Most recently, in a cohort of 271,810 newborns in Sao Paolo, Brazil, investigators based the cutoff values on BW and sample collection time (48 to 72 hours vs $\geq$72 hours) and reported a FP rate of 0.2% and 0.5% using the 99.8th and 99.5th percentiles, respectively. They concluded that the former was the best cutoff value to distinguish between affected and unaffected newborns (19).

Because the commonly used strategies did not collectively ameliorate the relatively high FP rates of NBS for CAH, second-tier testing was introduced with biochemical (liquid chromatography–tandem mass spectrometry, measuring adrenal steroid levels in DBS) or molecular (4, 20–24) methods. However, two-tier testing of a single sample resulted in an increased false negative (FN) rate, without significantly reducing the FP rate (23).

With the purpose of further reducing the FP rates of newborn screening for classic CAH, the National Newborn Screening Program in Israel has been implementing a unique set of cutoff values, combining

Guidelines

HORMONE RESEARCH IN PÆDIATRICS

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Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective

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Abstract
The Growth Hormone Research Society (GRS) convened a Workshop in March 2019 to evaluate the diagnosis and therapy of short stature in children. Forty-six international experts participated at the invitation of GRS including clinicians, basic scientists, and representatives from regulatory agencies and the pharmaceutical industry. Following plenary presentations addressing the current diagnosis and therapy of short stature in children, breakout groups discussed questions produced in advance by the planning committee and reconvened to share the group reports. A writing team assembled one document that was subsequently discussed and revised by participants. Participants from regulatory agencies and pharmaceutical companies were not part of the writing process. Short stature is the most common reason for referral to the pediatric endocrinologist. History, physical examination, and auxology remain the most important methods for understanding the reasons for the short stature. While some long-standing topics of controversy continue to generate debate, including in whom, and how, to perform and interpret growth hormone stimulation tests, new research areas are changing the clinical landscape, such as the genetics of short stature, selection of patients for genetic testing, and interpretation of genetic tests in the clinical setting. What dose of growth hormone to start, how to adjust the dose, and how to identify and manage a suboptimal response are still topics to debate. Additional areas that are expected to transform the growth field include the development of long-acting growth hormone preparations and other new therapeutics and diagnostics that may increase adult height or aid in the diagnosis of growth hormone deficiency.

Introduction and Background

The Growth Hormone Research Society (GRS) convened a 3-day workshop to provide an expert perspective on the diagnosis and therapy of short stature in children [1]. Short stature and growth deceleration are common pediatric concerns [2]. Although established diagnostic and management paradigms exist, recent advances in molecular technologies have greatly broadened our understanding of the genetic causes of short stature, and this is altering our approach to children with these common problems. In particular, while evaluation of the growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis is often part of the initial clinical assessment in growth disorders, the evolving understanding of growth plate physiology has led to an increasing focus on abnormalities in this tissue resulting in the potential for the development of innovative therapies [3]. In addition, discovery of novel mutations in genes encoding proteins responsible for pituitary development has increased our understanding of the genetic basis of hypopituitarism. The increased capability and availability of genetic and epigenetic testing in clinical practice has the potential to enhance the diagnostic process and inform appropriate treatment. Furthermore, novel treatment approaches, including use of long-acting GH formulations as well as new GH secretagogues that may serve both as diagnostic tools and as therapeutic agents, have prompted expert consideration.

Methods

The structure of this Workshop was adapted from prior workshops organized by the GRS [4]. The Program Organizing Committee invited 46 GH experts from 14 countries across 5 continents. These included pediatric and adult endocrinologists, basic scientists, representatives from the European Medicines Agency and the United States Food and Drug Administration, and representatives from the pharmaceutical industry. A review of the status of GH therapy and evaluation of short stature in children was published prior to the meeting [2].

Following presentations that summarized the relevant literature, 3 breakout groups addressed each topic in greater detail by discussing a list of questions formulated by the Program Organizing Committee and subsequently agreed upon by all participants. All attendees reconvened after each breakout session to share reports from the groups. At the end of days 1 and 2, a writing team compiled the breakout group reports into a document that was discussed and reviewed in its entirety and revised by participants on the final day. In a few cases where there was not a clear consensus, the majority opinion was determined by a vote of the participants. This draft document was edited further for formatting and references, and subsequently circulated to the academic attendees for final review after the meeting. Participants from pharmaceutical companies and regulatory agencies who were present at the Workshop joined in the breakout session debates but were not part of the writing team, did not

CLINICAL TRIAL

JBMR

Effects of Estrogen Replacement on Bone Geometry and Microarchitecture in Adolescent and Young Adult Oligoamenorrheic Athletes: A Randomized Trial

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ABSTRACT

Oligoamenorrheic athletes (OAs) have lower bone mineral density (BMD) and greater impairment of bone microarchitecture, and therefore higher fracture rates compared to eumenorrheic athletes. Although improvements in areal BMD (aBMD; measured by dual-energy X-ray absorptiometry) in OAs have been demonstrated with transdermal estrogen treatment, effects of such treatment on bone microarchitecture are unknown. Here we explore effects of transdermal versus oral estrogen versus no estrogen on bone microarchitecture in OA. Seventy-five OAs (ages 14 to 25 years) were randomized to (i) a 100-μg 17β-estradiol transdermal patch (PATCH) administered continuously with 200 mg cyclic oral micronized progesterone; (ii) a combined 30 μg ethinyl estradiol and 0.15 mg desogestrel pill (PILL); or (iii) no estrogen/progesterone (NONE) and were followed for 12 months. Calcium (≥1200 mg) and vitamin D (800 IU) supplements were provided to all. Bone microarchitecture was assessed using high-resolution peripheral quantitative CT at the distal tibia and radius at baseline and 1 year. At baseline, randomization groups did not differ by age, body mass index, percent body fat, duration of amenorrhea, vitamin D levels, BMD, or bone microarchitecture measurements. After 1 year of treatment, at the distal tibia there were significantly greater increases in total and trabecular volumetric BMD (vBMD), cortical area and thickness, and trabecular number in the PATCH versus PILL groups. Trabecular area decreased significantly in the PATCH group versus the PILL and NONE groups. Less robust differences between groups were seen at the distal radius, where percent change in cortical area and thickness was significantly greater in the PATCH versus PILL and NONE groups, and changes in cortical vBMD were significantly greater in the PATCH versus PILL groups. In conclusion, in young OAs, bone structural parameters show greater improvement after 1 year of treatment with transdermal 17β-estradiol versus ethinyl estradiol–containing pills, particularly at the tibia. © 2019 American Society for Bone and Mineral Research.

KEY WORDS: BONE QCT/μCT; DXA; ESTROGENS AND SERMs; FRACTURE PREVENTION; HORMONE REPLACEMENT/RECEPTOR MODULATORS

Introduction

The prevalence of amenorrhea in female athletes ranges from 3.4% to 66%, varying by exercise type, intensity and duration, and nutritional status,[1–3] compared with only 3% to 4% in the general population.[4] Athletes who participate in endurance activities in which leanness is believed to confer a performance advantage are especially at risk for developing Female Athlete Triad (Triad), described as decreased energy availability (EA), menstrual dysfunction, and low bone mineral density (BMD).[5,6] Low EA occurs when caloric intake does not keep pace with caloric expenditure, and may be inadvertent or purposeful. Such low EA, even while allowing for a normal body mass index (BMI), has negative effects on menstrual function and bone.[7–9] In addition to the detrimental effects of hypogonadism to bone,[10,11] low EA has negative effects on other hormones

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Public clinical trial registration: http://clinicaltrials.gov/show/NCT00946192. Fat Mediated Modulation of Reproductive and Endocrine Function in Young Athletes.

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Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial

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Summary

Background **Levoketoconazole is a ketoconazole stereoisomer in development for treatment of Cushing's syndrome and has not been assessed previously in a clinical trial in patients with Cushing's syndrome. We aimed to investigate the efficacy and safety of levoketoconazole in patients with endogenous Cushing's syndrome.**

Methods **SONICS is a phase 3, multicentre, open-label, non-randomised, single-arm study in which we recruited adults (≥18 years) with confirmed Cushing's syndrome and a mean 24-h urinary free cortisol (mUFC) of at least 1·5 times the upper limit of normal from 60 hospital and community sites in 19 countries (15 countries in Europe, and Canada, Israel, Turkey, and the USA). Patients were treated with oral levoketoconazole in a 2–21 week incremental dose-titration phase starting at 150 mg twice daily (150 mg increments until mUFC normalisation, maximum 600 mg twice daily) and a 6-month maintenance phase. The primary outcome was the proportion of patients with mUFC normalisation at end of maintenance, without dose increase during the maintenance phase (in the intention-to-treat population). Prespecified adverse events of special interest were potential liver toxicity, corrected QT prolongation, and adrenal insufficiency. This trial is registered with ClinicalTrials.gov, NCT01838551.**

Findings **Between July 30, 2014, and June 30, 2017, 201 individuals were screened and 94 patients were enrolled and received at least one dose of study medication. Of the 94 patients, 80 (85%) had pituitary Cushing's syndrome. Mean mUFC at baseline was 671·4 nmol/24 h (243·3 μg/24 h), which is 4·9 times the upper limit of normal. Of the 77 patients who advanced to the maintenance phase, 62 (81%) had mUFC normalisation by end-of-dose titration. At the end of the 6-month maintenance phase, 29 (31%) of 94 patients were responders; the least-squares mean estimate of the proportion of responders was 0·30 (95% CI 0·21–0·40; p=0·0154 *vs* null hypothesis of ≤0·20). The most common adverse events in the 94 patients were nausea (30 [32%]) and headache (26 [28%]). Adverse events led to study discontinuation in 12 (13%) of 94 patients. Two patients had a QT interval (Fridericia corrected) of more than 500 ms, and three patients had suspected adrenal insufficiency. Alanine aminotransferase reversibly increased to more than three times the upper limit of normal in ten (11%) patients. Four patients had serious adverse events that were considered probably or definitely related to the study drug: abnormal liver function test results (n=1), prolonged QT interval (n=2), and adrenal insufficiency (n=1). One person died from colon carcinoma unrelated to study medication.**

Interpretation **Twice-daily oral levoketoconazole treatment led to sustained improvements in urinary free cortisol, with an acceptable safety and tolerability profile. Levoketoconazole might represent a useful therapeutic option for the medical treatment of Cushing's syndrome.**

Funding **Strongbridge Biopharma.**

Introduction

Endogenous Cushing's syndrome is a rare, serious endocrine condition characterised by chronic over-production of cortisol, most often caused by a pituitary adenoma (ie, Cushing's disease).[1] Other causes include ectopic adrenocorticotropic hormone production or primary adrenal neoplasia.[2] Patients with Cushing's syndrome have increased mortality, mainly as a result of cardiovascular complications.[3–5]

Surgical removal of the underlying lesion is first-line therapy, sometimes preceded by preoperative medical treatment.[6] The choice of second-line therapy (medications, further surgery, or radiotherapy) depends on individual patient characteristics and treatment efficacy and risks.[6,7] Medical treatments suppress excessive adrenocorticotropic hormone or cortisol production or decrease cortisol activity.[5,8]

Ketoconazole, a racemic mixture of two enantiomers (2S,4R-ketoconazole and 2R,4S-ketoconazole), is an azole antifungal drug that is approved for treatment of endogenous Cushing's syndrome by the European Medicines Agency[9] and is used off-label for this purpose in the USA (where the recognised use by the US Food and Drug Administration [FDA] is for endemic mycoses

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Exposure to Glucocorticoids in the First Part of Fetal Life is Associated with Insulin Secretory Defect in Adult Humans

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Objective: High glucocorticoid levels in rodents inhibit development of beta cells during fetal life and lead to insulin deficiency in adulthood. To test whether similar phenomena occur in humans, we compared beta-cell function in adults who were exposed to glucocorticoids during the first part of fetal life with that of nonexposed subjects.

Research Design and Methods: The study was conducted in 16 adult participants exposed to glucocorticoids during the first part of fetal life and in 16 nonexposed healthy participants with normal glucose tolerance who were matched for age, sex, and body mass index (BMI). Exposed participants had been born to mothers who were treated with dexamethasone 1 to 1.5 mg/day from the sixth gestational week (GW) to prevent genital virilization in children at risk of 21-hydroxylase deficiency. We selected offspring of mothers who stopped dexamethasone before the 18th GW following negative genotyping of the fetus. Insulin and glucagon secretion were measured during an oral glucose tolerance test (OGTT) and graded intravenous (IV) glucose and arginine tests. Insulin sensitivity was measured by hyperinsulinemic-euglycemic-clamp.

Results: Age, BMI, and anthropometric characteristics were similar in the 2 groups. Insulinogenic index during OGTT and insulin sensitivity during the clamp were similar in the 2 groups. In exposed subjects, insulin secretion during graded IV glucose infusion and after arginine administration decreased by 17% ($P = 0.02$) and 22% ($P = 0.002$), respectively, while glucagon secretion after arginine increased.

Conclusion: Overexposure to glucocorticoids during the first part of fetal life is associated with lower insulin secretion at adult age, which may lead to abnormal glucose tolerance later in life. **(*J Clin Endocrinol Metab* 105: e191–e199, 2020)**

Key Words: glucocorticoids, insulin secretion, fetal programming

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Abbreviations: ACTH, adrenocorticotropin; ANCOVA, analysis of covariance; AUC, area under the curve; BMI, body mass index; CAH, congenital adrenal hyperplasia; DXM, dexamethasone; GC, glucocorticoid; GR, glucocorticoid receptor; GW, gestational week; HPA, hypothalamic-pituitary-adrenal; IAUC, incremental area under the curve; ISR, insulin secretion rate; IV, intravenous; OGTT, oral glucose tolerance test.

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CLINICAL RESEARCH ARTICLE

Frequency and Incidence of Carney Complex Manifestations: A Prospective Multicenter Study With a Three-Year Follow-Up

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Introduction: Carney Complex (CNC) is a rare multiple endocrine and nonendocrine neoplasia syndrome. Manifestations and genotype-phenotype correlations have been described by retrospective studies, but no prospective study evaluating the occurrence of the different manifestations has been available so far.

Methods: This multicenter national prospective study included patients with CNC, primary pigmented nodular adrenal disease (PPNAD), or a pathogenic *PRKAR1A* mutation; after a full initial workup, participants were followed for 3 years with annual standardized evaluation.

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Abbreviations: CNC, Carney complex;CT, computed tomography;GH, growth hormone; IGF-1, insulin-like growth factor 1; LCCSCT, large cell calcified Sertoli cell tumors; MRI, magnetic resonance imaging;NICHD, National Institute of Child Health & Human Development;oGTT, oral glucose tolerance test;PMS, psammomatous melanotic schwannoma;PPNAD, primary pigmented nodular adrenal disease; TRH, thyrotropin releasing hormone;TTE, transthoracic echocardiography;UFC, urinary free cortisol;US, ultrasound;V0, baseline evaluation;V1, 1-year evaluation;V2, 2-year evaluation;V3, 3-year evaluation.

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Results: The cohort included 70 patients (50 female/20 male, mean age 35.4 ± 16.7 years, 81% carrying *PRKAR1A* mutation). The initial investigations allowed identification of several manifestations. At the end of the 3-year follow-up, the newly diagnosed manifestations of the disease were subclinical acromegaly in 6 patients, bilateral testicular calcifications in 1 patient, and cardiac myxomas in 2 patients. Recurrences of cardiac myxomas were diagnosed in 4 patients during the 3-year follow-up study period. Asymptomatic abnormalities of the corticotroph and somatotroph axis that did not meet criteria of PPNAD and acromegaly were observed in 11.4% and 30% of the patients, respectively. Patients carrying the *PRKAR1A* c.709-7del6 mutation had a mild phenotype.

Conclusion: This study underlines the importance of a systematic follow-up of the CNC manifestations, especially a biannual screening for cardiac myxoma. By contrast, regular screening for the other manifestations after a first extensive workup could be spread out, leading to a lighter and more acceptable follow-up schedule for patients. These are important results for recommendations for long-term management of CNC patients. (***J Clin Endocrinol Metab* 105: e436–e446, 2020)**

Keywords: Carney complex, PRKAR1A, multiple endocrine neoplasia, Cushing's syndrome, myxoma

Carney complex (CNC) is a rare multiple endocrine and nonendocrine neoplasia syndrome, described for the first time in 1985 by J, Aidan Carney as "the complex of myxomas, spotty pigmentation and endocrine overactivity" (1). In 2001, diagnostic criteria of CNC were revised based on the description of clinical manifestations reported in a worldwide collection of records of patients from the National Institute of Child Health & Human Development (NICHD), part of the National Institutes of Health (Bethesda, Maryland) (2). Diagnostic criteria includes dermatologic manifestations (spotty skin pigmentation with typical periorificial distribution [known as lentigines], cutaneous myxomas), cardiac myxoma, primary pigmented nodular adrenal disease (PPNAD) causing adrenal Cushing, acromegaly by growth hormone (GH)-producing pituitary adenoma, breast myxomatosis and breast ductal adenoma, large cell calcified Sertoli cell tumors (LCCSCT), thyroid carcinoma or multiple nodules, psammomatous melanotic schwannoma (PMS) and osteochondromyxoma (2). Diagnosis is based on the presence of 2 or more manifestations. In addition, some manifestations are suggestive of CNC, such as hyperprolactinemia, elevated IGF-1 or abnormal GH suppression response during an oral glucose tolerance test (oGTT), or paradoxical GH responses to thyrotropin releasing hormone (TRH) stimulation in the absence of clinical acromegaly, blue nevi, or a single thyroid nodule. Several other manifestations possibly associated with CNC have been described, such as cardiomyopathy, colonic polyps, bronchogenic cysts, hepatocellular adenoma and carcinoma, colonic or gastric carcinomas, retroperitoneal fibrous histiocytomas (2) and pancreatic tumors (2, 3).

About 30% of cases are considered as sporadic and the other 70% are dominantly inherited (2). The Carney complex gene located at 17q22-24 was identified in 2000 as the tumor suppressor gene *PRKAR1A*, encoding for the regulatory subunit type 1 alpha of the protein kinase A (4, 5). Affected patients harbor a germline heterozygous *PRKAR1A* alteration, more often a mutation than an intragenic deletion, with large deletions being rarely observed.

The analysis on retrospective data of the phenotype and genotype of a cohort of 353 patients led by the NICHD and the Hospital Cochin (Paris, France) allowed in 2009 the analysis of the genotype-phenotype correlations. In this cohort, 62% of the index cases had a germline *PRKAR1A* alteration. Correlations were: (1) exonic mutations were more often associated with acromegaly, cardiac myxomas, lentigines, and PMS; (2) intronic mutations led to a less serious phenotype; (3) the hotspot c.491_492del mutation was more often associated with cardiac myxoma, lentigines, and thyroid tumors; (4) the hotspot c.709(-7)del was more often associated with isolated PPNAD; and (5) patients without *PRKAR1A* mutations had a less serious phenotype with late occurrence of the manifestations (6).

With the possibility of a genetic diagnosis of CNC, after the identification of *PRKAR1A* more than 15 years ago, the disease is now better recognized and more physicians, especially endocrinologists, are aware of its numerous manifestations and the need for long-term follow-up. Furthermore, familial genetic screening after identification of a *PRKAR1A* mutation in an index case leads to an increased number of individuals to monitor. Due to the multiplicity of the manifestations of CNC and the retrospective nature of the studies published

Long-Term Outcome of Primary Bilateral Macronodular Adrenocortical Hyperplasia After Unilateral Adrenalectomy

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Context: Unilateral adrenalectomy has been proposed in selected patients with primary bilateral macronodular adrenocortical hyperplasia (PBMAH), but its long-term outcome is unclear.

Objective: The aim of this study was to analyze long-term clinical and biochemical outcomes of unilateral adrenalectomy vs bilateral adrenalectomy in patients with PBMAH in comparison with the outcome of cortisol-producing adenoma (CPA) treated with unilateral adrenalectomy.

Design: Retrospective observational study in three German and one Italian academic tertiary care center.

Patients and Methods: Twenty-five patients with PBMAH after unilateral adrenalectomy (unilat-ADX-PBMAH), nine patients with PBMAH and bilateral adrenalectomy (bilat-ADX-PBMAH), and 39 patients with CPA and unilateral adrenalectomy (unilat-ADX-CPA) were included.

Results: Baseline clinical and biochemical parameters were comparable in patients with unilat-ADX-PBMAH, bilat-ADX-PBMAH, and unilat-ADX-CPA. Directly after surgery, 84% of the patients with unilat-ADX-PBMAH experienced initial remission of Cushing syndrome (CS). In contrast, at last follow-up (median, 50 months), 32% of the patients with unilat-ADX-PBMAH were biochemically controlled compared with nearly all patients in the other two groups ($P = 0.000$). Adrenalectomy of the contralateral side had to be performed in 12% of the initial patients with unilat-ADX-PBMAH. Three of 20 patients with unilat-ADX-PBMAH (15%) died during follow-up, presumably of CS-related causes; no deaths occurred in the other two groups ($P = 0.008$). Deaths occurred exclusively in patients who were not biochemically controlled after unilateral ADX.

Conclusions: Our data suggest that unilateral adrenalectomy of patients with PBMAH leads to clinical remission and a lower incidence of adrenal crisis but in less sufficient biochemical control of hypercortisolism, potentially leading to higher mortality. **(*J Clin Endocrinol Metab* 104: 2985–2993, 2019)**

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Abbreviations: ADX, adrenalectomy; CPA, cortisol-producing adenoma; CS, Cushing syndrome; IQR, interquartile range; PBMAH, primary bilateral macronodular adrenocortical hyperplasia; QoL, quality of life; UFC, urinary free cortisol.

Using Kisspeptin to Predict Pubertal Outcomes for Youth with Pubertal Delay

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Disclosure summary:

Y.-M.C. reports personal fees from Abbvie, Endo Pharmaceuticals, and Becker Pharmaceuticals. Y.-M.C. and S.B.S. have a provisional patent for kisspeptin-10. The remaining authors have nothing to disclose.

Trial registration: ClinicalTrials.gov NCT01438034

Abstract

Context: The management of youth with delayed puberty is hampered by difficulty in predicting who will eventually progress through puberty and who will fail to attain adult reproductive endocrine function. The neuropeptide kisspeptin, which stimulates GnRH release, can be used to probe the integrity of the reproductive endocrine axis.

Objective: We sought to determine whether responses to kisspeptin can predict outcomes for individuals with pubertal delay.

Design, Setting, and Participants: We conducted a longitudinal cohort study in an academic medical center of 16 children (3 girls and 13 boys) with delayed or stalled puberty.

Intervention and Outcome Measures: Children who had undergone kisspeptin- and GnRH-stimulation tests were followed every six months for clinical evidence of progression through puberty. Inhibin B was measured in boys. A subset of participants underwent exome sequencing.

Results: All participants who had responded to kisspeptin with a rise in LH of 0.8 mIU/mL or greater subsequently progressed through puberty (n = 8). In contrast, all participants who had exhibited LH responses to kisspeptin ≤0.4 mIU/mL reached age 18 years without developing physical signs of puberty (n = 8). Thus, responses to kisspeptin accurately predicted later pubertal outcomes (p = 0.0002).

Moreover, the kisspeptin-stimulation test outperformed GnRH-stimulated LH, inhibin B, and genetic testing in predicting pubertal outcomes.

Conclusion: The kisspeptin-stimulation can assess future reproductive endocrine potential in prepubertal children and is a promising novel tool for predicting pubertal outcomes for children with delayed puberty

Keywords: Delayed puberty, kisspeptin, constitutional delay, hypogonadotropic hypogonadism

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Précis

In 16 children with delayed or stalled puberty, the kisspeptin-stimulation test accurately distinguished the 8 children who later progressed through puberty from the 8 children who did not.

Γυναικεία Αναπαραγωγή

ΠΡΟΕΔΡΟΣ: Ευάγγελος Μακράκης
ΟΜΙΛΗΤΗΣ: Μαρία Ανδρίκουλα

ORIGINAL ARTICLE: INFERTILITY

Female infertility is associated with an altered expression of the neurokinin B/neurokinin B receptor and kisspeptin/kisspeptin receptor systems in ovarian granulosa and cumulus cells

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Objective: To analyze and compare the expression profile of *TAC3*, *TACR3*, *KISS1*, and *KISS1R* in mural granulosa and cumulus cells from healthy oocyte donors and patients with different infertility etiologies, including advanced maternal age, endometriosis, and low ovarian response.
Design: Genetic association study.
Setting: Private fertility clinic and public research laboratory.
Patient(s): Healthy oocyte donors and infertile women undergoing in vitro fertilization (IVF) treatment.
Intervention(s): IVF.
Main Outcome Measure(s): Gene expression levels of *KISS1*, *KISS1R*, *TAC3*, and *TACR3* in human mural granulosa and cumulus cells.
Result(s): Infertile women showed statistically significantly altered expression levels of *KISS1* (-2.57 ± 2.30 vs. -1.37 ± 2.11), *TAC3* (-1.21 ± 1.40 vs. -1.49 ± 1.98), and *TACR3* (-0.77 ± 1.36 vs. -0.03 ± 0.56) when compared with healthy oocyte donors. Advanced maternal age patients, endometriosis patients, and low responders showed specific and altered expression profiles in comparison with oocyte donors.
Conclusion(s): Abnormal expression levels of *KISS1*/*KISS1R* and *TAC3*/*TACR3* systems in granulosa cells might be involved in the decreased fertility associated to advanced maternal age, endometriosis, and low ovarian response. (Fertil Steril® 2020;114:869-78. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Granulosa cells, human infertility, kisspeptin, neurokinin B

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V.B. and F.M.P. should be considered similar in author order.
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Infertility is a growing health problem that affects millions of people around the world. As a consequence, the use of assisted reproductive technology (ART) is continuously increasing and accounts for approximately 1% to 3% of annual births in developed countries (1). Causes of infertility may vary greatly depending on socioeconomic and geographical factors, affecting one or both members of a couple. According to global statistics, 50% of infertility cases are due to female factors, 30% to male factors, and 20% to combined factors. Yet many cases are included within the category of "unexplained infertility" to reflect that the cause remains unknown after a complete diagnosis (2, 3). Three major disorder categories contribute to 75% to 80% of those infertility cases that can be explained: disorders of the female tract, ovulation disorders, and poor quality of spermatozoa. The increasing delay in parenthood that characterizes Western societies also impacts greatly the chances of achieving pregnancy (3, 4). If we focus on female infertility, the main indications that lead our patients to seek in vitro fertilization (IVF) treatment are advanced maternal age, low ovarian response (LOR), polycystic ovarian syndrome (PCOS), and endometriosis.

The rising prevalence and global character of infertility make absolutely necessary the improvement of assisted reproductive treatments and the finding of biomarkers that could serve as diagnostic tools to quickly and accurately assess the current fertility status of a patient. In recent years, it has been demonstrated that neurokinin B (NKB) and its cognate receptor, NK3R, and kisspeptin (KISS1) and its receptor, KISS1R, play a key role in the regulation of reproduction, and their discovery has allowed a breakthrough in our knowledge of reproductive function (5–12). In humans, kisspeptin and KISS1R are encoded by the *KISS1* and the *KISS1R* genes, respectively (6, 10, 12). NKB and NK3R belong to the family of tachykinins and are encoded by the *TAC3* and *TACR3* genes, respectively (13–15).

The NKB/NK3R and KISS1/KISS1R systems act primarily at the hypothalamic level of the gonadotropic axis where they modulate gonadotropin-releasing hormone (GnRH) secretion and gonadotropin release (7, 12, 14, 16, 17). In addition, different reports have shown that NKB, NK3R, KISS1, and KISS1R mRNAs or proteins are expressed in peripheral reproductive tissues, particularly in the uterus, the ovary, and the placenta of different mammalian species, including humans (8, 9, 18–26). However, further studies are necessary to increase our knowledge about their role in peripheral tissues and their local effects in the regulation of fertility (5, 7, 27).

Results from other laboratories and ours have shown that NKB, KISS1, and their corresponding receptors are present in human ovarian mural granulosa cells (MGCs) and cumulus cells (CCs) (19, 24–26, 28), and their expression is altered in women with PCOS (23). Nevertheless, little is known about the expression of these systems in infertile women with other etiologies. In this work, we have analyzed the expression of *KISS1*, *KISS1R*, *TAC3*, and *TACR3* in human MGCs and CCs from healthy oocyte donors (as controls) and patients with different infertility diagnoses, including endometriosis, LOR, age-related infertility, PCOS, and unexplained infertility, to investigate the expression pattern of these systems in association with the most common causes of women infertility.

MATERIALS AND METHODS

Study population

Approval for this Genetic Association Study was obtained from the institutional ethics committees of CSIC and Hospital Virgen Macarena (Seville, Spain), and all patients gave informed written consent. The study was registered on ClinicalTrials.gov with the code NCT02877992. Human MGCs and CCs were collected from the preovulatory follicles of Caucasian women, aged 19–45 years, who were undergoing oocyte retrieval after controlled ovarian stimulation (COS) treatment at the clinic IVI-RMA Seville (IVI-RMA Global) for Reproductive Care.

In a first set of experiments, CCs were collected from 162 women divided into two groups: healthy oocyte donors and infertile patients of any etiology, including age-related infertility, endometriosis, PCOS, and unexplained infertility. The donors group included 52 women, and the infertile group included 110 women: 33 with PCOS, 40 with age-related infertility, 15 with unexplained infertility, and 22 with endometriosis. In a second series of experiments, human MGCs and CCs were collected from 118 women divided into four groups: 45 were healthy oocyte donors, 27 were women with age-related infertility ($\geq$38 years old), 25 had endometriosis, and 21 were low responders. The intention of this division was to detect specific expression profiles for each infertility indication.

A general clinical examination of all patients was performed during the first visit to the fertility practice. Blood samples were obtained during the early follicular phase of their menstrual cycle (day 3) and after administration of the ovulation inductor. Serum hormone levels were assayed enzymatically using an automated biochemistry analyzer (cobas e 411; Roche Diagnostics GmbH).

Eligibility criteria

The healthy oocyte donors group included women between the ages of 18 and 33 years who had functional ovaries and uterus, an antral follicle count (AFC) between 12 and 35, and a normal karyotype. They also underwent a thorough study to exclude mental disorders, hereditary diseases, and common genetic disorders including cystic fibrosis, fragile-X syndrome and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The advanced maternal age group included women of age $\geq$38 years old with infertility linked primarily to age factor. The endometriosis group included women with infertility associated primarily with endometriosis as diagnosed through transvaginal ultrasound analysis or laparoscopy according to European Society of Human Reproduction and Embryology (ESHRE) criteria (29). The LOR group included women diagnosed as low responders to COS according to Bologna criteria (30)—that is, presenting two episodes of low response after maximal ovarian stimulation (condition sufficient to define a patient as low responder) or at least two of the following

three features: advanced maternal age (≥40 years) or any other risk factor for LOR; a previous LOR (≤3 oocytes with conventional stimulation); and an abnormal ovarian reserve test (AFC <5–7 and antimüllerian hormone [AMH] <1.1 ng/mL). In the PCOS group, the disease was diagnosed according to 2003 Rotterdam Criteria (31), including any two of the following three clinical features: menstrual dysfunction (oligo/anovulation); clinical and/or biochemical hyperandrogenism; and polycystic ovaries on ultrasound. The unexplained infertility group included women with infertility of unknown etiology after a complete infertility evaluation.

The eligibility criteria for women of all groups were as follows: body mass index ≤28 kg/m^2, nonsmokers, lack of alcohol consumption, lack of diseases such as hydrosalpinx, congenital adrenal hyperplasia, thyroid disease, Cushing syndrome, androgen-secreting tumors, and lack of use of any drug (medication) that could interfere with ovarian folliculogenesis.

Ovarian Stimulation Protocol

Women were given a standard GnRH-antagonist protocol for COS. We used a combination of two gonadotropins: recombinant follicle-stimulating hormone (FSH) (Gonal F; Merck Serono) and human menopausal gonadotropin (hMG) (Menopur; Ferring Pharmaceuticals). Depending on the AMH level and BMI, the gonadotropin daily doses ranged from 150 IU of recombinant FSH + 37.5 IU of hMG to 225 IU of recombinant FSH + 75 IU of hMG. Gonadotropin administration started the second day of the menstrual cycle, after we had checked the ovarian basal status during either the luteal phase of the previous cycle or the first 2 days of menses, using ultrasound scanning. The GnRH-antagonist (Orgalutran; MSD) was introduced the fifth or sixth day of COS or when the leading follicle had reached a 14-mm diameter. The GnRH-antagonist was administered in a daily dose of 0.25 mg until the day of ovulation induction. Ovulation was induced when at least two follicles had reached a diameter of 17 mm, using 6,500 IU of human chorionic gonadotropin (hCG) (Ovitrelle; Merck Serono) or 0.2 mg of the GnRH-agonist triptorelin (Ipsen Pharmabiotech). The latter option was chosen when the risk of ovarian hyperstimulation syndrome had been determined. Gonadotropin doses were adjusted according to patient characteristics and follicular development, which was monitored through periodical ultrasound scans and blood estradiol (E_2) analysis.

Collection of Human MGCs and CCs

We collected MGCs from the follicular fluids obtained via ultrasound-guided transvaginal oocyte retrieval, which was performed under intravenous anesthesia 36 hours after ovulation induction. After removal of oocyte–cumulus complexes, the remaining follicular aspirates from each patient were pooled and MGCs collected by using the Dynabeads methodology, as described elsewhere (24).

Human CCs were also obtained from these same patients and were collected after procedures described elsewhere (24). After follicular aspiration, the CCs surrounding the oocyte were removed using cutting needles by subsequent treatment of cumulus–oocyte complexes with Sydney IVF Hyaluronidase (80 IU/mL, K-SIHY; Cook Medical) and by carefully removing the CCs of the corona radiata with very thin glass pipettes (Swemed denudation pipette, 0.134–0.145 mm; Vitrolife).

RNA Extraction and Real-Time Quantitative Polymerase Chain Reaction

Total RNA was extracted from fresh MGCs and CCs using the RNA/Protein purification kit (Norgen Biotek), and residual genomic DNA was removed with RNase-free DNase I and RNasin (Promega). Complementary DNAs (cDNAs) were synthesized using the Transcriptor First Strand cDNA Synthesis kit (Roche). Samples were then preamplified using the SsoAdvanced PreAmp supermix (Bio-Rad Laboratories) following the manufacturer's protocol.

Real-time quantitative polymerase chain reaction (RT-qPCR) was used to quantify the expression of *KISS1*, *KISS1R*, *TAC3*, and *TACR3* in CCs and MGCs using the $2^{-\Delta\Delta C}{}_T$ method, as reported elsewhere (24, 32). We performed RT-qPCR on a Bio-Rad iCycler iQ real-time detection apparatus using SsoAdvanced Universal SYBR Green Supermix (Bio-Rad Laboratories). The parameters of PCR amplification were 10 seconds at 94°C, 20 seconds at 60°C, and 30 seconds at 72°C, for 50 cycles. The sequences of the specific primer pairs designed to amplify each target gene are shown in Supplemental Table 1 (available online). Supplemental Table 1 also shows the primers used to amplify β-actin (*ACTB*), hypoxanthine phosphoribosyltransferase 1 (*HPRT1*), cyclophilin A (*PPIA*), and succinate dehydrogenase complex subunit A (*SDHA*), which were chosen as housekeeping genes on the basis of previous studies from other laboratories and ours (24, 33). The specificity of the PCR reactions was confirmed by melting curve analysis of the products and by size verification of the amplicon in a conventional agarose gel.

A human universal reference total RNA (BD Biosciences Clontech) was used as a positive control of amplification, and three negative controls were run for each assay: no template, no reverse transcriptase, and no RNA in the reverse transcriptase reaction. Each assay was performed in triplicate, and the fold change of each target gene expression was expressed relative to the geometric mean mRNA expression of the reference genes in each sample (24, 32).

Statistical Analysis

The results are expressed as mean ± standard deviation, and *n* represents the number of experiments in *n* different women. Data distribution and homogeneity of variances were analyzed with the Kolmogorov-Smirnov test and Levene test. For gene expression data, a logarithmic transformation was adapted to meet the normality assumptions and the statistical differences between these log-transformed values were assessed using Student's *t*-test. The relative quantification values are shown in figures without log transformation. General linear models were performed to control for

confounding variables, and all models were adjusted by BMI and E_2 serum levels after ovulation induction. $P<.05$ was considered statistically significant. All the statistical analyses were performed using IBM SPSS Statistics software, version 24.0.

RESULTS

Expression of *KISS1*/*KISS1R* and *TAC3*/*TACR3* in Women with Infertility of any Etiology

We analyzed the expression of the KISS1 and NKB systems in CCs from oocyte donors and infertile women of different etiologies, including the most common disorders with indication of IVF treatment. The anthropometric and biochemical characteristics of healthy donors and infertile patients are shown in Supplemental Table 2 (available online).

Controlled ovarian stimulation for IVF induces a multiple follicular growth that causes great variation in follicular steroids compared with the physiological levels of a natural cycle (see Supplemental Table 2). To avoid any impact of these variations, all women included in the present study, both donors and patients, were given the same treatment, and serum levels of E_2 and progesterone (P_4) were measured after administration of the ovulation inductor.

In our study, there was a statistically significant variation in E_2 serum levels in infertile patients ($P<.0001$, n = 110) with respect to healthy donors (n = 52) (Supplemental Table 2) and no variation in P_4 serum levels ($P>.05$) (Supplemental Table 2). There were statistically significant differences between fertile and infertile women in age and BMI (Supplemental Table 2). The serum hormone levels and the expression levels of all the genes examined were not influenced by the use of recombinant hCG or triptorelin for ovulation induction.

The expression of *KISS1* was down-regulated in CCs from infertile patients, in comparison with mRNA levels in control healthy women (Supplemental Table 2). The differences remained statistically significant when adjusted for BMI and serum levels of E_2 after ovulation induction ($\beta = -0.303$, $P=.001$). Conversely, no statistically significant differences were observed in relation to the *KISS1R* expression when comparing both groups (Supplemental Table 2).

The expression of *TAC3* was lower in CCs from infertile patients (Supplemental Table 2), and these differences remained statistically significant after adjusting for BMI and serum E_2 after ovulation induction ($\beta = -0.259$, $P=.008$). A multiple linear regression analysis shows that infertility was also associated with a lower expression of *TACR3* mRNA in CCs, which remained statistically significant after adjusting for BMI and E_2 serum levels after ovulation induction ($\beta = -0.335$, $P=.001$) (Supplemental Table 2).

Clinical Characteristics of Healthy Donors and Women with Age-Related Infertility, Endometriosis, and Low Ovarian Response

The biochemical and anthropometric parameters of the women included in the study are shown in Table 1. The serum concentrations of E_2, AMH, FSH, and luteinizing hormone (LH) fell within the reference range values in the early follicular phase of the menstrual cycle in healthy donors and in women with infertility due to age (≥38 years old), endometriosis, and LOR (Table 1). The serum concentrations of day-3 E_2, day-3 LH, and P_4 measured after administration of the ovulation inductor were similar in the control and infertile groups. There were statistically significant differences between the groups in relation to the other parameters analyzed (Table 1).

Expression of *KISS1*/*KISS1R* and *TAC3*/*TACR3* in Women with Age-Related Infertility

The expression of *KISS1*, *TAC3*, and *TACR3* was statistically significantly lower in CCs and MGCs of the older women (≥38 years) in comparison with mRNA levels in the control healthy women (Fig. 1A, C, and D). The expression levels of *KISS1R* were lower in older women but showed great

TABLE 1

Anthropometric and biochemical data of study participants.

Characteristic	Healthy donors (n = 45)	Age-related infertility (n = 27)	Endometriosis (n = 25)	Low responders (n = 21)
Age (y)	25.07 ± 3.45	40.37 ± 1.55[a]	35.32 ± 3.44[a,b]	38.67 ± 3.14[a,b,c]
BMI (kg/m^2)	22.35 ± 2.79	23.23 ± 1.97	23.78 ± 3.43	25.32 ± 6.18[a]
Day-3 serum value				
E_2 (pg/mL)	57.75 ± 36.98	51.55 ± 28.06	59.26 ± 65.69	62.03 ± 53.87
AMH (ng/mL)	2.02 ± 1.02	2.27 ± 1,10	1.96 ± 1.06	0.61 ± 0.59[a,b,c]
FSH (mIU/mL)	6.42 ± 1.27	7.03 ± 1.56	6.86 ± 1.90	10.10 ± 4.27 [a,b,c]
LH (mIU/mL)	5.67 ± 1,62	5.72 ± 2.14	6.02 ± 2.44	5.95 ± 2.41
LH/FSH	0.90 ± 0.29	0.84 ± 0,33	0.97 ± 0.54	0.54 ± 0,16[a,b,c]
After ovulation induction				
E_2 (pg/mL)	3,158 ± 1,516	2,062 ± 888[a]	1,640 ± 1,050[a]	949 ± 527[a,b,c]
P (pg/mL)	0.90 ± 0.58	0.82 ± 0.58	0.64 ± 0.40	0.58 ± 0.63

Note: Data presented as mean ± standard deviation, unless specified otherwise. Statistically significant differences between groups were assessed using the Student's *t*-test. AMH = antimüllerian hormone; BMI = body mass index; E_2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; P = progesterone.

[a] $P<.05$ versus donors.

[b] $P<.05$ versus older, infertile women.

[c] $P<.05$ versus women with endometriosis.

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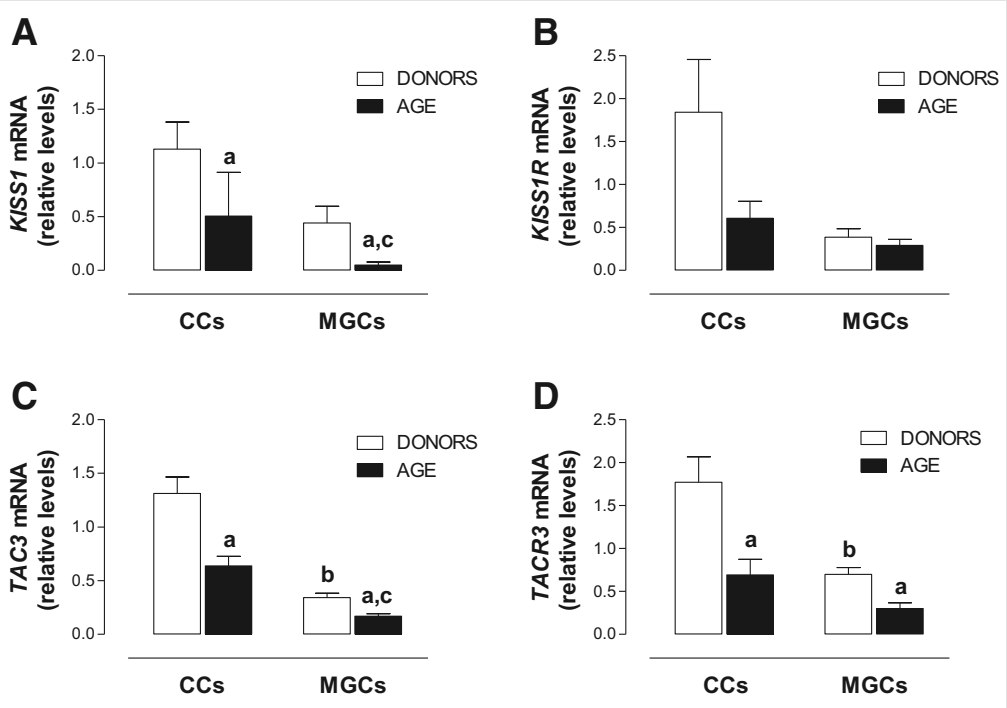
FIGURE 1



Expression levels of (**A**) *KISS1,* (**B**) *KISS1R,* (**C**) *TAC3*, and (**D**) *TACR3* in human cumulus cells and mural granulosa cells of healthy oocyte donors and women of advanced maternal age (≥38 years). Results are presented as mean ± standard deviation. Statistically significant differences at $P<.05$ are represented as (a) between donors and patients, (b) between cumulus and granulosa cells in donors, and (c) between cumulus and granulosa cells in older patients.

Blasco. NKB/NK3R *and* KISS1/KISS1R *in human ovary. Fertil Steril 2020.*

variations between samples; as a consequence, the differences between older infertile patients and control women did not reach statistical significance (Fig. 1B).

In agreement with our previous data (23, 24), the expression of *TAC3* and *TACR3* were higher in CCs than in MGCs from healthy donors (Fig. 1C and D). In older infertile patients there was also a statistically significant increase in the expression of *TAC3* mRNA in CCs, in comparison with MGCs, but this increase was not observed for *TACR3* (Fig 1D).

Expression of *KISS1*/*KISS1R* and *TAC3*/*TACR3* in Women with Endometriosis

This study was performed only in CCs to avoid the analysis of damaged MGCs from women with endometriosis. The expression levels of *KISS1*, *TAC3*, and *TACR3* were similar in infertile women with endometriosis and healthy women (Fig. 2A, C, and D). The expression of *KISS1R* was statistically significantly higher in CCs from women with endometriosis (Fig. 2B).

Within this group, there were nine patients ≥38 years old. In four of these women, the expression levels of *TAC3*/*TACR3* and *KISS1*/*KISS1R* were comparable with those observed in the group of older infertile women: they showed a lower expression of these genes in comparison with healthy control women. A decreased expression of *TAC3*, *TACR3*, and *KISS1* was also observed in five patients with endometriosis who were ≤38 years old.

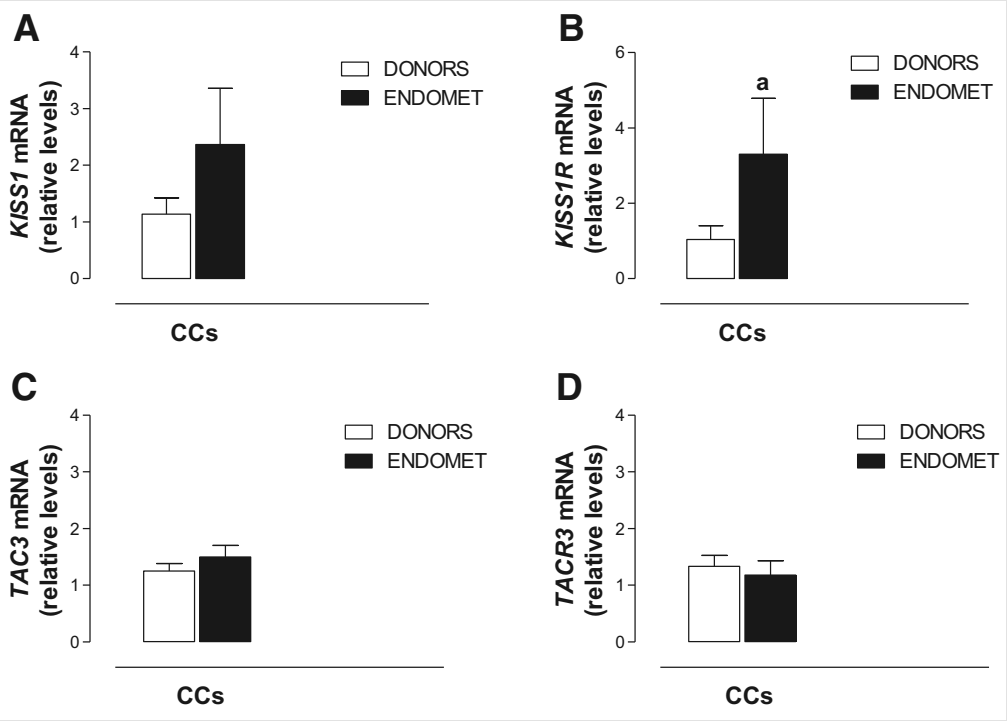
Expression of *KISS1*/*KISS1R* and *TAC3*/*TACR3* in Low-Responder Women

Due to the small quantity of CCs obtained from low-responder patients, this study was performed only on MGCs to use the same PCR experimental conditions with all samples analyzed. As occurs in MGCs from age-related infertile women (Fig. 1) and PCOS patients (23), the *TAC3* and *KISS1R* mRNA levels were not statistically significantly different between the controls and low responders (Fig. 3B and C) whereas the expression levels of *KISS1* and *TACR3* were statistically significantly lower in MGCs from infertile women with low response in comparison with healthy women (Fig 3A and D).

DISCUSSION

Neurokinin B and its receptor NK3R together with KISS1 and its receptor KISS1R exert an essential role in the brain as regulators of the hypothalamic-pituitary-gonadal axis. This discovery has contributed to an unprecedented advance in our knowledge about reproductive function regulation (11, 12, 34, 35). Moreover, experimental data gathered in recent years prove that these systems are also expressed in

FIGURE 2



Expression levels of (**A**) *KISS1*, (**B**) *KISS1R*, (**C**) *TAC3*, and (**D**) *TACR3* in human cumulus cells of healthy oocyte donors and patients with endometriosis. Results are presented as mean ± standard deviation. Statistically significant differences between donors and patients at $P<.05$ are represented as (a).

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the female genital tract (endometrium, oviduct, and ovary), suggesting that they act as important local regulators of reproductive function (8, 9, 18–20, 22, 28). Recent data also suggest that KISS1 signaling is necessary for a correct embryo implantation and placentation (21).

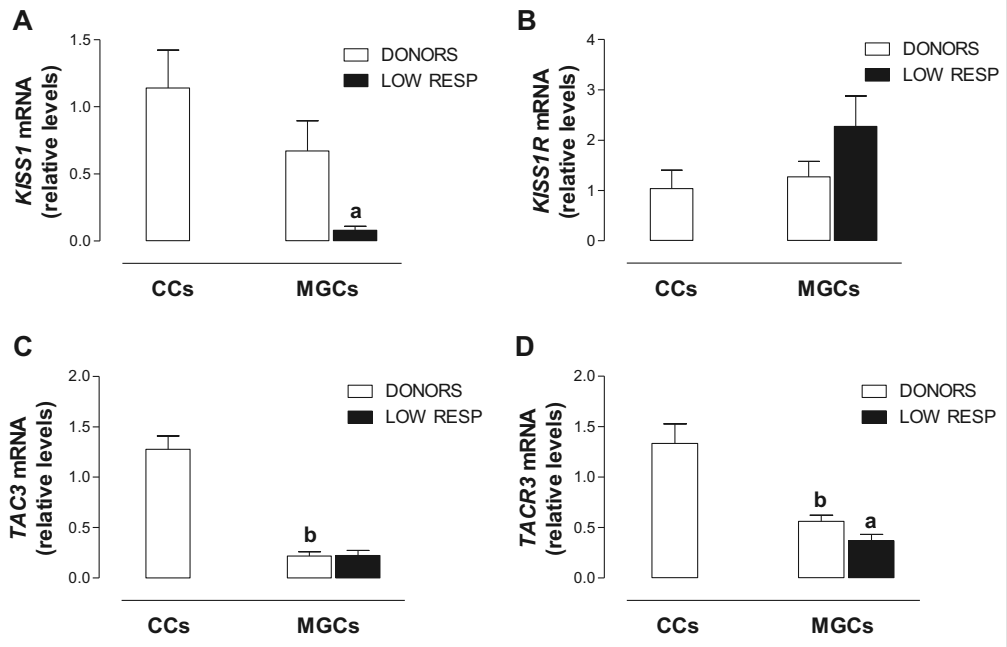
The main finding of this study is that expression of the NKB/NK3R and KISS1/KISS1R systems is altered in granulosa cells from infertile women with different infertility etiologies as compared with healthy oocyte donors. These results confirm that these systems are indeed important for correct ovarian function and fertility. We have observed that NKB (encoded by *TAC3*), NK3R (encoded by *TACR3*), and KISS1 (encoded by *KISS1*) expression is statistically significantly down-regulated in the cumulus cells of infertile patients considered as a whole group, including with the most frequent disorders in women attending an IVF treatment: advanced maternal age, PCOS, endometriosis, LOR, and unexplained infertility. These results suggest that altered expression of these genes might be responsible, at least in part, for the infertility experienced by the patients.

In previous studies, we found that NKB/NK3R and KISS1/KISS1R systems are present in human MGCs and CCs (19, 23–25). Moreover, we compared the expression of these systems between oocyte donors and infertile women with PCOS, and we found statistically significant differences (23). *TAC3*, *TACR3*, and *KISS1* mRNAs were down-regulated in MGCs and CCs from PCOS patients, which led us to wonder whether these results would repeat in patients with other infertility etiologies. In fact, in the present study we observed similar results in the infertile patients group, the one including all etiologies. This makes sense because oocyte quality is affected in all these etiologies.

Different ovarian stimulation programs did not modify or were unable to induce a recovery of the expression of the TAC3/TACR3 and KISS1/KISS1R systems to the levels observed in healthy donors. All in all, an expression analysis of the NKB and KISS1 systems in MGCs or CCs would thus be useful to assess the fertility status of a patient. In the case of PCOS, it is very probable that other genes are affected and their expression levels vary depending on how PCOS is manifested in the patient because it is a very heterogeneous disease. New knowledge on the genetic alterations behind this syndrome could allow us to stablish a better, more specific genetic profile for PCOS.

Each cause of infertility displayed different anthropometric and hormone data, allowing a specific profile for each type of disease. Controlled ovarian stimulation for IVF induces multiple follicular growth, which causes a dramatic variation of ovarian steroids E_2 and P_4 in comparison with the physiologic levels of a natural menstrual cycle. According to our results, the observed dysregulation of the NKB/NK3R

FIGURE 3



Expression levels of (**A**) *KISS1*, (**B**) *KISS1R*, (**C**) *TAC3*, and (**D**) *TACR3* in human mural granulosa cells of healthy oocyte donors and patients with low ovarian response. Results are presented as mean ± standard deviation. Statistically significant differences between donors and patients at $P<.05$ are represented as (a) between donors and patients and (b) between cumulus and granulosa cells in donors.

Blasco. NKB/NK3R *and* KISS1/KISS1R *in human ovary. Fertil Steril 2020.*

and KISS1/KISS1R systems cannot be attributed to differences in the hormone state. Instead, it seems to be directly related to the infertility status (Table 1 and Supplemental Table 2).

Two fertility trends of the 21st century have become evident in the Western countries: women are having fewer children, and they are delaying births to a later age. Furthermore, women who choose to delay motherhood may encounter delays and/or disappointment due to decreased fecundity (36). Age-related infertility comprises several causes leading to infertility. On the one hand, there is a reduction in the number of oocytes (ovarian reserve) as age increases. On the other hand, oocyte quality is also impaired with advancing age due to a widely described correlation between female age and oocyte chromosomal abnormalities, leading to a higher rate of miscarriage and genetic disorders in the fetus. This higher frequency of aneuploidies is due to alterations in the regulatory machinery responsible for assembly of the oocyte meiotic spindle.

Furthermore, aging is also associated with the appearance of other infertility-related disorders such as tubal disease, leiomyomas, and endometriosis (37). In this study, the group of women of advanced maternal age showed a statistically significant down-regulation in *KISS1*, *TAC3*, and *TACR3* levels, suggesting that altered expression of these genes might be involved in the impaired oocyte quality and/or the decreased ovarian reserve associated with advancing age. In fact, previous studies performed in different animal models have already found an association between kisspeptin and follicle development and oocyte maturation (18, 20, 26, 38).

Endometriosis is a chronic inflammatory disease that cause pain and infertility in women, with a prevalence of 0.8% to 6.0% in population-based studies (39–41) and 20% to 50% in subfertile women (42, 43). Endometriosis is characterized by the growing of endometrial-like tissue in ectopic locations such as the oviduct, ovary, or peritoneal cavity. The origin and pathogenesis of this disease remains unclear, and different theories have been postulated to explain this phenomenon. Some theories propose that endometrial implants come from uterine endometrium, and other theories propose that these implants arise from other tissues, involving a process of transformation (44). The abnormally implanted tissue responds cyclically to hormones, developing inflammatory responses. Consequently, patients may develop pelvic adhesions and experience pain and infertility (45). Endometriosis has been related to impaired oocyte quality, reduced fertility, and lower implantation rates after IVF, but the link between infertility and endometriosis is still poorly understood (46). Genetic and epigenetic changes have been associated with endometriosis, which is considered a hereditary disease, and many cases have been attributed to hereditary factors (47).

A recent study has detected that *KISS1* expression is statistically significantly higher in endometriosis lesions in comparison with eutopic glandular endometrium, suggesting a possible role of *KISS1* in endometriosis pathogenesis (48).

However, a different study did not detect *KISS1* expression in any sample from endometriosis patients (49), which could be due to methodological or design differences between the studies. In our case, we analyzed granulosa cells from endometriosis patients and found that they constituted a very heterogeneous group in relation to the expression of the *TAC3/TACR3* and *KISS1/KISS1R* systems; when considered as a whole, only the expression of *KISS1R* was altered. *KISS1R* mRNA levels were statistically significantly higher in CCs from endometriosis patients in comparison with healthy oocyte donors. Thus, the increased expression of *KISS1R* could be one of the multiple factors involved in the origin of endometriosis and related infertility.

These data suggest that endometriosis is a very different entity in comparison with advanced maternal age and LOR as a cause of infertility. As mentioned earlier, there is still much to know about the origin and causes of this disease. Further studies are needed to clarify the reasons behind the increase in *KISS1R* expression and investigate the potential relationship between *KISS1*/*KISS1R* and endometriosis. If confirmed, *KISS1* and/or its receptor could serve as biomarkers for endometriosis diagnosis and detection.

Low ovarian response indicates a reduction in the number of oocytes retrieved after an ovarian puncture due to a diminished follicular response to COS (30, 50). The existence of LOR was unveiled thanks to the increasing acceptance and spreading of ART. Approximately 10% of women undergoing IVF treatment will show LOR to COS. However, this incidence can be higher in the infertile population, as many affected women never undergo an ART treatment (51).

Regarding the results of our study, lower expression levels of *KISS1* and *TACR3* were observed in the MGCs of women with LOR in comparison with healthy oocyte donors. This altered expression profile suggests the possible involvement of these factors in the correct follicle recruitment and development in response to gonadotropin stimulation. These results are concordant with previous studies that have identified the involvement of *KISS1*/*KISS1R* system in the regulation of follicular development, oocyte maturation, ovulation, and ovarian steroidogenesis (28). Our results suggest that, besides kisspeptin expression levels, correct expression levels of NKB might also be necessary for normal folliculogenesis.

In relation to advanced-age patients and those with LOR, it is worth pointing to a previous study performed in mice that revealed that a defect in the *KISS1*/*KISS1R* system induced a state similar to premature ovarian failure. Mutant mice showed a premature decline in ovulatory rate, progressive loss of oocytes and antral follicles, and reduced fertility. This is concordant with results of our study because both older patients and low responders showed decreased levels of *KISS1* in comparison with healthy oocyte donors (20).

CONCLUSION

Our study has revealed a differential and altered regulation of the *NKB*/*NK3R* and *KISS1*/*KISS1R* systems in cumulus and granulosa cells from women with infertility of different etiologies, particularly in patients with advanced age, endometriosis, and LOR. We provide evidence that an abnormal expression of these systems at the ovarian level might be involved in the decreased fertility of these patients.

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Role of kisspeptins in the control of the hypothalamic-pituitary-ovarian axis: old dogmas and new challenges

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In humans and other mammals, a hallmark of female reproductive function is the capacity to episodically release fertilizable oocytes under the precise control of a cascade of hormonal regulators that interplay in a cyclic manner within the hypothalamic-pituitary-ovarian (HPO) axis. Although the basic elements of this neurohormonal system were disclosed several decades before, a major breakthrough in our understanding of how the HPO axis is controlled during the lifespan came in the first decade of the 21st century, when the reproductive dimension of kisspeptins was disclosed by seminal studies documenting that genetic inactivation of the kisspeptin pathway is linked to central hypogonadism and infertility. Kisspeptins are a family of peptides, encoded by the Kiss1 gene, that operate via the surface receptor, Gpr54 (also called Kiss1r), to regulate virtually all aspects of reproduction in both sexes. The primary site of action of kisspeptins is the hypothalamus, where Kiss1 neurons engage in the precise control of the pulsatile release of GnRH to modulate gonadotropin secretion and, thereby, ovarian function. Nonetheless, additional sites of action of kisspeptins within the HPO axis, including the pituitary and the ovary, have been proposed; yet, the physiologic relevance of such extrahypothalamic actions of kisspeptins is still a matter of debate. In this review, we summarize the current consensus knowledge and open questions on the sites of action, physiologic roles, and eventual therapeutic implications of kisspeptins in the control of the female reproductive axis. (Fertil Steril® 2020;114:465–74. ©2020 by American Society for Reproductive Medicine.)

Key Words: Kisspeptins, Gpr54, GnRH, gonadotropins, ovulation

FIRST THINGS FIRST: THE HYPOTHALAMIC-PITUITARY-OVARIAN AXIS

Ovarian maturation and its exquisite cyclic function during the reproductive lifespan fully rely on the coordinate action of the neurohormonal elements of the hypothalamic-pituitary-ovarian (HPO) axis (1). As is the case for other neuroendocrine axes, the HPO axis is a hierarchic system, in which a scarce neuronal population located in the basal forebrain and producing the decapeptide GnRH, operates as a major conduit for the brain to control the reproductive system. Thus, GnRH is released in a pulsatile manner to the hypothalamic-hypophyseal portal circulation to reach the anterior pituitary, where GnRH pulses act on gonadotropes, to elicit the secretion of both gonadotropins, LH and FSH. These, in turn, are released to the systemic circulation to reach the ovary, where, acting in concert on different cellular components, they promote ovarian maturation and production and release of female gametes, as well as the secretion of sex steroids and other gonadal hormones of peptidergic nature (2).

An essential aspect of the functionality of the HPO system is the characteristic secretory modes of their upstream elements, namely, GnRH and gonadotropins (1). Indeed, acquisition of a mature pattern of pulsatile secretion of GnRH, which occurs at puberty, is mandatory for dictating appropriate secretory profiles of LH and FSH needed to ensure ovarian maturation and function (3). Perturbation of such pulsatile patterns, e.g., by continuous exposure to GnRH analogues, results in receptor desensitization and suppression of gonadotropins and, thereby, ovarian function, a feature

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that has been exploited therapeutically in hormone-dependent disorders (4). Moreover, deregulation of GnRH pulsatility is seemingly implicated in various reproductive pathologies, such as polycystic ovary syndrome (PCOS) and hypothalamic amenorrhea (5).

Realization of these fundamental pathophysiologic roles has prompted active investigation of the mechanisms whereby GnRH neurons are capable to release, in a synchronized and timely manner, pulses of GnRH; a phenomenon that is driven by a complex circuit of neuronal and nonneuronal afferents to GnRH neurons (6–9), which form the GnRH pulse generator (10). This functional hub is able to integrate a wide range of regulators of ovarian function, from environmental cues (e.g., light cycle and nutritional inputs) to endogenous signals (e.g., metabolic hormones). In this network, Kiss1 neurons, producing kisspeptins, have recently been pointed out as a major component, with key roles in dictating GnRH pulsatility (11) and, thereby, cyclic ovarian function, as summarized in the following sections.

In addition, the elements of the so-called Kiss1 system have been detected at other levels of the HPO axis, where they may operate as local modulators of gonadotropin secretion at the pituitary and/or ovarian function In addition, uterine and gestational actions of kisspeptins have been described. Yet, the physiologic relevance of these extrahypothalamic actions of kisspeptins remains debatable and largely undefined. In this minireview, we summarize the current consensus knowledge and open questions about the roles of kisspeptins in control of the female reproductive axis. For a summary of the major biologic effects and sites of action of kisspeptins in the HPO axis, see also Table 1.

THE BOSS ALWAYS WORKS FOR SOMEONE ELSE: EMERGENCE OF KISSPEPTINS IN REPRODUCTIVE PHYSIOLOGY

Despite the indisputable role of GnRH as the major output pathway whereby the brain controls the reproductive axis (12), compelling evidence gathered in recent decades has documented that GnRH neurons themselves are devoid of the main receptors for key regulators of the HPO axis, such as estrogens and leptin, just to mention two paradigmatic examples. This feature illustrates that a substantial component of the central regulation of the reproductive axis takes place upstream from GnRH neurons, so that integration of different regulatory inputs occurs at the level of neuronal and nonneuronal afferents of this neuronal population, which dictate the activation (or, eventually, inactivation) of the ultimate effector, GnRH.

Kisspeptins, a family of peptides encoded by the Kiss1 gene, initially regarded to be metastasis suppressors, were first recognized as gatekeepers of the reproductive axis in late 2003, when inactivating mutations of the gene encoding their receptor, Gpr54, were reported in patients affected of isolated central hypogonadism (13, 14). Short after the disclosure of the reproductive dimension of kisspeptins, the mechanism(s) and site of action whereby the Kiss1 system activates the reproductive axis began to be actively investigated. Compelling evidence conclusively demonstrated that the ability of kisspeptins to potently stimulate gonadotropin secretion, which has been documented in a wide variety of species, including humans, involves a primary action at the hypothalamic level, where kisspeptins are produced by discrete neuronal populations to operate as major synaptic excitatory input on GnRH neurons (1, 6).

The contention that kisspeptins elicit gonadotropin secretion via a GnRH pathway was initially suggested by the fact that blockade of GnRH actions, by the use of a pharmacologic antagonist, completely suppressed the gonadotropin-releasing actions of kisspeptins in vivo. In addition, in situ hybridization in rat brain sections showed that a majority (>75%) of GnRH neurons coexpress the mRNA encoding the kisspeptin receptor (Gpr54) and that kisspeptin is able to activate GnRH neurons, as measured by c-Fos induction and electrical firing of GnRH neurons (6). In addition, the capacity of kisspeptins to elicit GnRH secretion was documented both ex vivo, with the use of rat hypothalamic explants, and in vivo, where central infusion of kisspeptin was shown to induce a marked rise of GnRH levels in the cerebrospinal fluid of sheep. As a whole, these data convincingly pointed out that kisspeptins operate primarily on hypothalamic GnRH neurons to induce GnRH secretion, which in turn drives LH and FSH release from the pituitary.

The advent of more incisive techniques for neuronal monitoring and manipulation has allowed confirming and refining those initial observations. Thus, by using an elegant combination of fiber photometry and optogenetic approaches, Clarkson et al. recently documented that populations of Kiss1 neurons located in the hypothalamic arcuate nucleus (ARC) play a fundamental role in the generation of GnRH pulses (11) as an essential driver for the pulsatile secretion of gonadotropins. ARC Kiss1 neurons have been shown to display discrete calcium bursts, which perfectly coincide with LH secretory pulses. In addition, whereas optogenetic activation of ARC Kiss1 neurons evoked LH pulses, their inhibition, with the use of hyperpolarizing optogenetic tools, suppressed LH pulsatility (11). These functional studies are concordant with data from genetically modified mouse models, showing that kisspeptin actions solely at the level of GnRH neurons are sufficient to attain puberty and grossly maintain fertility (15). Altogether, this evidence unambiguously demonstrates that the effects of kisspeptins occur primarily at the level of GnRH neurons to centrally activate the HPO axis.

Despite the consensus on the indispensable role of these direct actions of kisspeptins, compelling evidence has also suggested that part of their central modulatory effects may derive from the ability of kisspeptins to indirectly modulate GnRH neurosecretion, via intermediary afferents. Thus, blockade of fast synaptic transmission, to globally eliminate ionotropic glutamatergic and GABAergic inputs, caused a decrease of GnRH neuronal responses to kisspeptin (16). Moreover, besides their direct postsynaptic effects on GnRH neurosecretion, kisspeptins operating presynaptically have been shown to increase glutamatergic and GABAergic transmission to GnRH neurons (17). These findings point out that at least part of the kisspeptin effects on GnRH neurons might be indirectly mediated via activation of glutamate and/or

GABA afferents to GnRH neurons. In favor of this possibility, more recent work with a mouse model engineered to preserve kisspeptin signaling selectively in GnRH neurons, but not elsewhere, revealed subtle, albeit detectable indirect actions of kisspeptins in the central modulation of the GnRH-gonadotropin axis (18). Admittedly, however, these indirect actions are modest and possibly less relevant than the direct effects of kisspeptin on GnRH neurons.

ESSENTIAL ROLES OF KISSPEPTINS IN SEX STEROID FEEDBACK AND GONADOTROPIN SECRETORY PATTERNS

Proper function of the adult HPO axis critically relies on appropriate secretory patterns of GnRH and, thereby, gonadotropins. In contrast to males, where only tonic, pulsatile secretion occurs, in females two different modes of GnRH/gonadotropin secretion take place: the pulsatile and the surge modes (1, 19). The latter is responsible for triggering the ovulation and will be reviewed in the next section. The pulsatile mode is more predominant across the ovarian cycle and is shaped, to a large extent, by the negative feedback actions of ovarian steroids at the hypothalamic-pituitary unit. This pulsatile secretory pattern, which is responsible for driving follicular maturation and hormone production by the ovaries (12), is dictated to a large extent by the oscillatory activity of Kiss1 neurons located in the ARC in different mammalian species, or its equivalent infundibular area in humans (1, 11).

The tonic mode of secretion of GnRH is defined by a discrete burst of hormone release to the portal circulation, interspaced by periods of (very) low GnRH concentrations. Because the secretion of both LH and FSH is elicited by GnRH, but their secretory patterns diverge partially, it has been proposed that the frequency of GnRH pulses is critical for encoding preferential secretion of LH (high-frequency pattern) or FSH (low-frequency pattern) (20). Other parameters, such as the magnitude of hormone peaks and the threshold levels, contribute also to define the secretory profiles of gonadotropins, so that changes especially in circulating LH are thought to reflect similar changes in the portal patterns of secretion of GnRH.

As mentioned above, a major mechanism whereby pulsatile secretion of GnRH is homeostatically controlled is via the negative feedback actions of ovarian steroids, which contribute to keeping LH and FSH levels at check along the ovarian cycle (21). An apparent conundrum regarding negative feedback control was that GnRH neurons are devoid of estrogen receptor (ER) α, which is responsible for mediating the major inhibitory effects of ovarian E_2 on the gonadotropic axis (12). This paradox was solved by the demonstration that Kiss1 neurons in the ARC do express ERα and are tonically repressed by estrogen, so that conditions of high E_2 levels are associated with inhibition of Kiss1 expression in the ARC (12). This provided a plausible pathway for transmitting the negative feedback actions of estrogen on GnRH.

This ARC population of Kiss1 neurons has been the subject of active investigation in the past decade. After the demonstration of its key role as target and transmitter for the negative feedback actions of estrogens, much excitement was caused by the finding that ARC Kiss1 neurons coexpress other transmitters with important functions in the central control of the HPO axis. Thus, in 2009, compelling evidence was presented for the colocalization of the tachykinin neurokinin-B (NKB) and the endogenous opioid dynorphin (Dyn) in a substantial fraction of ARC Kiss1 neurons in rodents and sheep (22, 23), a population that was named KNDy because of the co-expression of Kiss1, NKB, and Dyn (24). Contemporary to this finding, inactivating mutations of the genes encoding NKB (TAC3) or its receptor (TACR3) in humans were found to cause a state of central hypogonadism similar to that associated to inactivating mutations of the kisspeptin pathway (25). This, together with the realization that, to a variable extent, KNDy neurons are also found in the human hypothalamus, reinforced the interest for the role of this neuronal population in the control of the HPO axis also in humans. Functional analyses conducted in preclinical models led to the proposal of an oscillatory network within KNDy neurons, in which NKB and Dyn would operate as autoregulatory signals, modulating the output of kisspeptin onto GnRH neurons in a reciprocal manner. Thus, while NKB stimulates kisspeptin release via KNDy neurons, therefore inducing GnRH secretion, Dyn seemingly operates as an inhibitory input, suppressing kisspeptin secretion, and thereby GnRH pulsatility (26). Therefore, NKB and Dyn would act, in concert with other signals converging on Kiss1 neurons, in a yin-yang fashion, to shape kisspeptin pulses, which in turn dictate the generation of GnRH pulses as described above.

KEY FUNCTION OF KISSPEPTINS IN THE CENTRAL CONTROL OF OVULATION: THE PREOVULATORY SURGE

Besides the tonic pattern of secretion described above, a massive discharge of gonadotropins, called the preovulatory surge, occurs periodically at mid-cycle to induce ovulation in adult females (1). This key event in female reproduction is driven by the surge mode of GnRH secretion, in which escalating levels of GnRH are detected over a period of hours in the portal circulation. This preovulatory surge of GnRH occurs in a timely fashion, which in rodents corresponds to the afternoon of proestrus (i.e., the phase preceding ovulation at estrus) and in women takes place in the later follicular phase of the menstrual cycle. Generation of this preovulatory surge critically relies on a switch from a predominant negative feedback to a positive feedback of estrogen, in which the increasing levels of circulating E_2 coming from the dominant follicles convey a stimulatory signal to GnRH neurons to enhance, rather than suppress, GnRH secretion (21). The cellular and molecular basis of such a dynamic and timely switch, which occurs only in the adult female, had remained to a large extent an enigma until the discovery of the key roles of specific populations of Kiss1 neurons in this phenomenon.

The first evidence for a putative role of Kiss1 neurons in estrogen positive feedback came from rodent studies, which documented that, whereas Kiss1 mRNA levels in the ARC are suppressed by estrogen, Kiss1 gene expression in a more rostral area of the hypothalamus, corresponding to the

anteroventral periventricular nucleus (AVPV), was reduced by ovariectomy and increased by estrogen replacement (27). Notably, the AVPV had long been known to act as a hypothalamic area involved in the positive feedback of estrogen. Thus, these initial observations strongly suggested the participation of AVPV Kiss1 neurons, which express ERα as well, in the positive feedback of E_2 on gonadotropin secretion during the preovulatory period (21). In good agreement, it was later demonstrated that, in the female rat, AVPV Kiss1 mRNA levels increase during the window of the preovulatory surge, whereas immunoneutralization of central kisspeptin or selective blockade of kisspeptin actions with the use of a specific antagonist blocked the preovulatory LH surge in cyclic rats (28, 29).

Although the connection of AVPV Kiss1 neurons with the preovulatory surge and estrogen positive feedback has been solidly documented in rodents, the role of equivalent populations, distinct from ARC/infundibular Kiss1 neurons, in humans and other mammals is still under debate. Admittedly, a region equivalent to AVPV is not found in primates or sheep, but Kiss1 neurons in the preoptic area have been described in these species. In addition, functionally different subpopulations of Kiss1 neurons within the ARC have been described in sheep, which might differentially contribute to mediate negative and positive feedback effects of estrogen. For example, Kiss1 neurons in the caudal portion of the ARC may collaborate with preoptic area Kiss1 neurons to mediate positive feedback in sheep (30). In humans, there is a lack of functional evidence for a specific subpopulation of Kiss1 neurons mediating the positive estrogen feedback to induce the preovulatory surge. Nonetheless, it is plausible that distinct Kiss1 neuronal pathways may participate in the generation of the surge mode of GnRH secretion in women (1). In fact, pharmacologic studies have revealed commonalities in other aspects of kisspeptin effects in the control of the HPO axis between women and rodents. For example, in both rat and human females, the efficiency of kisspeptin to elicit LH secretion changes across the ovarian cycle, it being maximal at the preovulatory stage (31, 32). It is worth noting that, in addition to changes at the hypothalamic level, an increase in GnRH signaling in the pituitary also occurs during the cycle (33, 34), which seems to play a major role in the generation of the preovulatory surge in women.

PITUITARY ACTIONS OF KISSPEPTINS: WHAT IS THEIR PHYSIOLOGIC RELEVANCE?

While the predominance of the hypothalamic actions of kisspeptins in the control of the HPO axis is undisputed, fragmentary evidence has suggested the possibility of additional sites of expression and action at the pituitary level, where kisspeptins have been proposed to directly regulate gonadotrope function. Thus, initial in vitro analyses documented the capacity of kisspeptin-10 to stimulate pituitary LH secretion (35, 36). Yet these responses were modest in magnitude and clearly lower than those evoked by GnRH, despite the need of higher concentrations kisspeptin (35). In addition, kisspeptins have been shown to directly activate LHβ and FSHβ gene expression in murine primary pituitary cells and the LβT2 gonadotrope cell line (37). Furthermore, Ca^{2+} responses in gonadotropes have been reported after kisspeptin stimulation in vitro in a variety of species, including rat (38), ovine (39), porcine (40), and bovine species (40, 41). Time- and dose-dependent LH responses have been detected also in primary cultures of pituitary cells from female baboons (42), which closely correspond to different aspects of human physiology. In addition, detectable concentrations of kisspeptins have been found in the hypophyseal portal circulation in the sheep, and secretion of kisspeptins at the level of the median eminence, with capacity to reach the portal system, has been documented in the rhesus monkey (43). Altogether, these data provided the basis for potential direct actions of kisspeptins of the control of the gonadotropic axis at the pituitary level.

In addition, Kiss1 and Gpr54 mRNAs, and their corresponding peptides, have been shown to be expressed at the rat pituitary (38, 44), with detectable levels in gonadotropes (44). This pituitary expression seems to be hormonally regulated: estrogens, acting via ERα, enhance Kiss1 but reduces Gpr54 mRNA levels, whereas GnRH selectively enhances Gpr54 expression at the pituitary (44). Along the same lines, kisspeptin-positive cells have been found in the intermediate and anterior lobes of the rhesus monkey pituitary (45), although no evidence for the actual localization of kisspeptins in primate gonadotropes has been presented to date (45).

The consistency of the above findings, however, has been challenged by other studies that could not detect any effects of kisspeptins directly at the rat pituitary (46, 47), although differences in the experimental settings, including the age of the animals tested, might partially explain the apparent discrepancies across studies. In addition, kisspeptin levels in the portal circulation in the sheep did not change during relevant reproductive states, such as the preovulatory surge (39), which casts further doubts on the physiologic relevance of such pituitary effects of kisspeptins in the control of the HPO axis. Altogether, although direct pituitary actions of kisspeptins may contribute to the fine-tuning of the female gonadotropic axis, the potential physiologic relevance of such actions remains debatable and requires further investigation.

DIRECT KISSPEPTIN ACTIONS IN THE OVARY: FACTS AND HYPOTHESES

In addition to potential pituitary effects, the possibility of additional, peripheral actions of kisspeptins in the control of reproduction has been suggested by a number of studies documenting the expression of Kiss1 and Gpr54 in the gonads, including the ovaries (48–50). However, it must be stressed that the eventual physiologic relevance of kisspeptin signaling in the gonads remains debatable. As mentioned in previous sections, direct kisspeptin actions in GnRH neurons appear to be sufficient to complete puberty and attain fertility (15, 18), and global Gpr54-null mice and humans can be forced to ovulate if appropriately primed with gonadotropins (14, 51). However, rodent models with ablation of kisspeptin actions elsewhere than in GnRH neurons present modest but detectable alterations

of the reproductive axis and display premature reproductive aging (18). Moreover, rescue of ovulation in global Gpr54-null mice is quantitatively incomplete and requires intensive gonadotropin priming (51). Therefore, actions of kisspeptins downstream from gonadotropins (e.g., at the ovarian level) might contribute to the fine-tuning of reproductive function.

Regarding the female reproductive axis, ovarian expression of the elements of the Kiss1 system has been demonstrated in different mammals, including rodent (rat, mouse, hamster), porcine, bovine, and primate ovaries (48, 49). The latter group includes marmoset monkeys and humans (52). Of note, Kiss1 mRNA expression in the rat ovary changes according to the stage of the cycle, with maximum levels at the preovulatory phase (49). This activation is caused by the ovulatory surge of gonadotropins. In turn, inhibition of prostaglandin synthesis, which is known to severely perturb ovulation, caused a marked drop of ovarian Kiss1 mRNA levels and prevented the capacity of ovulatory doses of hCG to induce Kiss1 expression in the rat ovary (52). Altogether, these data are suggestive of a role of locally born kisspeptins in the control of ovarian functions, whose physiologic importance has yet to be elucidated.

Local kisspeptin signaling in the ovary has been implicated in a variety of relevant functions, which include the control of steroidogenesis (53), follicular maturation, ovulation, and ovarian senescence (48). Intra-ovarian infusion of a kisspeptin antagonist resulted in delayed puberty and perturbed estrous cyclicity in rats, without changes in circulating LH levels (54). In addition, not only was the pattern of ovarian expression of Kiss1 severely perturbed in rat models of disrupted ovulation (52), but also blockade of local kisspeptin signaling by intra-ovarian infusion of a kisspeptin antagonist in adult female rats reduced the number of large (type III) follicles and corpora lutea, the latter being a marker of ovulation (55). Conversely, direct ovarian injection of kisspeptin caused the opposite effect (55). Altogether, these data support a discernible role of local kisspeptins in the control of follicular dynamics and ovulation.

However, the relative importance of such direct ovarian actions remains controversial, because they are subordinated to the dominant central effects of kisspeptins in the control of the GnRH/gonadotropin system. In fact, the inherent difficulty to tease apart central versus local actions of kisspeptins has shadowed the relevance of ovarian kisspeptin signaling that, despite being globally dispensable for ovulation, is likely to play a role in follicular dynamics and oocyte survival, with potential impact in the precise modulation of ovulatory efficiency and, eventually, ovarian aging (51, 56). Thus, Gpr54 heterozygosity, which results in decreased ovarian expression of Gpr54 mRNA, in face of preserved (if not increased) gonadotropin secretion, caused late-onset ovarian failure (51). In addition, signaling via the neurotropin receptor NTRK2 in the oocyte requires preserved kisspeptin signaling to promote oocyte survival and prevent premature ovulatory failure (56). This evidence, together with the fact that the oocyte expresses Gpr54 in a number of species, including rodent, canine, and porcine species (56–58), strongly suggests that direct kisspeptin actions in the oocyte may contribute to modulate follicular survival and ovulation. This contention is solidly supported by our findings in a novel mouse line engineered to lack Gpr54, and thus direct kisspeptin actions, in the oocyte, which displays distinctive features of progressive premature ovarian insufficiency.

KISSPEPTIN ROLES IN THE UTERUS AND PREGNANCY

In addition to local expression and function in the gonads, kisspeptins are reportedly expressed in the uterus (59), where they have been implicated in the control of endometrial gland formation and placentation, key phenomena for reproductive success. Mice with congenital ablation of Kiss1 or Gpr54 suffer from severe uterine hypoplasia and absence of endometrial glands (60), which may be mainly due to the hypogonadal state of these animals caused by the the lack of central stimulatory actions of kisspeptins. Yet, experimental evidence suggests that part of this hypoplastic phenotype might derive from the lack of kisspeptin effects directly at the uterus. In detail, with the use of genetically modified murine models with global or conditional ablation of kisspeptin signaling, it has been documented that, while uterus growth is largely dependent on the estrogenic input driven by the central activity of the HPO axis, endometrial adenogenesis (i.e., the process of endometrial gland generation) is severely compromised in conditions of preserved estrogen levels but lack of peripheral kisspeptin signaling (61). Considering the key role of endometrial glands in the local production of factors essential for uterine receptivity and embryo implantation, such local actions of kisspeptins at the endometrial level might be relevant in achieving maximal reproductive efficiency.

In addition, kisspeptins have long been associated with different aspects of human placentation and gestation, although the actual physiologic roles of kisspeptins during pregnancy remain ill defined. An exhaustive recapitulation of such gestational roles of kisspeptins is beyond the scope of this review, but it is worth mentioning that the elements of the Kiss1 system are known to be expressed in human endometrium and placenta (62) and that kisspeptins have been suggested to participate in the control in human placentation (62, 63). Thus, kisspeptin signaling seems to operate as a repressor of human trophoblast migration and invasion (64), but has also been suggested to operate as a promoter of embryo implantation (62). Of note, kisspeptins and Gpr54 seem to be appropriately located at the fetal-maternal interface to modulate placental invasion. Kiss1/kisspeptins are highly expressed in the syncytiotrophoblast in normal human placenta (64), whereas Gpr54 is present in the villous and invasive extravillous human cytotrophoblasts (64, 65), thus providing the basis for putative autocrine and paracrine regulation of invasion by trophoblast cells. Altogether, these data suggest a putative function of kisspeptins in human placentation. In addition, the circulating levels of kisspeptins dramatically increase during human gestation (66), with a ~1,000-fold increase in the first trimester, and up to a ~7,000-fold increase in the third trimester (66). The physiologic

TABLE 1

Major biologic effects and sites of action of kisspeptins at different levels of the female reproductive axis. For specific references, see the corresponding sections in the text.

Site of action	Distribution and biologic effect
Hypothalamus	
Distribution	Kiss1 neurons are found in the hypothalamic ARC/infundibular region in mammals of both sexes, including rodents and primates; a set of ARC Kiss1 neurons coexpress neurokinin B and dynorphin and are termed KNDy
	In the female, a second population of Kiss1 neurons is found in the AVPV in rodents and the preoptic area in sheep and primates
Actions on GnRH neurons	Kisspeptins potently stimulate firing of GnRH neurons and GnRH secretion in mammals, including rodents, sheep, and primates
	ARC Kiss1/KNDy neurons are involved in mediating the negative feedback of sex steroids and are an essential component of the GnRH pulse generator
	AVPV Kiss1 neurons play a major role in generation of preovulatory surge of gonadotropins and ovulation (mostly documented in rodents)
Non-GnRH neuron actions	Primary actions of kisspeptins on brain targets other than GnRH neurons have been suggested, but the physiologic relevance of such non-GnRH actions has yet to be fully characterized
Pituitary	
Distribution	Kiss1/kisspeptin and Gpr54 have been found in rat pituitary gonadotropes. Kisspeptins have detected in the monkey pituitary as well, but colocalization in gonadotropes is unclear in primates
Effects in gonadotropes	Kisspeptins can directly stimulate LH secretion by rat pituitary explants ex vivo, although some reports have failed to detect such direct stimulatory actions
	Kisspeptins induce transcriptional activation of LHβ and FSHβ gene in pituitary cells
	Kisspeptins elicit Ca^{2+} responses in gonadotropes in a variety of species, including rat, ovine, porcine, bovine, and primate species
Ovary	
Distribution	Kiss1/kisspeptin and Gpr54 have been shown to be expressed in rodent (rat, mouse, hamster), porcine, bovine, and primate ovaries. Gpr54 expression has been documented in oocytes
	Kiss1 expression in the rat ovary is cyclic and hormonally regulated, with peak levels preceding ovulation being driven by the preovulatory surge of gonadotropins
Biologic effects	Local kisspeptin actions have been involved in different ovarian functions, including modulation of steroidogenesis, ovulation, and ovarian senescence; the physiologic relevance, however, remains ill defined
	Blockade of local kisspeptins in the rat ovary delays puberty onset and reduces ovulatory efficiency in adulthood, as denoted by decreased number of corpora lutea
	Haplo-insufficiency of Gpr54, which reduces ovarian Gpr54 expression, results in premature ovarian failure in mice; progressive premature ovarian insufficiency is also found in a model of conditional ablation of Gpr54 from oocytes
Uterus	
Distribution	Elements of the Kiss1 system are expressed in the mouse uterus, including the luminal and glandular epithelia on the day of implantation
Biologic effects	Absence of kisspeptin signaling causes severe uterine hypoplasia and absence of endometrial glands
	Uterine hypoplasia due to global elimination of kisspeptin signaling is mainly due to the lack of central effects of kisspeptins, which results in low estrogenic input to the uterus
	Proper endometrial gland formation in the mouse uterus is not dependent on central kisspeptin signaling and requires peripheral actions of kisspeptins, possibly at the level of the uterus
Placenta and gestation	
Distribution and levels	Kiss1/kisspeptins are highly expressed in the syncytiotrophoblast in normal human placenta, whereas Gpr54 is present in the villous and invasive extravillous human cytotrophoblast
	Plasma levels of kisspeptins dramatically increase in human gestation, with a >1,000-fold increase in the first trimester, and up to a ~7,000-fold increase in the third trimester
Biologic actions	Kisspeptins have been suggested to participate in the control in human placentation, acting as repressor of human trophoblast migration and invasion
	Local kisspeptins may promote embryo implantation in mice
	Placentation and pregnancy can progress despite the absence of kisspeptin signaling
	The putative role of increased plasma levels of kisspeptins during gestation remains unknown; they might contribute to hormonal and metabolic adaptations during pregnancy

Note: ARC = arcuate nucleus; AVPV = anteroventral periventricular nucleus; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

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consequences of such elevation remain an enigma, however, although it has been suggested that it might contribute to the metabolic adaptations of pregnancy.

Of note, few women who are infertile due to inactivating mutations of the GPR54 gene have been reported to give birth to healthy children after ovulatory induction (67). This would dismiss an indispensable role of kisspeptin signaling at the maternal side for completion of human pregnancy. It must be stressed, however, that the particular characteristics of placentation of these patients could not be evaluated in detail; therefore, it is possible that the absence of kisspeptin signaling might have caused modest alterations of placental morphology or function that, even if not being incompatible with successful gestation, may affect optimal organ

TABLE 2

Potential clinical applications of kisspeptins and related factors in reproductive medicine.

Medical condition	Potential medical application
Infertility	
IVF	Peripheral administration of kisspeptins has been shown to induce ovulation in different mammals, and subcutaneous injection of kisspeptin can induce egg maturation and ovulation in protocols of IVF
	The reported protocols of kisspeptin stimulation do not clearly improve the efficiency of current procedures of gonadotropin stimulation and require pretreatment with recombinant FSH; are new analogues needed?
Prevention of OHSS	Kisspeptin stimulation likely evokes a more physiologic gonadotropin stimulation and is less prone to cause the most serious complication of IVF, i.e., OHSS
	Women at risk of OHSS do not commonly display such adverse complication after kisspeptin stimulation, despite application of a second dose of kisspeptin to extend the duration of LH secretion
PCOS	
Pathophysiology	Fragmentary evidence suggests alterations of hypothalamic expression of Kiss1 in preclinical models of PCOS
	Inconclusive evidence has pointed out alterations of circulating levels of kisspeptins in women with PCOS
Treatment	Repeated injections of kisspeptin-54 induced gonadotropin responses and rescued ovulation in preclinical models of PCOS, but with incomplete efficacy
	A pilot study in anovulatory women with PCOS showed that treatment with kisspeptin-54 can induce gonadotropin responses in patients with PCOS, but ovulation was rescued in only a fraction of treated women
Hormone-dependent conditions	
Endometriosis	Data from preclinical models suggest that kisspeptin analogues (antagonists or agonists, via desensitization) may cause suppression of ovarian function without reaching castration levels; no evidence from clinical studies yet
Uterine fibroids	Data from preclinical models suggest that kisspeptin analogues (antagonists or agonists, via desensitization) may cause suppression of ovarian function without reaching castration levels; no evidence from clinical studies yet
Hot flushes	Antagonists of NKB, a peptide coexpressed with Kiss1 in KNDy neurons, are novel pharmacologic tools for the control of menopausal hot flushes; NKB analogues are currently in clinical trials to test for efficacy and safety
Biomarkers	
Gestational diseases	Low circulating levels of kisspeptin have been proposed as biomarker of gestational alterations, such as intrauterine growth restriction and preeclampsia
	Low circulating levels of kisspeptins, together with suppressed levels of miR-324-3p, were recently proposed as biomarker of ectopic pregnancy
Risk of abortion	Decreased circulating levels of kisspeptins have been proposed as a putative predictor of miscarriage risk
Gestational tumors	Circulating levels of kisspeptins increase in gestational trophoblastic neoplasia and decrease with treatment

Note: Conditions and applications are predicted based on preclinical and clinical research; no kisspeptin-based protocols are currently in routine practice. FSH = follicle-stimulating hormone; IVF = in vitro fertilization; KNDy = Kiss1/neurokinin B/dynorphin; LH = luteinizing hormone; NKB = neurokinin B; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome.

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physiology. Along the same line, placentas from global Kiss1- or Gpr54-null mice have been shown to display grossly preserved structure and basic function, as evaluated by stereologic studies and analyses of amino acid and glucose transport in placentas from Gpr54 and/or Kiss1 knockout mice (68). Though direct extrapolation of these findings to humans must be made with caution, these data suggest that congenital lack of kisspeptin signaling at either the maternal or the fetal side is not incompatible with completion of gestation, even if distinct functions of kisspeptins in the control of embryo implantation, placentation, and gestation have been documented by clinical and experimental studies.

CLINICAL APPLICATIONS OF KISSPEPTINS: WHERE ARE WE; WHERE DO WE GO?

Given the paramount importance of kisspeptins in the control of HPO axis, and their capacity to potently activate gonadotropin secretion in humans and other mammals, kisspeptin analogues (both agonists and antagonists) have been explored as potential pharmacologic tools for the management of various reproductive disorders. Likewise, changes in kisspeptin levels have been proposed as putative markers for improved diagnosis of some conditions. While the clinical use of kisspeptins, either for diagnostic or therapeutic purposes, has yet to be consolidated, some illustrative examples along these potential medical applications of kisspeptins are discussed here and summarized in Table 2.

A number of studies in various animal species have documented that peripheral administration of kisspeptins can evoke ovulation (46, 69, 70). Of particular interest, subcutaneous injection of kisspeptin has been shown to induce egg maturation and ovulation in protocols of in vitro fertilization (IVF) in women, thus paving the way for the use of kisspeptins in the protocols of ovarian stimulation in IVF techniques (69). In principle, it is arguable that kisspeptin stimulation might evoke a more physiologic gonadotropin stimulation than exogenous gonadotropin priming, therefore reducing the potential of off-target and side-effects. In fact, the protocols of kisspeptin administration to induce oocyte maturation are less prone to cause the most serious complication of IVF, ovarian hyperstimulation syndrome (OHSS) (71). Of note, even women at risk of OHSS do not commonly display such an adverse complication after kisspeptin stimulation, despite application of a second dose of kisspeptin to extend the duration of LH secretion (72). Admittedly, however, the reported protocols of kisspeptin stimulation do not improve the efficiency of current protocols of gonadotropin stimulation and require pretreatment with

recombinant FSH (69). In this scenario, the use of longer-acting analogues of kisspeptins might pose an advantage for IVF procedures, which has yet to be clinically proven.

Along the same lines, the possibility that kisspeptin-based treatments might improve the management of common anovulatory conditions, such as PCOS, has been recently addressed. PCOS is a prevalent endocrinopathy, commonly associated with oligo/anovulation. Even though it affects a notable fraction of the human female population in reproductive age, the treatments for PCOS remain mostly symptomatic and are of moderate efficacy when conception is desired, they being linked with potentially life-threatening complications, such as OHSS. Thus, kisspeptins might provide a therapeutic advantage for induction of ovulation in PCOS women. In a recent study, we reported the effects of administration of kisspeptin-54 in a pilot exploratory cohort of anovulatory women with PCOS (73). Our data showed that administration of kisspeptin-54 twice daily for 21 days elicited LH responses in five of the seven women, but only two presented growth of a dominant follicle with subsequent ovulation. In the same study, the ability of repeated injections of kisspeptin-54 to induce LH and FSH responses and to cause ovulation was evaluated in three different preclinical models of PCOS (73). While kisspeptin administration consistently induced LH and FSH responses, albeit with differences in magnitude across the rat models, efficiency of this treatment in terms of ovulatory induction was variable, and it evoked ovulation only in models of postnatal androgenization, but not in those of continuous exposure to high androgen levels. Altogether, this combination of preclinical and clinical data demonstrates that kisspeptin administration in anovulatory preclinical models and in women with PCOS can stimulate reproductive hormone secretion and ovulation, albeit with incomplete efficacy, thus arguing for the need of personalized management of anovulatory dysfunction in women with PCOS, some of whom may benefit from kisspeptin-based treatments.

Development of kisspeptin antagonists and realization of the coexpression of kisspeptins with other neuropeptides with key roles in the control of reproductive function, such as NKB in KNDy neurons, has led to the proposal of additional therapeutic uses of kisspeptin analogues or related compounds. Based on preclinical data, kisspeptin antagonists might be useful to prevent the preovulatory surge, decrease gonadotropin levels without achieving the castration range, and manage endocrine-dependent female reproductive disorders ranging from endometriosis to uterine fibroids. Admittedly, however, clinical data supporting these applications are still missing. On the other hand, demonstration that NKB produced by KNDy neurons might contribute to the generation of menopausal hot flushes has led to active clinical investigation of the potential utility of NKB receptor antagonists (74), which are now in clinical trials. In addition, evidence for the eventual use of NKB antagonists in normalizing GnRH/LH hypersecretion, seen in women with PCOS, has been proposed very recently (75).

Finally, because tissue Kiss1 and/or Gpr54 expression, as well as circulating kisspeptin levels, have been reported to change in some pathophysiologic conditions, the possibility that they might serve as biomarkers of disease has been explored, for example, in gestational pathologies. As described in the preceding section, blood levels of kisspeptins have been reported to dramatically increase during human gestation; accordingly, inappropriately low kisspeptin levels have been proposed as biomarker of gestational alterations, such as intrauterine growth restriction and preeclampsia (76, 77). Likewise, altered circulating levels of kisspeptins might serve as a putative predictor of miscarriage risk (78). In line with this possibility, a recent pilot study comparing women with viable intrauterine pregnancy versus women with confirmed spontaneous abortion suggested that kisspeptin levels during an early gestational window (weeks 6–10) might serve as a biomarker of pregnancy viability (79). In the same vein, we recently described that disproportionately low kisspeptin levels, together with decreased circulating levels of its regulator, miR-324-3p, might serve as putative biomarkers for accurate screening of ectopic pregnancy at early gestational ages (80).

CONCLUSION

Discovery of the reproductive dimension of kisspeptins has revolutionized our understanding of the basic mechanisms responsible for the precise control of the female reproductive axis, kisspeptins now regarded as indispensable elements for the proper maturation and function of the HPO axis. Although realization of the fundamental reproductive roles of kisspeptin dates back only to late 2003, the progress in the field has been astonishingly rapid and has allowed us to decipher key aspects of kisspeptin physiology. Conclusive evidence has demonstrated that the primary site of actions of kisspeptins is the population of GnRH neurons in the hypothalamus, where kisspeptins mediate the feedback effects of ovarian steroids and are able to induce potent excitatory effects that are essential for normal puberty onset, proper pulsatile gonadotropin secretion, and ovulation, a contention that can be regarded as dogma in the field. In addition, as yet fragmentary evidence has been gathered over the past 15 years for additional actions of kisspeptins, not only on neuronal circuits other than for GnRH, but also at other reproductive tissues, such as the pituitary, the gonads, the uterus, and the placenta. We can consider these actions to be less striking and of modest magnitude and possibly subordinated to the central GnRH-centric effects of kisspeptins in the HPO axis. In any event, characterization of such peripheral actions of kisspeptins and their actual physiologic relevance can be considered as open challenges for reproductive physiology and medicine, and their elucidation will help to reveal the whole set of pathophysiologic, diagnostic, and therapeutic implications of kisspeptins in the context of female reproduction.

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ORIGINAL ARTICLES: GENETICS

Novel pathogenic mutations in minichromosome maintenance complex component 9 (*MCM9*) responsible for premature ovarian insufficiency

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Objective: To investigate whether mutations in the minichromosome maintenance complex component 9 (*MCM9*) gene were present in 192 patients with sporadic premature ovarian insufficiency (POI) of Chinese descent.
Design: Genetic and functional study.
Setting: University-based reproductive medicine center.
Patient(s): A total of 192 patients with sporadic POI and 192 control women with regular menstruation.
Intervention(s): Sanger sequencing performed in 192 sporadic POI patients, and potential pathogenic variants were excluded in matched controls. Functional effects of mutations on MCM9 were explored based on etoposide-induced DNA damage response, and DNA repair capacity was evaluated by histone H2AX phosphorylation level.
Main Outcome Measure(s): Sanger sequencing and functional characteristics.
Result(s): Three novel heterozygous mutations in *MCM9,* c.C1423T (p.L475F), c.T2921C (p.L974S), and c.G3388A (p.A1130T), were identified in three POI patients separately, which were absent in 192 controls. Functional studies showed that the human embryonic kidney 293 (HEK293) cells overexpressing mutant *MCM9* presented with diminished DNA repair capacity compared with wild type.
Conclusion(s): This study identified novel mutations in *MCM9* that are potentially causative for sporadic POI in Chinese women and further highlighted the role of DNA repair capacity in maintenance of ovarian function. (Fertil Steril® 2020;113:845–52. ©2019 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: DNA repair, MCM9, mutation, POI

Premature ovarian insufficiency (POI) is defined as loss of ovarian function before 40 years of age, characterized by amenorrhea, infertility, estrogen deprivation, and elevated follicle-stimulating hormone (FSH) serum levels (1). Approximately 1% to 5% of women are affected by POI and are at high risk of osteoporosis, cardiovascular disease, and other long-term health complications due to estrogen deficiency (2).

Premature ovarian insufficiency is a heterogeneous condition both clinically and etiologically. Besides iatrogenic factors such as ovarian surgery, chemotherapy, or radiation therapy, POI may be caused by chromosomal abnormalities, gene mutations, immune disease, or infections, although

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in most of the patients causes are still unknown (1). Genetic defect accounts for 20% to 25% of POI cases (3). Then causative genes for POI have been found via sanger sequencing according to the phenotypes of animal models, such as *FIGLA, NOBOX, NR5A1, FSHR,* and *BMP15* (3–8), which participate in folliculogenesis or steroid hormone synthesis and response. Recent approaches using whole-exome sequencing in POI pedigrees have found a few novel causative genes involved in meiosis or DNA damage repair, such as *HFM1, STAG3, SYCE1, MCM9, MCM8, MSH5,* and *BRCA2* (9–17).

Among the novel genes, minichromosome maintenance complex component 8 (*MCM8*) and 9 (*MCM9*) are DNA helicases participating in DNA replication and homologous recombination (HR), which are crucial for gonadal development and ovarian function (18). *Mcm9* knockout mice have atrophic ovaries completely devoid of follicles (19, 20). Homozygous pathogenic variants in *MCM9* have been found in POI pedigrees (14, 21). Desai et al. (22) found nearly 5% of patients with sporadic POI carried damaging heterozygous mutations of *MCM9*. However, the contribution of *MCM9* for POI in Chinese patients is unclear. Here, we performed Sanger sequencing of *MCM9* in 192 Chinese women with sporadic POI and identified three novel heterozygous mutations. Functional studies found the three mutations impaired DNA repair efficiency of *MCM9*, indicating that haploinsufficiency of *MCM9* contributes to pathogenesis of POI in women of Chinese ethnicity.

MATERIALS AND METHODS

Study Population

A total of 192 patients with sporadic POI and 192 control women were recruited from the Center for Reproductive Medicine at Shandong University. The criteria for sporadic POI included primary or secondary amenorrhea for at least 4 months before 40 years of age, along with at least two instances of serum FSH levels >40 IU/L detected at an interval of 4–6 weeks, 46,XX karyotype, and no family history of POI. Known causes, such as autoimmune diseases, pelvic surgery, and chemo/radiotherapy treatment were excluded.

As controls, we recruited 192 women with regular menstruation and normal levels of FSH (<10 IU/L), who were receiving intracytoplasmic sperm injection (ICSI) treatment owing to male factor infertility. All the control women had normal ovarian responses during ovarian stimulation (Table 1).

Written informed consent was obtained from all participants. This study was approved by the institutional review board of Reproductive Medicine at Shandong University.

Sanger Sequencing

Genomic DNA was extracted from peripheral blood samples with QIAamp DNA minikit (Qiagen) according to the manufacturer's protocol. All exons and exon-intron boundaries of human *MCM9* gene (ENST00000316316.10) was amplified by polymerase chain reaction (PCR). The PCR products were purified, labeled by Bigdye (Applied Biosystems), and sequenced on an ABI 3730-Avant Genetic Analyzer (Applied Biosystems). All the variants were confirmed by three independent PCR runs, sequenced in forward and/or reverse directions. The novel variations were verified in the 192 controls. Amino acid sequences of other species were obtained from the Uniprot database, and the conservation analysis was conducted on the ClustalW2 Web site (www.clustal.org/clustal2).

TABLE 1

Clinical features of patients with sporadic premature ovarian insufficiency and controls.

Characteristics	Sporadic POI	Control	*P* value
No. of patients	192	192	—
Age (y)	28.75 ± 4.22	27.03 ± 2.74	<.001
Age of amenorrhea (y)	23.01 ± 5.19	—	—
FSH (IU/L)	77.07 ± 25.84	6.02 ± 1.08	<.001
Amenorrhea type			
Primary (n)	14	—	—
Secondary (n)	178	—	—

Note: FSH= follicle-stimulating hormone; POI = primary ovarian insufficiency.

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Plasmids Construction and Mutagenesis

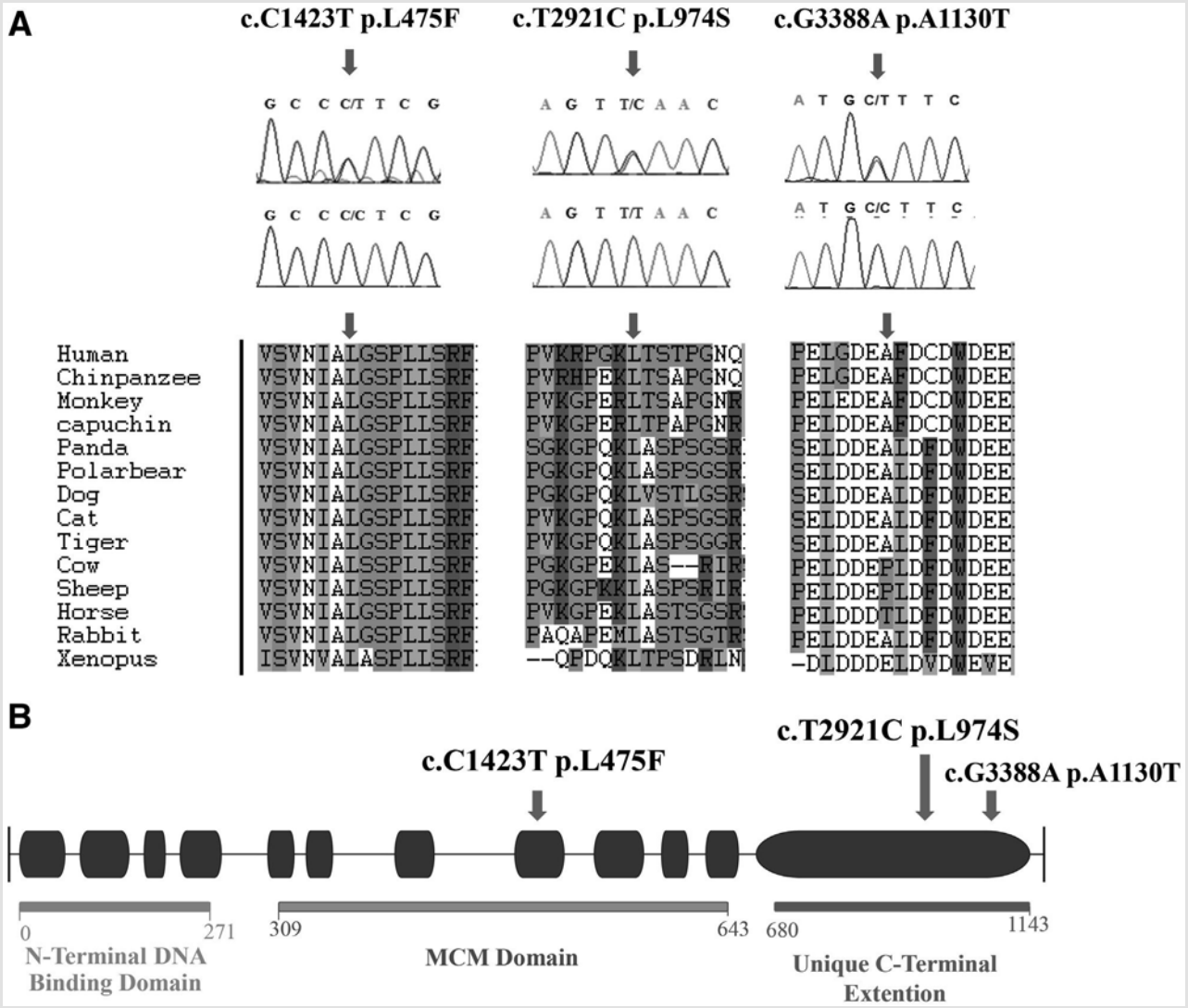
The wild-type plasmid was constructed by inserting human *MCM9* cDNA directly into the pcDNA3.1 vector. The mutant plasmids were generated with wild-type plasmid as the template, using the QuikChange Lightning Site-Directed Mutagenesis Kit (Agilent), and were confirmed by Sanger sequencing.

DNA Repair Assay

Human embryonic kidney 293 (HEK293) cells were cultured in Dulbecco's modified Eagle's medium/high glucose (ThermoFisher) medium supplemented with 10% fetal bovine serum at 37°C with 5% CO_2 for 24 hours. They were then transiently transfected with wild-type or mutant MCM9 plasmids with the use of lipofectamine (Invitrogen). After 24 hours, the cells were incubated in culture medium containing etoposide (ETO, 5 μg/mL) for 2.5 hours at 37°C to induce DNA double-strand breaks (DSBs). Then the culture medium was dropped, and the cells were harvested immediately, or they were cultured with normal medium for an additional 3 or 6 hours at 37°C whereupon the cell were harvested after recovery. Phosphorylation of the Ser-139 residue of histone variant H2AX (γH2AX; Cell Signaling Technology) was tested as a sensitive marker for DSBs by use of Western blot analysis. To further assess the potential dominant negative effect, the mutant plasmids and wild-type plasmids (in a 1:1 ratio, amount equal to isolated wild-type group) were cotransfected into HEK293T cells, followed by the DNA repair assay.

Three independent experiments were conducted. To compare the change in γH2AX level, we quantified the grayscale scores of Western blot bands using ImageJ software (National Institute of Health). The grayscale scores of γH2AX in the cells treated with ETO and recovered at specific time points were divided by those of untreated cells in each group. We compared the relative grayscale score between the wild-type and the mutant groups after 6 hours of recovery.

FIGURE 1



MCM9 mutations identified in premature ovarian insufficiency (POI) patients of Chinese descent. (**A**) The sequence chromatograms of *MCM9* variations identified in three Chinese patients with isolated sporadic POI, compared with normal control sequences, followed with the conservation analysis among species. (**B**) The domain architecture of *MCM9* and the position of the variations.

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GFP-based HR Reporter Assay

The HEK293 cells carrying green fluorescent protein (GFP)-cased HR reporter substrates and I-SceI-vector were generously provided by professor Fengli Wang from Huazhong University of Science and Technology and professor Hailong Wang from Capital Normal University (23). The DSBs could be generated by transfecting I-SceI into the HR reporter cells. If the DSBs had been repaired through HR, GFP would be expressed, and the percentage of GFP-positive cells would reflect the HR efficiency. Therefore, we cotransfected I-SceI and MCM9-pcDNA3.1 plasmids (wild type and/or mutant) into the HR reporter cells.

The cells were collected for flow cytometry analysis after 48 hours of culture. The pcDNA3.1 vector was transfected into the HR reporter cells as negative controls (NC). The percentage of GFP-positive cells was calculated, and the ratio of HR efficiency was obtained by the percentage of GFP-positive cells in the wild-type or mutant groups divided by that of NC group. Three independent experiments were conducted, and at least 40,000 cells were counted at one time.

Statistical Analysis

Software SPSS 20 (IBM) was used for data analysis. The age and serum FSH concentration were checked for normality and described as mean ± standard deviation. The frequency of genotypes was tested by Pearson's chi test or Fisher's exact test. The relative grayscale of the Western blots and HR repair efficiency were tested by independent sample *t*-tests. All the *P* values were two-sided, and $P < .05$ was considered statistically significant.

RESULTS

Three Novel Mutations Identified in POI

Through Sanger sequencing in 192 patients with POI, three novel heterozygous missense variations in *MCM9* (ENST00000316316.10) were identified: c.C1423T (p.L475F), c.T2921C (p.L974S), and c.G3388A (p.A1130T), which were absent in 192 controls. Variants p.L475F and p.L974S were highly conserved across species (Fig. 1). Variant p.L475F in exon 8 was located at the minichromosome maintenance (MCM) domain, which promotes hydrolysis of adenosine triphosphate (ATP), and p.L974S and p.A1130T in exon 12 were located at the C-terminal extension domain. In addition, 12 single nucleotide polymorphisms (SNP) were identified (Supplemental Table 1, available online). Among them, the frequencies of the SNPs rs768968338 (allele frequency: 99.74% vs. 99.994%, $P=.043$) and rs79670608 (allele frequency: 99.74% vs. 98.24, $P=.02$) were statistically significantly different between our POI cohort and the 1000 Genomes Project database (www.internationalgenome.org).

The two patients, who carried p.L475F and p.A1130T, experienced menarche at 16 years old, followed by irregular menses (30 to 180 days per menstrual cycle) that ceased at the ages of 25 and 26, respectively. The carrier of mutation p.L974S experienced menarche at 14 years old, had spontaneous menstruation for 4 years, and underwent menopause at the age of 19. Ultrasound examination of the three patients showed small ovaries with no follicles. None of these patients had a history of pregnancy (Table 2).

Mutant *MCM9*-impaired DSB Repair Capacity

To illustrate the effect of mutants p.L475F, p.L974S, and p.A1130T on DNA repair capacity, we induced DSBs with ETO treatment to evaluate the repair efficiency via the level of γH2AX. In HEK293 cells overexpressing wild-type MCM9, γH2AX increased immediately after ETO treatment and disappeared after recovery for 6 hours. However, the cells overexpressing mutant p.L475F, p.L974S, or p.A1130T showed a higher level of γH2AX after recovery for 3 or 6 hours compared with the wild type.

To examine whether a dominant negative effect of the three mutations existed, we cotransfected the mutant and wild-type plasmids at ratio1:1 into HEK293 cells. The γH2AX level in cotransfected cells after recovery for 3 or 6 hours was lower than that in cells isolated transfected with mutant plasmids but still higher than found in the cells isolated transfected with wild-type *MCM9* after recovery for 6 hours, indicating that haploinsufficiency of mutant *MCM9* would be an possible explanation (Fig. 2A and B). The cells isolated transfected with mutant MCM9 plasmids demonstrated statistically significantly lower HR efficiency than the wild type, whereas the cotransfected cells showed a median HR efficiency between wild-type and mutant cells that was consistent with the results of the DNA repair assays (see Fig. 2C and D).

DISCUSSION

In Chinese patients with POI, our study identified three novel heterozygous missense mutations of *MCM9* that adversely affect DNA repair function, giving more evidence to the pathogenesis of DNA repair defects in the etiology of POI. Primordial follicles are the storage unit of the female germline, and their genetic integrity is essential for maintaining oocyte quantity and quality (24). To protect genome integrity, cells have evolved a network of pathways called DNA damage response, which is responsible for detecting DNA damage, activating checkpoints leading to cell cycle arrest, and coordinating the whole repair process (25). In the germline, DSBs are the most common and severe form of DNA damage, and they are deliberately induced and efficiently repaired through homologous recombination during pachytene of meiosis I (26). Genetic studies of POI have found causative mutations in genes involved in HR, such as *MSH4, MSH5, MCM8, MCM9, HFM1, BRCA2,* and *MEIOB* (10, 13, 14, 16, 27–29), which emphasizes the pivotal role of DNA repair genes in folliculogenesis and maintenance of ovarian function.

The *MCM8–MCM9* complex has been considered to be a participant in DNA replication and resolution of DSBs during HR (30). The two processes are important for germ cell proliferation and meiotic recombination, disturbances of which would lead to insufficient oocyte generation or accelerated oocyte apoptosis (31). Moreover, mice deficient in *Mcm8* and *Mcm9* are infertile and have small gonads due to germ-cell depletion, which mimics the phenotype of POI in humans (20). Whole-exome sequencing has identified homozygous mutations of *MCM8* and *MCM9* in consanguineous pedigrees of POI, suggesting the pathogenetic effect of a dysfunctional *MCM8–MCM9* complex in POI (14, 21). In previous study we found *MCM8* heterozygous mutations in sporadic patients (32). In our present study, we have identified three novel heterozygous missense mutations in *MCM9*. The frequencies of

TABLE 2

Clinical profiles of three women with premature ovarian insufficiency who carry *MCM9* mutations.

Patient	Menarche age (y)	Menopause age (y)	FSH (IU/L)	E_2 (pg/mL)	Stature (cm)	Karyotype	Ovary size (mm) Right	Ovary size (mm) Left	Follicle	*MCM9* variants
POI-1	16	25	138.2	14.4	160	46,XX	15*10	14*8	Absent	c.C1423T (p.L475F)
POI-2	14	18	66.81	<5	153	46,XX	12*5	Invisible	Absent	c.T2921C (p.L974S)
POI-3	16	26	107	<5	160	46,XX	Invisible	Invisible	Absent	c.G3388A (p.A1130T)

Note: E_2 = estradiol; FSH = follicle-stimulating hormone; *MCM9* = minichromosome maintenance complex component 9; POI = premature ovarian insufficiency.

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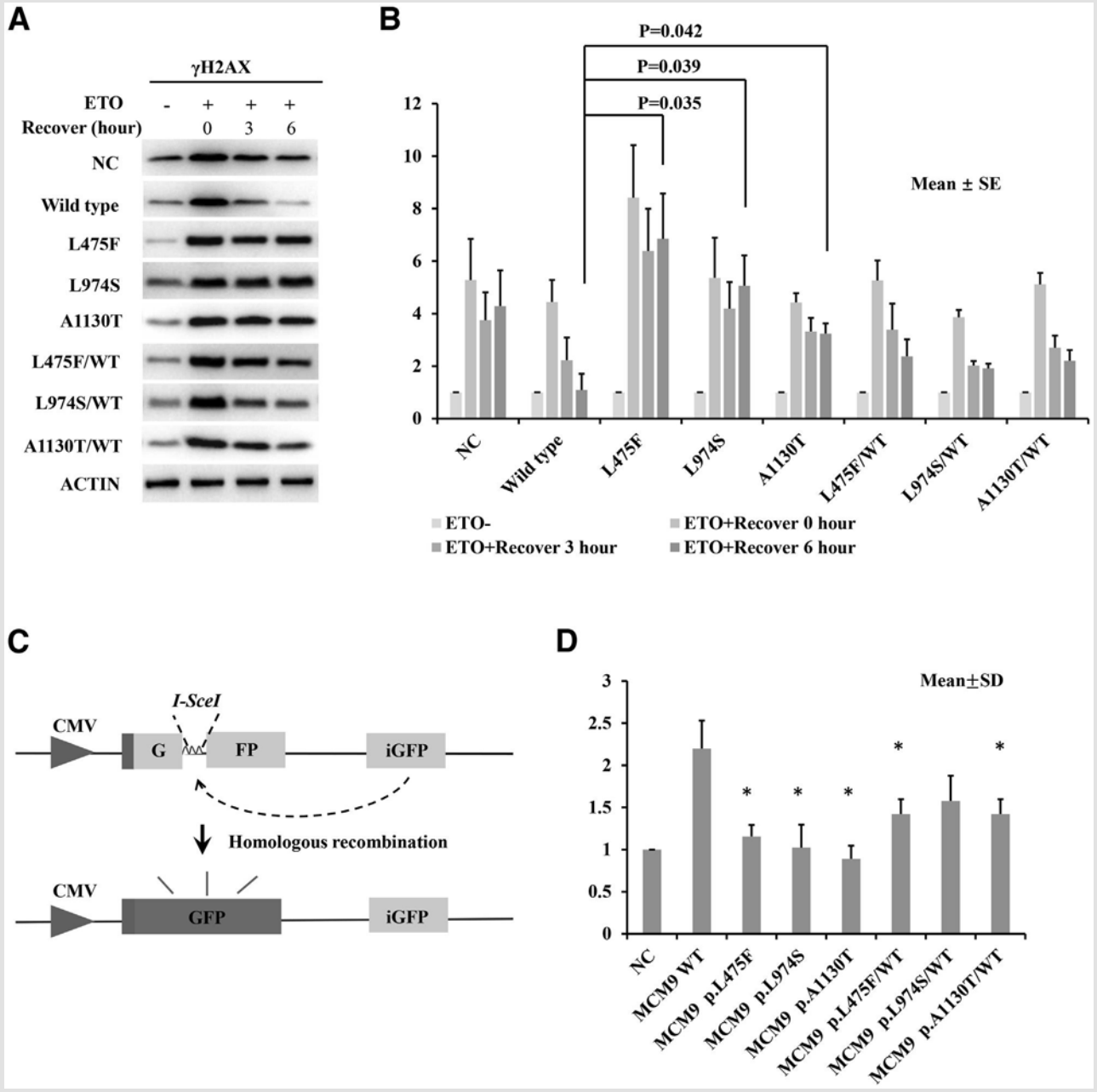
FIGURE 2



MCM9 mutations adversely affect the DNA repair capacity. (**A**) The cells overexpressing MCM9 with mutation p.L475F, p.L974S or p.A1130T showed higher level of γH2AX after recovery for 3 or 6 hours compared with the wild type. To test the dominant negative effect of the three mutations, we cotransfected the mutant and wild-type plasmids with ratio 1:1 into HEK293 cells. The γH2AX level in cotransfected cells after recovery for 3 or 6 hours were lower than that in cells isolated transfected with mutant plasmids. Three independent experiments were conducted (NC = negative control, which was transfected with pcDNA3.1 vector). (**B**) The relative grayscale of γH2AX after etoposide (ETO) treatment compared with no ETO treatment according to the Western blot image of three independent experiments (the grayscale of no ETO treatment was considered as 1 in each group of transfected cells). Independent sample *t*-test was used to compare the relative γH2AX. (**C**) Homologous recombination (HR) reporter system working principle. (**D**) The HR efficiency of wild-type or mutant MCM9 compared with NC group. (NC = cells transfected with I-SceI-vector and pcDNA3.1 vector.) Three independent experiments were conducted. **P*<.05.

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SNPs rs768968338 and rs79670608 were substantially different when we compared our POI findings with the 1000 Genomes Project database, which also indicates the association between POI and *MCM9*.

Our DNA repair assays showed that the cells overexpressing mutant *MCM9* had impaired DNA-repair capacity, and we speculate about the haploinsufficiency of *MCM9*. Nearly all the biallelic variation carriers of *MCM9* presented with

primary amenorrhea. In sporadic POI, Desai et al. (22) found 1 in 151 patients carried homozygous variations of *MCM9*, while seven cases (7 of 151, 4.6%) had heterozygous variations with potential pathogenetic effects. The heterozygous carriers most likely experienced secondary amenorrhea, which would be consistent with the phenotype observed in our cohort. Therefore, we assume that the effect of *MCM9* mutations on ovarian function might be dosage dependent. Haploinsufficiency of *MCM9* caused by heterozygous variations predisposes women to secondary amenorrhea owing to residual functional MCM9, whereas biallelic variations might lead to more severe defects in ovarian development leading to primary amenorrhea. Desai et al. (22) also found heterozygous variations in *MCM8*, *BRCA1*, and *RAD54L* combined with *MCM9* variations coexisting in patients, which indicates that the cumulative effect of genetic defects affects the clinical severity of POI (33).

More importantly, the relationship between *MCM9* and tumors has still been elusive. The *Mcm9* knockout mice had a high risk of hepatocellular carcinoma and ovarian tumors (19). Goldberg et al. (34) reported a homozygous mutation carrier of *MCM9* had early colorectal carcinoma and POI. However, the three mutation carriers in our study had no history of tumors at the time of our investigation. Long-term follow-up observation for tumors, especially for hormone-sensitive tumors, should be recommended for patients with *MCM9* mutations.

CONCLUSION

We identified novel pathogenic mutations in *MCM9* in Chinese women with POI, which further expands the genotype spectrum of *MCM9* in POI.

Acknowledgments: The authors thank all of the participants involved in this study. We also thank Professor Hailong Wang (Beijing Key Laboratory of DNA Damage Response and College of Life Sciences, Capital Normal University, Beijing, China) and Fengli Wang (Institute of Reproductive Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) for the generous gift of GFP-based HR reporter system.

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REVIEW

Premature ovarian insufficiency: an International Menopause Society White Paper

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ABSTRACT

The aim of this International Menopause Society White Paper on premature ovarian insufficiency (POI) is to provide the latest information regarding this distressing condition. The impact of POI has far-reaching consequences due to its impact on general, psychological, and sexual quality of life, fertility prospects, and long-term bone, cardiovascular, and cognitive health. Progress in fully understanding the etiology, diagnosis, and optimal management options has been slow thus far due to the complexity of the condition and fragmented research. Recent advances in epidemiological and genetic research have improved our understanding of this condition and randomized prospective trials are being planned to determine the intervention strategies, which will optimize quality of life and long-term well-being. The International Menopause Society has commissioned a number of experts at the forefront of their specialty to define the state of the art in the understanding of this condition, to advise on practical management strategies, and to propose future research strategies. It is hoped that a global task force will subsequently be convened in order to formulate a consensus statement across key societies, to accelerate date collection and analysis of a global POI registry, and to facilitate progress in the key defined areas of research.

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KEYWORDS
Premature ovarian insufficiency; hormone therapy; cardiometabolic health; bone health; cognitive health; reproductive health; fertility; oocyte donation

Introduction

The development and diagnosis of premature ovarian insufficiency (POI) in a young woman has potentially life-changing physical and emotional consequences for the sufferer. It is therefore surprising that there has been relatively little expenditure of global resources to fully understand what causes this condition and how to optimally manage the many sequelae of a premature cessation of ovarian activity resulting in a chronic hypoestrogenic state. There is still ongoing controversy in the nomenclature used to describe this condition. Fuller Albright, a Harvard endocrinologist, first described the condition as primary ovarian insufficiency to indicate that the 'primary' defect was within the ovary. The view of the International Menopause Society and others is that it should be referred to as 'premature ovarian insufficiency', although many still refer to it as primary ovarian insufficiency, premature ovarian failure, and premature menopause. The term 'premature ovarian insufficiency' is recommended because 'premature' encompasses both spontaneous and iatrogenic conditions, and 'insufficiency', rather than failure, reflects the possibility of some intermittent ovarian activity, which can result in ovulation and even pregnancy. There has also been controversy regarding the precise diagnostic criteria and optimal management options. All of these factors often lead to a delay in the diagnosis and effective treatment of POI. The International Menopause Society has therefore commissioned a number of experts for this White Paper to define the state of the art in the understanding of this condition and to propose practical management and future research strategies.

The topics discussed in this White Paper include: Demographics and etiology; Pathophysiology and causes; Presentation and diagnosis; Psychosexual and psychosocial health; Cardiometabolic health; Bone health; Cognitive health; Reproductive health; Practical management; POI registry; Executive summary; and Conclusion.

Demographics and etiology of premature ovarian insufficiency

POI, or hypergonadotropic hypogonadism, refers to loss of ovarian activity that occurs under the age of 40 years. It may be associated with intermittent resumption of ovarian

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human reproduction update

Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis

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TABLE OF CONTENTS

BACKGROUND: Polycystic ovary syndrome (PCOS) is associated with cardiometabolic disease, but recent systematic reviews and meta-analyses of longitudinal studies that quantify these associations are lacking.

OBJECTIVE AND RATIONALE: Is PCOS a risk factor for cardiometabolic disease?

SEARCH METHODS: We searched from inception to September 2019 in MEDLINE and EMBASE using controlled terms (e.g. MESH) and text words for PCOS and cardiometabolic outcomes, including cardiovascular disease (CVD), stroke, myocardial infarction, hypertension (HT), type 2 diabetes (T2D), metabolic syndrome and dyslipidaemia. Cohort studies and case–control studies comparing the prevalence of T2D, HT, fatal or non-fatal CVD and/or lipid concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) between women with and without PCOS of ≥18 years of

age were eligible for this systematic review and meta-analysis. Studies were eligible regardless of the degree to which they adjusted for confounders including obesity. Articles had to be written in English, German or Dutch. Intervention studies, animal studies, conference abstracts, studies with a follow-up duration less than 3 years and studies with less than 10 PCOS cases were excluded. Study selection, quality assessment (Newcastle–Ottawa Scale) and data extraction were performed by two independent researchers.

OUTCOMES: Of the 5971 identified records, 23 cohort studies were included in the current systematic review. Women with PCOS had increased risks of HT (risk ratio (RR): 1.75, 95% CI 1.42 to 2.15), T2D (RR: 3.00, 95% CI 2.56 to 3.51), a higher serum concentration of TC (mean difference (MD): 7.14 95% CI 1.58 to 12.70 mg/dl), a lower serum concentration of HDL-C (MD: −2.45 95% CI −4.51 to −0.38 mg/dl) and increased risks of non-fatal cerebrovascular disease events (RR: 1.41, 95% CI 1.02 to 1.94) compared to women without PCOS. No differences were found for LDL-C (MD: 3.32 95% CI −4.11 to 10.75 mg/dl), TG (MD 18.53 95% CI −0.58 to 37.64 mg/dl) or coronary disease events (RR: 1.78, 95% CI 0.99 to 3.23). No meta-analyses could be performed for fatal CVD events due to the paucity of mortality data.

WIDER IMPLICATIONS: Women with PCOS are at increased risk of cardiometabolic disease. This review quantifies this risk, which is important for clinicians to inform patients and to take into account in the cardiovascular risk assessment of women with PCOS. Future clinical trials are needed to assess the ability of cardiometabolic screening and management in women with PCOS to reduce future CVD morbidity.

Key words: cardiometabolic health / polycystic ovary syndrome / hypertension / type two diabetes mellitus / dyslipidaemia / systematic review / meta-analysis / long term

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine condition in women of reproductive age and has been suggested as a risk factor for cardiometabolic disease. Depending on which diagnostic criteria are applied, approximately 6–10% of the women of reproductive age are affected by PCOS. PCOS is diagnosed based on the presence of a combination of clinical signs of menstrual irregularities or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries. It is often diagnosed in the reproductive phase of life when women with PCOS are confronted with infertility, or because of symptoms of hyperandrogenism, including acne, alopecia androgenica and hirsutism (McLuskie and Newth, 2017).

PCOS has been suggested to be a specific female reproductive risk factor for cardiometabolic diseases such as type 2 diabetes (T2D), myocardial infarction and stroke, which are the leading causes of death in women (Dokras, 2013; Harvey *et al.*, 2015). Obesity, one of the major modifiable risk factors for cardiometabolic disease, frequently co-occurs with PCOS: approximately half of the women with PCOS are obese (Figure 1) (Glueck *et al.*, 2005; Rojas *et al.*, 2014). However, there is no evidence that PCOS is caused by obesity (Legro, 2012). Both obesity and PCOS are linked to a higher metabolic and cardiovascular disease (CVD) risk, but there is conflicting evidence whether these are independent associations (Moran *et al.*, 2010; Karabulut *et al.*, 2012). Insulin clamp studies have shown that women with PCOS also have intrinsic insulin resistance, independent of weight, suggesting a higher T2D risk, even in the absence of obesity (Stepto *et al.*, 2013; Cassar *et al.*, 2016).

Current evidence regarding PCOS and cardiometabolic risk is mostly extracted from cross-sectional studies, comparing cardiometabolic risk factors, such as elevated blood pressure, hyperglycaemia and dyslipidaemia, between women with and without PCOS, providing information about associations (Moran *et al.*, 2010; Wild *et al.*, 2011). The current systematic review and meta-analysis evaluates all evidence from observational longitudinal studies comparing cardiometabolic risk factors, and fatal and non-fatal CVD events in women with and without PCOS.

Methods

Study design

This systematic review and meta-analysis is conducted following the PRISMA guidelines and recommendations of the Cochrane collaboration (Moher *et al.*, 2009; Higgins, 2011). The study protocol was published in PROSPERO on 15 July 2015 (Registration number: PROSPERO 2015 CRD42015023765).

Data sources

A medical information specialist (J.L.) performed a systematic search in OVID MEDLINE and OVID EMBASE from inception to 2 September 2019, to identify studies that reported the longitudinal association between PCOS and hypertension (HT), T2D and serum concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs), as well as (non)fatal cardiovascular events (myocardial infarction, stroke). The search consisted of controlled terms (e.g. MESH) and text words for PCOS, and cardiometabolic outcomes, including CVD, stroke, myocardial infarction, HT, T2D, metabolic syndrome and dyslipidaemia. The retrieved records were imported in ENDNOTE X7.5 and duplicate records were removed. Cited and citing references of the included studies were screened for additional relevant publications. The complete search is presented in Supplementary Data A.

Study selection

Cohort studies and case–control studies comparing the prevalence of HT, T2D, fatal or non-fatal cardiovascular events and/or lipid concentrations (TC, HDL-C, LDL-C and TG) between a group of women with, and a control group without, PCOS of ≥18 years of age were eligible for this systematic review and meta-analysis. The identification of PCOS cases could be based on: the National Institutes of Health (NIH) 1990 (Zawadzki and Dunaif, 1992), androgen excess (AE)-PCOS (Azziz *et al.*, 2009) and Rotterdam 2003 criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004);

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European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis

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ABSTRACT

Introduction: Worldwide, it is estimated that about 1.3 million new gynecological cancer cases are diagnosed each year. For 2018, the predicted annual totals were cervix uteri 569,847, corpus uteri 382,069, ovary 295,414, vulva 44,235 and vagina 17,600. Treatments include hysterectomy with or without bilateral salpingo-oophorectomy, radiotherapy and chemotherapy. These can result in loss of ovarian function and, in women under the age of 45, early menopause.

Aim: The aim of this position statement is to set out an individualized approach to the management, with or without menopausal hormone therapy, of menopausal symptoms and the prevention and treatment of osteoporosis in women with gynecological cancer.

Materials and methods: Literature review and consensus of expert opinion.

Summary recommendations: The limited data suggest that women with low-grade, early-stage endometrial cancer may consider systemic or topical estrogens. However, menopausal hormone therapy may stimulate tumor growth in patients with more advanced disease, and non-hormonal approaches are recommended. Uterine sarcomas may be hormone dependent, and therefore estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-hormonal strategies should be used. The limited evidence available suggests that menopausal hormone therapy, either systemic or topical, does not appear to be associated with harm and does not decrease overall or disease-free survival in women with non-serous epithelial ovarian cancer and germ cell tumors. Caution is required with both systemic and topical menopausal hormone therapy in women with serous and granulosa cell tumors because of their hormone dependence, and non-hormonal options are recommended as initial therapy. There is no evidence to contraindicate the use of systemic or topical menopausal hormone therapy by women with cervical, vaginal or vulvar cancer, as these tumors are not considered to be hormone dependent.

1. Introduction

Worldwide, it is estimated about 1.3 million new gynecological cancer cases are diagnosed each year. For 2018 the predicted annual totals were cervix uteri 569,847, corpus uteri 382,069, ovary 295,414, vulva 44,235 and vagina 17,600 [1].

Depending on tumor type and stage, treatments include hysterectomy with or without bilateral salpingo-oophorectomy, radiotherapy and chemotherapy. These can result in loss of ovarian function and, in women under the age of 45, early menopause, which increases the risk not only of osteoporosis but also of cardiovascular disease and cognitive decline [2,3]. Surgically induced menopause often leads to the immediate onset of vasomotor symptoms, which may be more severe than after natural menopause [4]. Vasomotor symptoms may last

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for many years after natural or surgical menopause [5–7]. Other symptoms, such as those related to vulvovaginal atrophy, are lifelong [8,9].

The management of menopausal symptoms in gynecological cancer survivors depends on their age, tumor type and stage, as well as the use of anti-estrogen therapies (for cancers considered to be hormone dependent) and concomitant morbidities. The aim of this position statement is to provide an individualized approach to the management of menopausal symptoms and the prevention and treatment of osteoporosis [10].

2. Hormonal and non-hormonal management strategies

In women without cancer, administration of systemic estrogen-based menopausal hormone therapy for menopausal symptoms and osteoporosis has a favorable risk–benefit profile for those under the age of 60 years or up to 10 years after menopause [8,11–14]. Systemic menopausal hormone therapy can be administered orally or transdermally. Estrogen alone is given to women who have undergone hysterectomy. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for women with an intact uterus to limit the increase in risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen [8,15]. Tibolone is a synthetic steroid compound that is, in itself, inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as menopausal hormone therapy [16]. Availability of different menopausal hormone therapy preparations varies worldwide.

In women with early or premature menopause, systemic estrogen-based menopausal hormone therapy is recommended at least until the average age of natural menopause. Anecdotally, young women may need higher doses of estrogen initially to alleviate menopausal symptoms than their older counterparts [12]. Some young women may find taking combined oral contraception more acceptable. Menopausal hormone therapy at very low doses or non-estrogen-based therapies should be considered for older women [12]. Symptoms due to vulvovaginal atrophy can be managed with low-dose topical estrogen. There are no data on the use of ospemifene or prasterone in this context [17,18].

The efficacy and safety of different regimens have not been examined in many studies of the use of systemic menopausal hormone therapy after gynecological cancer. While the data regarding the use of topical vaginal estrogen after gynecological cancer are sparse, it must be remembered that with current low-dose options, for example estradiol (10 μg twice weekly), absorption is very low and estrogen levels remain in the postmenopausal range [19]. The total administered vaginal dose per year is similar to one daily dose of systemic oral therapy, that is 1 mg.

In women who are taking anti-estrogenic therapies such as aromatase inhibitors, estrogen-based therapies are contraindicated [20]. Here, non-hormonal options are recommended as initial therapy. For vasomotor symptoms the pharmacological options include selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, clonidine and gabapentin. Clinicians should be aware of potential drug interactions with anticancer and adjuvant therapies [see for example 21 and 22]. Cognitive behavioral therapy may also improve menopause symptoms [23]. For problems related to vulvovaginal atrophy, a variety of lubricants and bioadhesive moisturizers are available. Laser therapy for vulvovaginal atrophy is a new approach, but larger, long-term studies are required to explore its efficacy and safety before definite conclusions can be drawn [12].

The main pharmacological options to consider for the prevention and treatment of osteoporosis are bisphosphonates, denosumab and parathyroid hormone [12]. As calcium and vitamin D play a key role in bone metabolism, correction of nutritional deficiencies is advised as part of osteoporosis management [24]. Strategies need to be holistic and include maintaining a healthy weight, diet, exercise and lifestyle [25,26]. This statement will not consider herbal supplements and botanicals as there is a lack of data regarding safety and efficacy [27]. In addition, some products may contain compounds with estrogenic activity or may interact with anticancer therapies.

3. Management options by tumor type

3.1. Endometrial cancer

While most cases of endometrial cancer are diagnosed after the menopause it can occur in younger women, such as those with Lynch syndrome or polycystic ovary syndrome or who are obese. The majority of endometrial cancers are diagnosed at an early stage (Federation of Gynecology and Obstetrics (FIGO) stage I–II) and so have a good overall prognosis, with a 5-year survival rate of over 85 %. Treatment usually involves hysterectomy and bilateral oophorectomy. Studies of menopausal hormone therapy after endometrial cancer are limited to one randomized trial undertaken in 1236 women recruited between 1997 and 2003 with a mean follow-up of 35.7 months [28] and small observational retrospective cohort or case-control studies [29–35]. All studies were undertaken in women with early-stage disease. The randomized trial did not specify which type of menopausal hormone therapy was used (estrogen alone or estrogen plus progestogen). The observational studies documented a variety of preparations: systemic menopausal hormone therapy with estrogen alone or combined with progestogen delivered orally or transdermally, as well as topical vaginal estrogens. No studies are available for women with Lynch syndrome, who are also at increased risk of other cancers [36].

In 2018 a Cochrane systematic review concluded that there is insufficient high-quality evidence to inform women considering menopausal hormone therapy after treatment of endometrial cancer. However, the evidence does not suggest significant harm after surgical treatment for early-stage disease based on FIGO classification [37]. There is no information available regarding the use of menopausal hormone therapy in higher-stage endometrial cancer. The National Comprehensive Cancer Network Panel states that estrogen replacement is a reasonable option for patients who are at low risk of tumor recurrence, but that initiating such therapy should be individualized and discussed in detail with the patient [38]. Furthermore, if adjuvant treatment is carried out, there should be a 6–12-month waiting period before starting menopausal hormone therapy.

3.1.1. Summary recommendation

Thus, the limited data suggest that women with low-grade, early-stage endometrial cancer may consider systemic or topical estrogens. However, menopausal hormone therapy may stimulate tumor growth in patients with more advanced disease or high-risk early-stage tumors, and non-hormonal approaches to management of menopausal symptoms are recommended. In addition, there are no long-term data regarding the safety of menopausal hormone therapy in women with Lynch syndrome, who are also at increased risk of other cancers whose treatment may lead to premature or early menopause. With regard to atypical endometrial hyperplasia, it would not be unreasonable to consider menopausal hormone therapy in women who have undergone hysterectomy, despite the paucity of data.

3.2. Uterine sarcoma

Stromal or mesenchymal sarcomas are rare tumors, accounting for less than 5 % of all uterine cancers. While most cases are diagnosed after the menopause, these tumors can occur in younger women. The most common types are low-grade endometrial sarcomas, high-grade endometrial sarcomas, undifferentiated uterine sarcomas and uterine leiomyosarcomas [38]. As these tumors may be hormone dependent, estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-

hormonal strategies should be used for the management of menopausal symptoms and the prevention and treatment of osteoporosis. Low-grade stromal sarcomas may be sensitive to aromatase inhibitors or progestogens (such as megestrol acetate or medroxyprogesterone acetate). Gonadotropin-releasing hormone analogues are also an option. Randomized controlled trials have shown that progestogens are effective in treating hot flushes [39,40]. There are no data regarding the use of menopausal hormone therapy in non-hormone-dependent tumors. In addition, there are no studies regarding the use of menopausal hormone therapy in smooth muscle tumors of uncertain malignant potential [41].

3.2.1. Summary recommendation

Uterine sarcomas may be hormone dependent, and therefore estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-hormonal strategies should be used. No clinical trial data are available to inform practice in women whose tumors are steroid receptor negative or who have smooth muscle tumors of uncertain malignant potential.

3.3. Ovarian, fallopian tube and peritoneal cancers

The three major types of ovarian cancer are epithelial, accounting for 90 % of cases, germ cell (3 %), and sex cord-stromal (2 %) [42]. As fallopian tube cancer, primary peritoneal cancer and epithelial ovarian cancer are indistinguishable and share the same genomic signature, the three are considered together.

Epithelial, fallopian tube and peritoneal cancer. While these cancers often occur after the menopause, they also affect a significant number of premenopausal women [43–45].

Epithelial cancers are subdivided into five histotypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma [46,47]. The different histotypes are now considered to be different diseases. While serous tumors are mostly high grade, which are characterized by involvement of both ovaries, aggressive behavior, late-stage diagnosis, and low survival rates, the other subtypes tend to affect only one ovary. It is thought that serous tumors originate in the epithelial cells of the fallopian tube as microscopic preliminary lesions that subsequently migrate to the ovaries and/or peritoneum. However, endometrioid and clear cell tumors are thought to originate in the endometrium, and mucinous tumors in the ovaries or fallopian tube peritoneal junction. One of the risk factors for ovarian cancer is prior use of menopausal hormone therapy but the association appears to be confined to serous and endometrioid histotypes [48].

Two randomized trials as well as prospective and retrospective cohort and case-control studies have shown no adverse effect menopausal hormone therapy on survival in women who have been treated for ovarian cancer [49–55]. They used a variety of regimens: estrogen alone or combined with a progestogen or testosterone. The randomized trial by Guidozzi and Daponte, in which 130 women with invasive epithelial ovarian carcinoma were followed up for 48 months, used oral continuous conjugated equine estrogen. It did not distinguish between sub-types [49]. The authors reported median overall survival of 44 months (95 % CI, 10–112 months) and 34 months (95 % CI, 8–111 months) in the menopausal hormone therapy and control groups respectively. The differences in disease-free interval ($P = 0.785$) and overall survival ($P = 0.354$) between the two groups were not statistically significant. Eeles et al. [50] studied 150 premenopausal and postmenopausal women who had been diagnosed with epithelial ovarian cancer (any FIGO stage) nine or fewer months previously. They were randomized to either menopausal hormone therapy or not for 5 years. The choice of menopausal hormone therapy for individual patients was pragmatic and was determined according to consultant preference, with guidelines to recommend that premenopausal women receive higher doses than perimenopausal/postmenopausal women. The median follow-up of patients still alive was 19.1 years: overall and relapse-free survival was greater in the menopausal hormone therapy than in the control group.

A retrospective cohort study using the Manitoba Cancer Registry and Drug Programs Information Network of 357 women found that use of menopausal hormone therapy ($n = 94$) for non-serous epithelial ovarian cancer was not associated with harm and did not decrease overall or disease-free survival [55]. It found that in menopausal hormone therapy users under 55 years of age, disease-free survival was longer but there was no statistical difference in overall survival for this age group. No associations between menopausal hormone therapy use and overall survival or disease-free survival were found among women aged 55 years or more.

With regard to **endometrioid ovarian cancers**, which are potentially estrogen sensitive, menopausal hormone therapy does not appear to have adverse effects. However, while menopausal hormone therapy appears to be safe in early-stage disease, this may not be the case in women with more advanced cancers, who commonly have residual, potentially hormone-responsive disease after surgery [54,55]. As there is no clear evidence of benefit of aromatase inhibitors in the treatment of **clear cell and mucinous carcinomas**, estrogen replacement is a reasonable option for patients who are at low risk of tumor recurrence, but initiating such therapy should be individualized. Given the benefits seen with maintenance hormone therapy with letrozole, anastrozole, tamoxifen and leuprolide acetate after primary cytoreductive surgery and platinum-based chemotherapy in women with stage II to IV **low-grade serous carcinoma** of the ovary or peritoneum, estrogen-based therapies are currently not recommended in advanced disease of these types [56]. There is a paucity of evidence to inform practice for **high-grade serous carcinoma.**

Borderline malignant tumors or tumors of low malignant potential most often affect younger women. Histological types include serous, mucinous, endometrioid, clear cell and transitional cell (or Brenner) tumor [57]. Five-year survival rates are greater than 98 %. There is a paucity of data regarding the use of menopausal hormone therapy, but it would not be unreasonable to consider it for women with completely resected disease (i.e. without invasive implants). As always, the benefits of menopausal hormone therapy for women who have undergone premature menopause through cancer treatment need to be balanced against the risks.

The ***BRCA1*** **and** ***BRCA2*** **gene mutations** are associated with increased risk of developing invasive epithelial ovarian cancer. Risk-reducing salpingo-oophorectomy is therefore recommended. However, this will lead to early/premature menopause. Data on menopausal hormone therapy after prophylactic oophorectomy are sparse, but short-term use seems to be safe [58]

Ovarian germ cell tumors commonly affect girls and young women between 10 and 30 years of age. In most cases, fertility-preserving staging surgery is followed by platinum-based combination chemotherapy, which may lead to ovarian failure. The prognosis is excellent and 5-year survival is more than 85 % [59]. There is currently no evidence to suggest that these young women should not take menopausal hormone therapy.

Granulosa cell tumors are the most common ovarian sex cord stromal tumors. They secrete steroid hormones and commonly present with symptoms of hyperestrogenism, as they secrete estrogens as well as other hormones. They may have an indolent course and can recur up to 20 years after initial diagnosis. It is generally believed that estrogens should not be used, as these tumors are estrogen-dependent. Hormone recurrence therapy includes aromatase inhibitors, leuprolide and tamoxifen [59]. No study, however, has demonstrated a deleterious effect of menopausal hormone therapy.

3.3.1. Summary recommendation

Menopausal hormone therapy, either systemic or topical, does not appear to be associated with harm and does not appear to decrease

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REVIEW ARTICLE

ANDROLOGY WILEY

European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males

Endorsing organization: European Society of Endocrinology

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Abstract

Background: Evidence regarding functional hypogonadism, previously referred to as 'late-onset' hypogonadism, has increased substantially during the last 10 year.

Objective: To update the European Academy of Andrology (EAA) guidelines on functional hypogonadism.

Methods: Expert group of academicians appointed by the EAA generated a series of consensus recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

Results: The diagnosis of functional hypogonadism should be based on both the presence of clinical symptoms supported by repeatedly low morning fasting serum total testosterone (T) measured with a well-validated assay, after exclusion of organic causes of hypogonadism. Lifestyle changes and weight reduction should be the first approach in all overweight and obese men. Whenever possible, withdrawal/modification of drugs potentially interfering with T production should be advised. Testosterone replacement therapy (TRT) is contraindicated in men with untreated prostate or breast cancer, as well as severe heart failure. Severe low urinary tract symptoms and haematocrit >48%-50% represent relative contraindications for TRT. Prostate-specific antigen and digital rectal examination of the prostate should be undertaken in men >40 years of age before initiating TRT to exclude occult prostate cancer. Transdermal T should be preferred for initiation of TRT, whereas gonadotrophin therapy is only recommended when fertility is desired in men with secondary hypogonadism. TRT is able to improve sexual function in hypogonadal men. Other potential positive outcomes of TRT remain uncertain and controversial.

Conclusion: TRT can reliably improve global sexual function in men with hypogonadism in the short term. Long-term clinical benefits, and safety of TRT in functional hypogonadism, remain to be fully documented. Clinicians should therefore explicitly discuss the uncertainties and benefits of TRT and engage them in shared management decision-making.

[Corrections added on 15 May 2020 after first online publication: Endorsing organization: European Society of Endocrinology has been moved from the footnote to the article byline].

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KEYWORDS

cardiovascular risk, erectile dysfunction, functional hypogonadism, late-onset hypogonadism, libido, obesity, testosterone

1 | INTRODUCTION

The last guidelines on male late-onset hypogonadism (LOH—now more appropriately referred to as functional hypogonadism) from the European Academy of Andrology (EAA) have been published 10 years ago in collaboration with several other international societies.[1] More recently, our understanding of underlying mechanisms of functional hypogonadism as well as of pros and cons of testosterone (T) replacement therapy (TRT) has improved. Comorbidities, obesity and the metabolic syndrome (MetS), amongst other causes (see later), may contribute independently to individual rates and extent of the apparent age-related decline of T observed in middle-aged and elderly men.[2,3] Thus, the emergent condition of functional hypogonadism, in contradistinction to the organic or classical hypogonadism, is gaining credence as a defined clinical entity and diagnosis.[4] According to Grossmann and Matsumoto,[4] functional hypogonadism (also referred to as late-onset, age-related or adult-onset hypogonadism) is defined as the coexistence of androgen deficiency-like features and low serum T concentrations occurring in the absence of both intrinsic structural hypothalamic-pituitary-testis (HPT) axis pathology and of specific pathologic conditions suppressing the HPT axis (such as microprolactinoma, endogenous Cushing syndrome) in middle-aged or older men. The community prevalence estimates of potentially functional hypogonadism in middle-aged and older men vary from 2.1% to 12.3%.[4] Functional hypogonadism may be potentially reversible if the underlying causes are identified and adequately treated or removed, whereas organic hypogonadism is generally an irreversible condition secondary to genetic faults or pathological perturbations of the HPT axis.[4] The EAA largely agrees with the guidelines of the United States (US) Endocrine Society[5] on the diagnosis and treatment of organic or classical hypogonadism.

The Testosterone trials (TTrials), a coordinated set of seven placebo-controlled randomized clinical trials (RCTs), recently provided evidence of moderate efficacy of TRT for 12 months in a variety of clinical endpoints in elderly men with functional hypogonadism.[6] The EAA recognizes that longer-term patient-important clinical benefits and potential adverse effects of TRT in older men remain controversial.[7] This latter is further highlighted by potential safety concerns, raised in the US, with respect to increased cardiovascular (CV) risks associated with the prescription of T in older men.[7]

The aim of the present paper is to provide a European perspective, based largely on high-quality RCTs and meta-analyses, on late-onset/functional (rather than classical/organic) hypogonadism. In this respect, only adult hypogonadism, including fertility issues, will be considered

SUMMARY OF RECOMMENDATIONS

Recommendation #01. We recommend the diagnosis of functional hypogonadism only on the basis of the presence of clinical symptoms or signs of T deficiency in combination with consistently low morning serum T concentrations (1⊕⊕⊕○) (see also recommendation #04).

Recommendation #02. We recommend against universal screening for hypogonadism in middle-aged or older men, by structured interviews or questionnaires and/or random total T measurements (1 ⊕⊕○○).

Recommendation #03. We recommend that the clinical diagnosis of functional hypogonadism should be confirmed by measurement of serum total T with a well-validated assay on fasting morning (before 11 AM) blood samples obtained on two different days (1 ⊕⊕⊕○).

Recommendation #04. Functional hypogonadism should be diagnosed only after exclusion of organic causes of hypogonadism. In addition, to morning total T, luteinizing hormone (LH) should be measured in all patients with suspected functional hypogonadism to differentiate between the primary and secondary causes (1⊕⊕⊕○).

Recommendation #05. We recommend either measuring or calculating free T (fT), in addition to total T, in patients with conditions that alter sex hormone-binding globulin (SHBG)and when total T concentrations are in the borderline range (~8-12 nmol/L) if the clinical suspicion of hypogonadism is strong(1 ⊕⊕⊕○).

Recommendation #06. We recommend lifestyle changes, incl-uding physical exercise and weight reduction, in overweight and obese men with functional hypogonadism since weight loss may increase T concentrations (1⊕⊕⊕○).

Recommendation #07. We suggest withdrawal/modification of drugs (eg opiates, anabolic steroids, glucocorticoids) potentially interfering with T production, when clinically permissible (2⊕⊕⊕○).

Recommendation #08. We suggest the use of transdermal T, as the preferred preparation in the initiation of TRT for functional hypogonadism (2 ⊕⊕○○).

Recommendation #09. We recommend gonadotrophin therapy in men with secondary hypogonadism only when fertility is desired (1⊕⊕⊕⊕).

Recommendation #10. We recommend TRT in hypogonadal men with sexual/erectile dysfunction(ED) to improve libido, erectile function and sexual satisfaction (1⊕⊕⊕⊕).

Recommendation #11. We recommend against TRT as a treatment for weight reduction in obese men (1 ⊕⊕○○).

Recommendation #12. We recommend against TRT to improve glycometabolic control in men with type 2 diabetes (T2DM) and/or metabolic syndrome (MetS) (1⊕⊕○○).

Recommendation #13. We recommend against TRT for the sole purpose of reducing fracture risk in hypogonadal men with high fracture risk (1 ⊕⊕⊕○).

Recommendation #14. We recommend against TRT for the sole treatment to improve depressive symptoms in hypogonadal men (1 ⊕⊕○○).

Recommendation #15. We recommend against the use of TRT, in the absence of symptomatic hypogonadism, to improve morbidity and/or mortality of several chronic diseases including human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS), heart failure, obstructive pulmonary disease, chronic kidney diseases, bowel inflammatory diseases or to prevent the long-term outcomes of subjects chronically treated with glucocorticoid or opioid therapy (2 ⊕⊕○○).

Recommendation #16. We recommend against routinely prescribing T to men >65 years as an anti-ageing therapy (1 ⊕⊕⊕⊕).

Recommendation #17. We recommend against TRT in frail men to improve exercise capacity/physical function (1 ⊕⊕⊕○).

Recommendation #18. We recommend against TRT in ageing men to improve cognitive function (1 ⊕⊕⊕○).

Recommendation #19. We recommend against TRT in men with untreated prostate or breast cancer (Good Clinical Practice statement).

Recommendation #20. We recommend, before initiation of TRT in men >40 years of age, discussing potential benefits and risks of prostate cancer screening and engaging the patient in shared decision-making regarding options for pre-treatment screening and on-treatment monitoring (see *Recommendations #21*, *#22*, *#31*, *#32*). These discussions should also take into account local guidelines for prostate cancer screening for the general population (Good Clinical Practice statement).

Recommendation #21. We recommend, before initiation of TRT in men >40 years of age, checking prostate-specific antigen (PSA) and performing digital rectal examination (DRE) of the prostate in order to minimize the risk of prescribing T to patients with undiagnosed prostate cancer(1⊕⊕○○).

Recommendation #22. We recommend against TRT in men with PSA > 4 ng/mL (or elevated PSA according to local/national guidelines) or prostate abnormalities on DRE without further evaluation and/or urological consultation (1⊕⊕○○).

Recommendation #23. We suggest that TRT should not be used in men with severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPPS) >19] (2⊕○○○).

Recommendation #24. We recommend against TRT in men with severe heart failure [New York Heart Association (NYHA) Class III or IV] (1⊕⊕○○).

Recommendation #25. We suggest against TRT in patients with a recent major acute CV event (including stroke) (2⊕⊕○○).

Recommendation #26. We suggest against TRT in men with documented polycythaemia and/or elevated haematocrit (>48%-50%) depending on CV risk and associated morbidities without further evaluation (2⊕⊕○○).

Recommendation #27. We suggest obtaining a detailed personal and family history of venous thromboembolism (VTE) and risk factors for VTE prior to initiating TRT (2⊕○○○).

Recommendation #28. We recommend against TRT in hypogonadal men who desire fertility (1⊕⊕⊕⊕).

Recommendation #29. We recommend assessing the clinical response as well as adverse effects to TRT at 3 and 12 months after initiation of treatment. Thereafter, clinical review should be scheduled at least yearly (1⊕⊕⊕⊕).

Recommendation #30. We suggest that on-treatment serum total T concentrations should be measured at each clinic visit to ensure that average total T concentrations achieve the targeted mid-normal range for young men (2 ⊕⊕○○).

Recommendation #31. We suggest performing digital rectal examination and checking PSA at 3 to 12 months for men >40 years of age after initiating T treatment. After the first 12 months, local guidelines for prostate cancer screening for the general population should be followed (2⊕○○○).

Recommendation #32. We suggest further evaluation and/or urological consultation if there is: (a) an increase in serum PSA concentration > 1.4 ng/mL within 12 months of initiating T treatment, (b) a confirmed PSA > 4 ng/ml at any time and (c) detection of a prostatic abnormality on DRE or a substantial worsening of LUTS(2⊕○○○).

Recommendation #33. We recommend measuring the haematocrit (Hct) 3-6 months after initiation of TRT and then annually. If Hct is >54%, TRT should be discontinued until Htc decreases to a safe level; evaluate the patient for hypoxia and sleep apnoea; consider reinitiating TRT with a reduced dose(1 ⊕⊕⊕⊕).

in the present guidelines. Delayed puberty and induction of secondary sexual development in adolescent patients will not be included.

2 | METHODS

The EAA guidelines committee commissioned an expert task force of academicians to update the previous guidelines on LOH published in 2009.[1]

Following scrutiny and discussion of the best evidence from published literature available in PubMed, the authors, comprising an expert group of academicians appointed by the EAA, generated a series of consensus recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.[8] In particular, according to GRADE, the number '1' denotes a strong recommendation and is expressed with the phrase 'we recommend', whereas the number '2' denotes a weaker recommendation and it is expressed with the phrase 'we suggest'. The quality of evidence is expressed through graphical descriptions: ⊕○○○denotes 'very low-quality evidence', ⊕⊕○○'low quality', ⊕⊕⊕○'moderate quality' and ⊕⊕⊕⊕ 'high quality'.

2.1 | Diagnosis

2.1.1 | Recommendations

Recommendation #01: We recommend the diagnosis of functional hypogonadism only on the basis of the presence of clinical symptoms and signs of T deficiency in combination with consistently low morning serum T concentrations (1 ⊕⊕⊕○) (see also *recommendation #04*).

Recommendation #02: We recommend against universal screening for hypogonadism in middle-aged or older men, by structured interviews or questionnaires and/or random total T measurement (1 ⊕⊕○○).

TABLE 1 Symptoms and signs that may be associated with functional hypogonadism

Specific symptoms
• Reduced libido • Decreased spontaneous erections • Erectile dysfunction
Less specific symptoms
• Decreased energy • Decreased physical strength/function/activity • Decreased motivation • Low mood • Decreased concentration • Hot flushes
Less specific signs
• Loss of body/facial hair • Decreased testicular volume • Increased body fat/reduced muscle mass • Osteoporosis/low bone density • Central obesity

2.1.2 | Evidence

Functional hypogonadism may present with clinical symptoms or signs similar to classical hypogonadism (Table1). Unlike classical hypogonadism, functional hypogonadism usually presents a more subtle clinical picture, with non-specific symptoms and usually no overt signs of androgen deficiency. Furthermore, these symptoms often overlap with those arising from co-existing co-morbidities and the effects of ageing in older men.[9] Nevertheless, sexual complaints, such as decreased libido, morning erections or erectile dysfunction (ED), were more frequently associated with low T in community-dwelling middle-aged and elderly European men.[10] Similar results were confirmed in a large cohort of patients presenting to a specialized sexual medicine clinic with ED.[11] In contrast, psychological or physical symptoms/signs were not significantly associated with low T concentrations.[10,11]

Obesity and in particular central obesity are frequently associated with functional hypogonadism, which is potentially reversible, for instance, following weight reduction.[12] Conversely, other clinical signs typically associated with classical hypogonadism, such as reduced testis volume, are less common (1).

2.1.3 | Values

For the clinical diagnosis of hypogonadism, we place a higher value on the presence and severity of sexual symptoms, particularly low libido and lower values on more non-specific symptoms such as lack of energy/fatigue, poor memory/concentration or decreased physical strength/function/mobility (Figure 1).

We also highly value the recognition of obesity of all grades, but particularly World Health Organization (WHO) class III, as a major and increasingly common cause of low T (total T—see later) in middle-aged and elderly men, since this is reversible after weight reduction, consequently also bringing multiple additional health benefits.

2.1.4 | Remarks

Self-reported questionnaire or structured interviews have poor specificity and should not be used for population screening of hypogonadism. It remains important to regularly reassess the diagnosis of functional hypogonadism, especially in the presence of reversible conditions (see below) that may temporarily lower T.

2.2 | T measurements

2.2.1 | Recommendations

Recommendation #03: We recommend that the clinical diagnosis of functional hypogonadism should be confirmed by

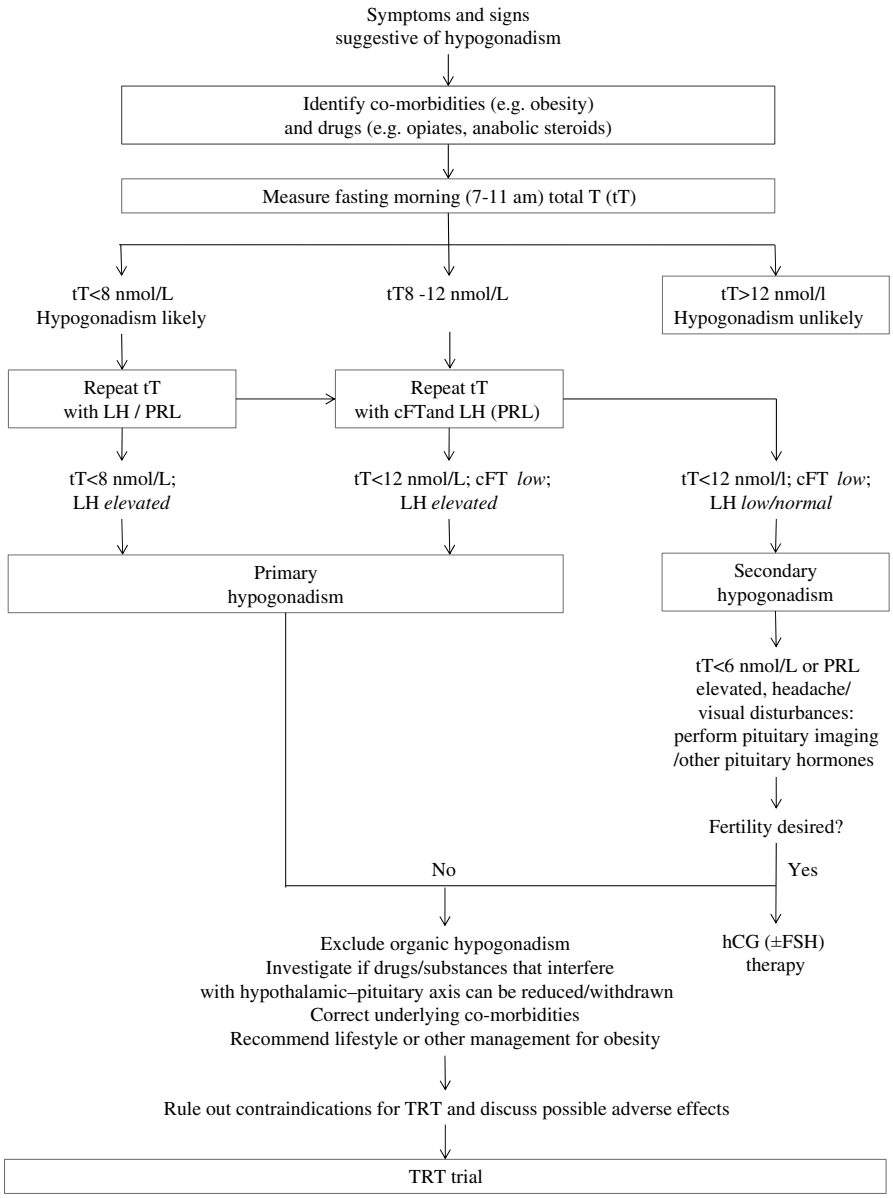

FIGURE 1 Proposed flow chart to correctly diagnose and manage functional hypogonadism. cFT, calculated free testosterone; FSH, follicular-stimulating hormone; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; PRL, prolactin; T, testosterone; TRT, testosterone replacement therapy

measurement of serum total T with a well-validated assay on fasting morning (before 11 AM) blood samples obtained on two different days (1 ⊕⊕⊕○).

2.2.2 | Evidence

T concentrations show significant diurnal as well as considerable day to day intra-individual variation in men.[13] T concentrations may also be temporarily decreased during acute illness or due to medication use.[14] Moreover, T may be lowered following ingestion of glucose or food.[15]

The most accurate and precise method for determination of T concentrations is liquid chromatography-tandem mass spectrometry (LC-MS/MS). However, this preferred method of choice is not universally available (due to financial and technical constraints) at present. Most laboratories continue to employ automated platform T immunoassays, which, if well-standardized, can show high correlation with LC-MS/MS within the adult male T range although they offer less precision in the hypogonadal range.[16]

The exact T concentration below which a diagnosis of functional hypogonadism can be confidently made remains elusive and controversial. Recently, T concentrations in healthy men were harmonized internationally between several large population cohorts in the US and Europe using a reference LC-MS/MS method.[17] The harmonized lower limits of the reference range for T in healthy, non-obese young men (aged 19-39 years) were 9.2 nmol/L (264 ng/dL) and 10.5 nmol/L (303 ng/dL) using, respectively, the 2.5th and 5th percentiles.[17] In the European Male Ageing Study (EMAS) (men aged 40-79 years), higher prevalence of sexual symptoms (poor morning erections, decreased libido, and ED) was associated with T concentrations <11 nmol/L (<320 ng/dL) after adjustment for age.[10] Available evidence derived from meta-analyses suggests less benefits of TRT in subjects with total T > 12 nmol/L (>350 ng/dL) and higher efficacy in patients with lowest T (T < 8 nmol/L; <231 ng/dL; Refs. [18,19]; see below).

Hence, there appears to be some degree of consistency pointing to the lower limit of normality of T concentrations being in the range of 8-12 nmol/L (231-350 ng/dL).

2.2.3 | Values

To minimize the above-mentioned biological variability in circulating T concentration in order to improve diagnostic precision, we place a high value in recommending that T should be measured in the fasting state between 7 and 11 AM on at least two different days. In addition, measurement of T during acute illness should be avoided.

Hypogonadism is highly unlikely with T values >12 nmol/L (>350 ng/dL; Figure 1) but more likely in patients with T concentrations consistently <8 nmol/L (<231 ng/dL). The lower the T concentration below the lower limit of the reference range, the higher is the likelihood that symptoms will be explained by testosterone deficiency. In those patients with borderline T concentrations between 8-12 nmol/L (231-350 ng/dL), a clear diagnosis cannot be confidently established, but free T (fT) measurements can often be helpful in this situation (see Section 6).

2.2.4 | Remarks

Due to significant inter-laboratory variations in T measurements, clinicians and clinical biochemists should ensure that their laboratories measure T concentrations with a reliable assay (either LC-MS/MS or immunoassay), that is regularly standardized by an accuracy-based (rather than peer-based) external quality assurance scheme, preferably calibrated against an internationally harmonized reference range.[17]Clinicians have a duty to seek assurance on the best quality of T results from their laboratories and demand improvements if necessary. Individual T results should be interpreted against a reference range established by regional laboratories in healthy men from a representative local general population. Although T concentrations decline with age,[10] there is currently insufficient evidence from prospective population data or clinical experience to support the use of an age-stratified reference interval (Z-score approach) for T, as suggested by the Endocrine Society of Australia.[20]

2.3 | Differential diagnosis

2.3.1 | Recommendations

Recommendation #04: Functional hypogonadism should be diagnosed only after exclusion of organic causes of hypogonadism. In addition to morning total T, luteinizing hormone (LH) should be measured in all patients with suspected functional hypogonadism to differentiate the primary from secondary causes (1⊕⊕⊕○).

2.3.2 | Evidence

The differential diagnosis between primary and secondary hypogonadism is essential for functional as well as classical hypogonadism. Most cases of functional hypogonadism have secondary or mixed hypogonadism with low to normal luteinizing hormone (LH; Table 2). Primary hypogonadism with elevated LH and even more follicle-stimulating hormone (FSH) indicating testicular failure is more commonly related to classical hypogonadism (Figure 1). However, functional testicular failure is possible in the elderly (>70 years), especially in association with co-morbidities.[21] Conversely, co-morbidities, and obesity in particular, are frequently associated with secondary hypogonadism.[21]

2.3.3 | Remarks

If organic secondary hypogonadism is suspected, further investigations should include magnetic resonance imaging (MRI) scanning of the pituitary-hypothalamus, iron saturation and prolactin measurement as well as determination of other pituitary hormones. The overall cost-effectiveness of MRI scanning (finding major lesions that requires intervention), in the absence of clinical evidence of pituitary mass effects such as visual disturbances, headache or hyperprolactinaemia, is relatively low, but should be considered when T concentrations are <6 nmol/L (<175 ng/dL) (Refs. [22,23]; Figure 1). However, it is important to recognize that underlying causes (potentially reversible or treatable) are often not identifiable in subjects with functional hypogonadism, and it may not always be possible to completely exclude occult organic abnormalities, even after appropriate investigations.

2.4 | Role of fT

2.4.1 | Recommendations

Recommendation #05: We recommend either measuring or calculating fT, in addition to total T, in patients with conditions that alter sex hormone-binding globulin (SHBG), and when total T concentrations are in the borderline range (8-12 nmol/L; 231-350 ng/dL), if the clinical suspicion of hypogonadism is strong (Table 3; 1⊕⊕⊕○).

2.4.2 | Evidence

Several clinical conditions and medications (Table 3) can substantially modify SHBG concentration, contributing to difficulties in interpreting total T results. Obesity, for instance, is frequently associated with insulin resistance, low SHBG concentration and hence low total T (but fT remains normal); this may spuriously lead to a diagnosis of functional hypogonadism in many symptomatic obese men (see below).[24] Recent data indicate that in obese men with apparent functional secondary hypogonadism, a decrease

TABLE 2 Causes of hypogonadism

Primary hypogonadism
Organic or classical
• Congenital: anorchia, Klinefelter syndrome and other chromosomal abnormalities, myotonic dystrophy, defects of testosterone biosynthesis, disorders of sex differentiation (gonadal dysgenesis),cryptorchidism • Acquired: varicocoele, trauma, torsion, surgery, chemotherapy, irradiation, orchitis
Functional
• Ageing • Drug-induced: ketoconazole, aminoglutethimide, mitotane, metyrapone • Chronic systemic diseases • Organ failure • Glucocorticoid excess: iatrogenic, Cushing syndrome • Alcohol abuse
Secondary hypogonadism
Organic or classical
• Congenital: Kallmann syndrome, idiopathic hypogonadotropic hypogonadism, Rathke's cleft cyst, haemochromatosis • Acquired: Traumatic brain injury, cranial or pituitary irradiation/ surgery, pituitary adenomas, hypothalamic tumours(eg craniopharyngiomas, germinomas and other germ tumours), pituitary stalk diseases, inflammatory and infection diseases (eg lymphocytic hypophysitis, infections, granulomatous lesions, sarcoidosis, Langerhans' histiocytosis), iron excess
Functional
• Acute or critical illness • Drug-induced: opioids, glucocorticoids, androgens/ anabolic-androgenic steroids, GnRH analogues, cyproterone acetate, psychotropic drugs causing hyperprolactinaemia • Malnutrition, excessive exercise • HIV/AIDS • Cannabinoid abuse • Obesity, T2DM, co-morbidities, sleep apnoea
Androgen resistance/decreased testosterone bioactivity
Organic or classical
• Congenital: Aromatase deficiency, Kennedy disease, partial or complete androgen insensitivity, 5α-reductase type II deficiency, 17β-hydroxysteroid dehydrogenase III deficiency
Functional
• Drug-induced AR blockade: steroidal anti-androgen (eg cyproterone acetate, spironolactone), non-steroidal anti-androgen (eg flutamide, bicalutamide, nilutamide) • Drug-induced 5α-reductase activity blockade: finasteride, dutasteride • Increased SHBG

Abbreviations: AIDS, acquired immunodeficiency syndrome; AR, androgen receptor; GnRH, gonadotrophin-releasing hormone; ER, oestrogen receptor; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin; T2DM, type 2 diabetes.

of total T is only associated with hypogonadal symptoms, when fT is also low.[25-27] Conversely, elevated SHBG (eg human immunodeficiency virus, HIV; liver disease and old age) may lead to high or normal total T, potentially masking the diagnosis of hypogonadism.[24-27]

2.4.3 | Values

We place a high value on the additional information offered by fT when SHBG is altered, or when T results are in the borderline range 8-12 nmol/L (231-350 ng/dL), especially when clinical suspicion of hypogonadism is strong (Figure 1).

2.4.4 | Remarks

Direct analogue assays are unreliable for the evaluations off T concentrations and should not be used.[28] Measurement of fT by equilibrium dialysis (EqD) remains the most accurate and should ideally be the method of choice.[28,29] However, EqD is technically difficult, expensive and seldom available to physicians. A pragmatic alternative, therefore, is to use calculated fT, with formulae or algorithms based on the binding characteristics of SHBG, and albumin to T. Different calculation methods for estimation of fT concentrations on the basis of total T, SHBG and albumin are available, but the best choice remains controversial.[28] In a recent comparison between calculated and EqD-measured fT, the Vermeulen method,[30] based on the law of mass action equations appeared to be the most consistent albeit with a small but systematic overestimation.[29] It is important to point out that reference ranges for fT (whether directly measured or calculated) have not been validated prospectively in relation to incident outcomes and in RCTs. Only few studies have attempted to correlate fT thresholds with higher prevalence of sexual and physical dysfunctions.[10,11] fT concentrations < 220 pmol/L (<6.3 ng/dL), with a range of 170-240 pmol/L (5.0-7.0 ng/dL), have been suggested to be compatible with a symptomatic androgen deficiency state.[10,11,31-36] Further standardization as well as validation of fT as a definitive marker of hypogonadism is an important task for clinical research in the near future.

TABLE 3 Conditions that may alter serum SHBG and thereby total T concentrations

Decreased SHBG
• Obesity • Glucocorticoids • Androgenic and progestogenic steroids • Nephrotic syndrome • Hypothyroidism • Acromegaly • Polymorphisms in the *SHBG* gene
Increased SHBG concentrations
• Ageing • AIDS/HIV disease • Cirrhosis and hepatitis • Hyperthyroidism • Anticonvulsants • Oestrogens • Polymorphisms in the *SHBG* gene

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SHBG, sex hormone-binding globulin; T, testosterone.

Adapted from Bhasin et al.[5,83]

3 | TREATMENT

3.1 | Lifestyle and concomitant medications

3.1.1 | Recommendations

Recommendation #06. We recommend lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with functional hypogonadism since weight loss may increase T concentrations (1⊕⊕⊕○).

Recommendation #07. We suggest withdrawal/modification of drugs (eg opiates, anabolic steroids and glucocorticoids) potentially interfering with T production, when clinically permissible (2⊕⊕⊕○).

3.1.2 | Evidence

Longitudinal data from the EMAS clearly documented that obesity at the baseline and weight gain during the follow-up increased the risk of developing functional secondary hypogonadism. In men who lost weight during follow-up, in contrast, T often increased with recovery from secondary hypogonadism.[37,38] A meta-analysis of available evidence confirmed that weight loss (obtained by either low-calorie diet of bariatric surgery) improves T concentrations proportionately to the weight loss obtained.[12,39] Similar results have also been reported for physical activity.[39] The mechanisms underlying such functional alterations in the HPT axis have not been completely clarified. However, it is plausible that metabolic disturbances and inflammatory states associated with obesity can directly interfere with T/gonadotrophin secretion at multiple levels.[24,40]

Several drugs may inhibit HPT axis function and impair T production. Other drugs may interfere with androgen receptor-mediated action in target tissues (1). Opioid treatment in men with chronic non-cancer pain (CNCP) is one of the most frequently encountered examples of drug-induced functional hypogonadism.[41,42] Opioid medication withdrawal usually normalizes T concentrations within 1 month.[41] The abuse of anabolic-androgenic steroids (AAS) and, in particular, their withdrawal after long-term use represents another increasingly serious issue, which may not always be immediately apparent unless there is a high level of suspicion and awareness by the clinician.[43] Patients should be informed and reassured that the overwhelming majority of AAS abusers will eventually recover normal gonadal function (may take more than 12 months after prolonged abuse) provided they comply with full abstinence. Clomiphene or human chorionic gonadotrophin (hCG) (attempting to hasten recovery) should not be used, as there is insufficient evidence of efficacy.

3.1.3 | Values

Weight reduction should be the first line of management and strongly encouraged in all overweight and obese men with low T. Significant collateral health benefits may also accrue from these lifestyle changes, potentially offering valuable opportunities for preventative care in middle-aged men. When drugs (prescribed as well as off-label) interfering with HPT axis are identified as the cause of functional hypogonadism, the possible benefit/risk ratio of their withdrawal/modification should be discussed with the patient as well as their primary care physician.

3.2 | Testosterone treatments

3.2.1 | Recommendations

Recommendation #08. We suggest the use of transdermal T, as the preferred preparation in the initiation of TRT for functional hypogonadism (2 ⊕⊕○○).

3.2.2 | Evidence

Several T preparations are available for oral, transdermal and parenteral administration (Rastrelli et al, [44]). Oral T undecanoate (TU) is no longer considered a viable therapeutic option, since its absorption is unpredictable and highly dependent on food intake (Rastrelli et al, [44]). The older T injectable formulations, such as T propionate and enanthate or T ester combinations, may cause wide fluctuations in serum T concentrations, frequently reported as unpleasant mood/energy swings by patients and possibly associated with increased risk of polycythaemia.[44] Nasal preparations, which may cause irritation of nasal mucosa, are not currently available in Europe.[44] T pellet implants, not available in European countries except the UK, require a minor surgical procedure with the risk of extrusion or infections. Presently, long-acting injectable TU and T gels are the most frequently prescribed and acceptable T preparations.[44] TRT for functional hypogonadism is often commenced as a therapeutic trial since the causal relationship between symptoms of hypogonadism, and low T is not always certain at start of treatment. Therefore, a short-acting preparation such as T gel rather than a long-acting depot injection may be more appropriate. Many clinicians also prefer starting TRT with T gel, due to the potentially reversible nature of functional hypogonadism with the need to reassess the patient after treatment interruption. In frail elderly patients with multiple morbidities, in whom the risks of adverse effects are higher, a short-acting gel T preparation at a lower starting dose is advisable.

We, therefore, suggest initiating TRT with a T gel for a period of three to six months in men considered to have functional hypogonadism. The TTrials[6] clearly showed improvement of most symptoms within three months following initiation of T gel treatment and recovery of T concentrations to the mid-normal range. If there is no clinical improvement after six months of sufficient T replacement, TRT should be discontinued and other causes of symptoms or alternate T modalities considered if therapeutic T concentrations have not been consistently achieved (Figure 1). If the patient shows significant clinical benefits, switching to longer-acting T preparations of TRT could

be discussed. It is important for clinicians to discuss frankly with their patients the uncertain risks and benefits of TRT in functional hypogonadism, as well as the pros and cons of available T preparations, in a process of shared decision-making on management choices.[45]

3.2.3 | Values

Due to the potentially reversible nature of functional hypogonadism, we prefer to initiate TRT with short-acting T gel preparations, particularly in older subjects with co-morbidities.

3.2.4 | Remarks

The most important side effect of T gel treatment is the possibility to cross-transfer T to others during contact with the skin's surface. In order to limit this possibility, a higher T concentration preparation (1.6%-2.0%) may be preferred.[44] This modification may allow a reduced amount of gel applied, thereby limiting the transfer risk.[44] A common problem with T gel is the variable transdermal absorption of T resulting in changing T concentrations from day to day. Regular monitoring of on-treatment T concentrations and dosage adjustments is, therefore, advisable. Similar to gels, the long-acting injectable TU has shown a good benefit/safety profile.[44] However, in case of side effects, rapid T withdrawal is not possible.[44] In addition, coughing as a potential sign of pulmonary oil microembolism has been observed following the intramuscular injections of long-acting TU and other esters.[44]

3.3 | Gonadotrophin treatment

3.3.1 | Recommendations

Recommendation #09. We recommend gonadotrophin therapy in men with secondary hypogonadism only when fertility is desired (1⊕⊕⊕⊕).

3.3.2 | Evidence

Testicular function is intact in functional secondary hypogonadism and should respond to exogenous gonadotrophin stimulation. The most widely used preparation is hCG. One meta-analysis on gonadotrophin treatment in patients with organic secondary hypogonadism, showed an overall successful outcome (defined as the appearance of at least one spermatozoon in the semen) in 75% of patients, with a mean sperm concentration achieved of 6 million/mL.[46] The same study showed that combined therapy with FSH and hCG was associated with a better outcome in patients with *organic* secondary hypogonadism.[46] Similar data on pregnancy outcomes following combined treatment with hCG and FSH in functional hypogonadism are not available.

3.3.3 | Values

In patients with functional secondary hypogonadism who desire fertility, in whom treatment is contraindicated (suppression of spermatogenesis—vide infra), we put a higher value on gonadotrophin (hCG) treatment and less emphasis on the current lack of outcome data. The place of FSH treatment in functional secondary hypogonadism has not been assessed. After fertility has been achieved, TRT may be reinitiated.

3.3.4 | Remarks

As alternatives to T, oestrogen receptor blockers (anti-oestrogens, eg clomiphene, tamoxifen, enclomiphene) or aromatase inhibitors (eg letrozole) have been suggested as off-label treatment to maintain fertility and restore hypogonadism-related symptoms in subjects with functional hypogonadism. However, the available evidence is poor due to limited number of RCTs, inadequate outcome data, short duration of the trials as well as small numbers of subjects enrolled.[47]

4 | TREATMENT OUTCOMES

The best evidence on outcomes of TRT in older men with functional hypogonadism comes from the recent TTrials. These studies comprised a set of seven placebo-controlled RCTs enrolling 788 symptomatic hypogonadal men > 65 years (mean age 72 years) with unequivocally low T of <9.4 nmol/L (<275 ng/dL) [mean baseline T 8.1 nmol/L (233 ng/dL)] in a 12-month study using T gel 5mg daily as the active treatment.[6] This contrasted with other available RCTs which often included a combination of both hypogonadal and eugonadal men—a crucial limitation.

Meta-analyses are often considered the gold standard for the evaluation of the efficacy of a specific treatment and particularly useful to address questions for which multiple data sources are conflicting. However, meta-analyses on various TRT outcomes of placebo-controlled RTCs in men with functional hypogonadism have been marred by significant heterogeneity, low study quality, small participant numbers as well as short duration in the studies included,[7,44] thereby devaluing the conclusions therefrom. Data derived from observational and uncontrolled studies on TRT are plentiful, but level of evidence in these studies is poor and therefore not taken into account in these guidelines.

4.1 | Subjects with sexual dysfunction

It is important to clarify that the ensuing recommendation and accompanying comments refer to men with functional hypogonadism who complain of sexual dysfunction—as distinct from men who present with erectile or sexual dysfunction, the vast majority of whom have normal T concentrations.

4.1.1 | Recommendations

Recommendation #10. We recommend TRT in hypogonadal men with sexual/erectile dysfunction to improve libido, erectile function and sexual satisfaction (1⊕⊕⊕⊕).

4.1.2 | Evidence

T critically regulates sexual function, in particular libido and to a lesser extent erectile function.[48,49] TTrials clearly documented that TRT, compared to placebo, modestly increased sexual interest and sexual activity, from flirting to sexual intercourse in hypogonadal men with T < 9.4 nmol/L (<270 ng/dL).[6] In addition, the effect size was inversely related to the baseline T concentrations and proportional to the increase in T concentrations during the study. Greater effects on libido and sexual activity than on erectile function were observed.[6] These data are in line with most recent meta-analyses on sexual function, which also showed that TRT is effective when T is <10.4 nmol/L (<300 ng/dL)[50] or12 nmol/L (350 ng/dL)[18,19] and ineffective in men with T > 12 nmol/L (>350 ng/dL).[18,19] In addition, a recent meta-analysis on men with functional hypogonadism suggested that TRT alone may modestly (International index of erectile function—Erectile function domain [IIEF-EFD] 2-3 points; effect size 0.30) improve mild (IIEF-EFD score 22-25), but not more severe (IIEF-EFD score < 22) ED.[19] Furthermore, TRT efficacy on erectile function was higher in those with more severe hypogonadism (T < 8 nmol/L or 231 ng/dL) and lower amongst men with T2DM and obesity.[19]

4.1.3 | Values

We place a high value on the proven efficacy of TRT in improving libido and overall sexual function in older men with functional hypogonadism. We place a lower value on the less consistent effects of TRT on erectile function in hypogonadism, especially in those with moderate or severe ED, who are prone to have concomitant underlying vascular disease.

4.1.4 | Remarks

The combination of TRT with phosphodiesterase-5 inhibitors (PDE5i) is often considered in hypogonadal men with more severe degrees of ED, especially if either treatment alone proved ineffective. However, available evidence is insufficient to clarify this point. A meta-analysis specifically addressing this issue did not find any benefits related to the combined use of PDE5i and TRT[18] although 3 out of 5[51-53] studies included enrolled mixed eugonadal/hypogonadal subjects. In addition, an RCT in men with ED and T concentrations <11.3 nmol/L (<330 ng/dL) also failed to demonstrate further improvements in erectile function with the addition of T to an optimized regimen of sildenafil.[54,55] Hence, at present, the efficacy and place of combination therapy with T and PDE5i in the management of ED in functional hypogonadism remains unclear. Similarly, the efficacy of the combined use of TRT and intracavernosal injection of prostaglandin E1 (PGE-1) is unknown. Finally, limited evidence suggests that TRT may also improve delayed ejaculation in hypogonadal men.[48,49,56]

4.2 | Obesity

4.2.1 | Recommendations

Recommendation #11. We recommend against TRT as a treatment for weight reduction in obese men (1 ⊕⊕○○).

4.2.2 | Evidence

RCTs specifically designed to study the effects of TRT on weight reduction in overweight or obese men are not available. Nevertheless, TRT consistently improves body composition (similar reduction of fat mass and increase of lean mass) in hypogonadal men, without any change in total bodyweight or body mass index (BMI) when compared with placebo or diet alone.[57-59] Long-term effects of TRT on body composition are unknown. Data derived from registry and uncontrolled studies suggest that TRT might reduce body weight and BMI in hypogonadal men[60]; however, these studies have important limitations, which mitigate against their validity.

4.2.3 | Values

We place a high value on the recommendation that TRT alone should not be considered as an anti-obesity drug.

4.3 | Metabolic syndrome and/or diabetes

4.3.1 | Recommendations

Recommendation #12. We recommend against the use of TRT to improve glycometabolic control in men with type 2 diabetes (T2DM) and/or metabolic syndrome MetS (1⊕⊕○○).

4.3.2 | Evidence

The metabolic effects of TRT in men with T2DM and MetS are conflicting. Only few placebo-controlled RCTs specifically investigated metabolic outcomes as primary endpoint of TRT in these populations. The TIMES-2, the largest study on T2DM or MetS subjects (n = 220), was unable to document a significant reduction in haemoglobin A_{1c}

(HbA_{1c}) concentrations or BMI after 26 weeks of T gel 1%, although some improvement in the homeostatic model assessment of insulin resistance (HOMA-IR) was observed.[61] The largest RCT conducted exclusively in 199 men with T2DM was the BLAST study.[62] Long-acting injectable TU for 30 weeks resulted in significant improvement of HbA_{1c} concentrations, particularly in poorly controlled men (baseline HbA_{1c} ≥ 58 mmol/mol; 7.5%). Waist circumference decreased without any modification of BMI.[62] In contrast, Gianatti et al[63] did not observe any improvement in HbA_{1c} concentrations or HOMA-IR index in 88 men with T2DM, despite an improvement of body composition (reduction of fat mass and increase in lean mass), after 40 weeks of long-acting injectable TU when compared to placebo. Uncontrolled registry studies suggest that TU treatment may improve glycometabolic controls in men with T2DM and MetS up to 8 years[64-67] and prevents pre-diabetes progression toT2DM in men with hypogonadism.[68] The unconfirmed results of these studies have important limitations as mentioned earlier and cannot therefore be accepted as generalizable evidence. The effects of TRT on other parameters of MetS such as lipid profile and blood pressure are inconsistent.

4.3.3 | Values

We place a higher value on the lack of clear evidence from RCTs that TRT consistently improves the metabolic profile (HbA_{1c}, fasting glycaemia) or longer-term benefits in clinical outcomes in men with T2DM or MetS. We place a lower value on the inconsistent, modest short-term improvement in insulin resistance (HOMA-IR) despite the consistent effect of T on body composition. However, TRT is indicated in men with MetS or T2DM who also have diagnosed hypogonadism for the management of traditional hypogonadal symptoms without the promise (or expectation) of improvements in metabolic status.[40]

4.4 | Subjects with bone diseases

4.4.1 | Recommendations

Recommendation #13. We recommend against TRT with the sole purpose of reducing fracture risk in hypogonadal men with high fracture risks (1 ⊕⊕⊕◯).

4.4.2 | Evidence

TRT may improve bone quality in hypogonadal men with low or moderate fracture risk.[69] TTrials also showed that TRT improves volumetric bone mineral density, more in the spine than (but also significantly) in the hip,[6] confirming earlier data that TRT increases areal spinal bone mineral density as measured by dual-energy X-ray absorptiometry (DEXA).[70,71] However, there are no data on the effects of TRT on fracture risk or incidence in men, unlike several bone-specific medical therapies (eg bisphosphonates).[69]

4.4.3 | Values

In hypogonadal men with osteoporosis and/or at high risk of fragility fracture, anti-osteoporotic therapy with proven benefits on reducing fracture risk is preferred. TRT can also be prescribed at the same time in these men for the management of extant hypogonadal symptoms.

4.4.4 | Remarks

Fracture risk rather than bone density is the more important outcome.[69] Fracture risk (estimated by FRAX or similar scores) remains the key metric for determining appropriate treatment option and assessment of efficacy in hypogonadal patients at high risk of osteoporosis.[69]

4.5 | Subjects with psychological symptoms

4.5.1 | Recommendations

Recommendation #14. We recommend against TRT for the sole treatment to improve depressive symptoms in hypogonadal men (1 ⊕⊕◯◯).

4.5.2 | Evidence

Few placebo-controlled RCTs have investigated the potential role of TRT for the treatment of depressive symptoms.[72] TRT improved mood, and depressive symptoms using several self-report instruments in the TTrials, although the magnitude of the effects was small.[6] This is in line with data reported in available meta-analyses.[73-76] The positive effect of TRT was confirmed only in hypogonadal patients, with apparently higher efficacy in those <60 years and those with minor depressive symptoms.[74]

4.5.3 | Values

We place a higher value on the use of established anti-depressive therapy, cognitive behavioural therapy and psychiatric consultation in men with depressive symptoms or in those with diagnosed major depression. We place a lower value on the possibility that TRT may modestly improve mood in hypogonadal men.

4.5.4 | Remarks

Information on the effects of TRT in major depressive disorders is lacking. Similarly, the outcomes on combination of TRT with established anti-depressive therapy are not available.

4.6 | Subjects with chronic diseases

4.6.1 | Recommendations

Recommendation #15. We recommend against the use of TRT, in the absence of symptomatic hypogonadism, to improve the morbidity and/or mortality of several chronic diseases including human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS), heart failure, obstructive pulmonary disease, chronic kidney diseases, bowel inflammatory diseases or to prevent the long-term outcomes of subjects chronically treated with glucocorticoid or opioid therapy (2 ⊕⊕○○).

4.6.2 | Evidence

Several chronic conditions including HIV-1 infection, particularly wasting syndrome, heart failure, chronic obstructive pulmonary disease (COPD), impaired renal function, in particular end-stage renal diseases (ESRD) as well as bowel inflammatory diseases, are frequently associated with lower T concentrations.[77,78] Limited evidence suggests that TRT might improve lean mass in HIV[77,79,80] and in COPD[81] patients. No data, however, indicate that TRT may impact on either natural course or long-term outcomes of chronic diseases. This also applies to men with chronic inflammatory diseases treated with glucocorticoids.[77]

4.6.3 | Values

We place a higher value on recommending against the use of TRT with the intention of modifying the natural course of chronic diseases, and a lower value on improving hypogonadal (mainly sexual) symptoms in patients with chronic diseases and low T, due to the lack of supportive evidence on overall clinical benefits and improvements in quality of life.

4.7 | Ageing men

4.7.1 | Recommendations

Recommendation #16. We recommend against routinely prescribing T to men >65 years as an anti-ageing therapy (1 ⊕⊕⊕⊕).

Recommendation #17. We recommend against TRT in frail men to improve exercise capacity/physical function (1 ⊕⊕⊕○).

Recommendation #18. We recommend against TRT in ageing men to improve cognitive function (1 ⊕⊕⊕○).

4.7.2 | Evidence

The role of TRT in elderly men remains a matter of considerable debate. The TTrials showed that TRT did not substantially increase walking distance in the cohort of men complaining of low physical function.[6] However, walking distance increased significantly when the whole study population was included in a sub-analysis. In line with these findings, the post hoc analysis of the data showed that TRT consistently improved self-reported walking ability as well as modestly improved 6 minutes walk test (across all TTtrial participants), but did not affect falls.[83] In addition, although TRT did not improve vitality as assessed by an increase above the pre-specified threshold value in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale as the primary outcome, it did improve vitality, mood and depressive symptoms as continuous measures by several instruments.[6] The magnitude of each of these improvements, however, was small and their clinical significance uncertain. Finally, TRT did not improve cognitive performance.[6]

4.7.3 | Values

We place a higher value on the view that the TRT has not been shown unequivocally to improve physical, cognitive function or energy level, in elderly men with low T concentrations, to an extent that is likely to provide patient-important benefits. We place a relatively lower value on the results of the TTrials, which show modest improvements in these functional domains. Our opinion is influenced by the current lack of data on long-term safety of TRT in elderly men (see below).

5 | SAFETY AND CONTRAINDICATIONS

Safety data on cardiovascular diseases (CVD), VTE and prostate cancer risks pertain only to short-term treatment, since the vast majority of RCTs on TRT exposed subjects to T for 6-24 months, with the maximum duration of 36 months.[7] Furthermore, none of the studies has been sufficiently powered to exclude adverse event risks in the longer term.

5.1 | Prostate and breast

5.1.1 | Recommendations

Recommendation #19. We recommend against TRT in men with untreated prostate or breast cancer (Good Clinical Practice statement).

Recommendation #20. We recommend, before initiation of TRT in men > 40 years of age, discussing potential benefits and risks of prostate cancer screening and engaging the patient in shared decision-making regarding options for pre-treatment screening and on-treatment monitoring (see *Recommendations #21, #22, #31,#32*). These discussions should also take into account local guidelines for prostate cancer screening for the general population (Good Clinical Practice statement).

Recommendation #21. We recommend, before initiating TRT in men > 40 years of age, checking prostatic-specific antigen (PSA) and performing digital rectal examination (DRE) of the prostate to minimize the risk of prescribing T to patients with undiagnosed prostate cancer (1⊕⊕○○).

Recommendation #22. We recommend against TRT in men with PSA > 4 ng/mL (or elevated PSA according to local/national guidelines) or prostate abnormalities on DRE without further evaluation and/or urological consultation (1⊕⊕○○).

Recommendation #23. We suggest TRT should not be used in men with severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPPS)>19] (2⊕○○○).

5.1.2 | Evidence

Androgens and/or oestrogens are known to stimulate proliferation and differentiation of prostate[84,85] and breast cancers.[86]

However, increased short-term (mostly < 12 months, maximum three years) risk of incident prostate cancer, prostate-related adverse events, increase in LUTS or prostate volume or breast cancer have not been documented following TRT in men with low T.[85,86] TRT in men with treated prostate cancer remains controversial, with only scarce evidence to support its safety.[84,85,87] Information on the use of TRT in men with breast cancer following curative treatment is not available.[86]

Low, rather than high T seems to be associated with benign prostatic hyperplasia (BPH) and LUTS.[88] A recent meta-analysis did not show an increase of LUTS severity in hypogonadal men treated with T vs placebo.[89] Limited information, however, is available in men with severe LUTS (ie IPSS score > 19) as well as in those with PSA concentrations > 4 ng/mL [88,89] since they are usually excluded from enrolment into TRT trials.

5.1.3 | Values

We place a high value on the current lack of long-term prostate safety data on TRT in men with functional hypogonadism. TRT is contraindicated in hypogonadal men with untreated prostate and breast cancer in accordance with good clinical practice. In view of the conflicting evidence and continuing controversies,[90] patients should be counselled about the potential benefits and risks of prostate cancer screening and be involved in shared decision-making regarding options for pre-treatment screening. When available, local guidelines for prostate cancer screening for the general population should also be considered.

5.1.4 | Remarks

PSA represents a continuous parameter directly related to the likelihood of prostate cancer, although an optimal PSA threshold for detecting non-palpable but clinically significant prostate cancer has not been completely identified.[90] An elevated PSA level of >4 ng/mL (or elevated PSA according to local/national guidelines) should be confirmed a few weeks later under standardized conditions (ie no ejaculation, prostate manipulations, and urinary tract infections) in the same laboratory. Elevated PSA concentrations, if confirmed, require further evaluation.[90]

In severely symptomatic hypogonadal men with treated (radical prostatectomy) low-grade prostate cancer (Gleason score < 7) who remained in remission (with undetectable PSA for at least two years), the possible risks and benefits of TRT should be discussed with the patient and his oncologist and/or urologist in order to reach an individually appropriate joint decision on management.[91] The safety of TRT in men with severe LUTS remains to be established but modest LUTS (IPSS ≤ 19) is not a contraindication to TRT.[88,89]

5.2 | CVD and venous thromboembolism risks

5.2.1 | Recommendations

Recommendation #24. We recommend against TRT in men with severe heart failure [New York Heart Association (NYHA) Class III or IV] (1⊕⊕○○).

Recommendation #25. We suggest against TRT in patients with a recent major acute CV event (including stroke) (2⊕⊕○○).

Recommendation #26. We suggest against TRT in men with documented polycythaemia and/or elevated haematocrit (>48%-50%) depending on associated morbidities and CV risk without further evaluation (2⊕⊕○○).

Recommendation #27. We suggest obtaining detailed personal and family history of venous thromboembolism (VTE) and risk factors for VTE prior to initiating TRT (2⊕○○○).

5.2.2 | Evidence

The risks of TRT in patients with class III or IV heart failure have not been formally documented. These patients often represent a frail immobile population, at risk of polycythaemia and VTE, which are further contraindications for TRT (see below).

The association between CVD and TRT was highlighted by the US Food and Drug Administration (FDA), which instigated a label warning on all T products. Similar conclusions were reached by Health Canada. Conversely, the European Medicine Agency (EMA) did not find sufficient evidence for declaring a TRT-associated CV risks (see for review Ref. [2]). A recent meta-analysis including 15 pharmaco-epidemiological and 93 RCTs showed no clear evidence of increased CV risk related to TRT[92] but none of these studies was designed (with sufficiently long duration of exposure) or powered (with sufficient numbers of participants) to exclude such a risk. At the behest of the US FDA, an industry-supported multi-centre RCT is underway to investigate the CV risk of TRT (clinicaltrials.gov: NCT03518034).

High haematocrit (Hct) is a risk marker of CV morbidity, mortality and VTE.[93] In a 28-year follow-up study amongst 670 men aged 55 years, Hct > 50% was associated with 1.8-fold increase in coronary heart disease (CHD) mortality even after adjustment for established coronary risk factors.[94] The Framingham Heart Study reported that in men older than 64 years of age, Hct > 48% was associated with higher CHD and CVD mortality.[95] Since no clear Hct threshold was associated with an increased CV risk, the final decision to start or not TRT should be left to the physician considering overall patient clinical conditions. Several associated morbidities including COPD, obstructive sleep apnoea syndrome, heart failure (HF) as well as smoking habit can potentially further contribute to TRT-associated increment of Hct. Hence, Hct > 48%-50%, depending on associated morbidities and CV risk, can be considered a contraindication for initiating TRT without further investigation. Several case series also documented VTE in patients who received TRT, and both the US FDA [96] and Health Canada [97] warned against the risk of VTE in all T products, requiring a label change. Conversely, two large population-based studies failed to find an association between endogenous T and VTE ([98,99]; see Ref. [100] for review). However, a more recent Mendelian randomization study from the UK Biobank, including around 500 000 men aged 40-69, showed that endogenous T, genetically predicted by variants in the JMJD1C gene region, was positively associated with thromboembolism.[101] It is also important to recognize that the vast majority of the previously reported cases of TRT-related VTE may have been related to undiagnosed thrombophilia-hypofibrinolysis, emphasizing the role of past and family history of thromboembolic diseases.[100,102]

5.2.3 | Values

We place a high value on the current lack of definitive long-term CVD risk data on TRT in men with functional hypogonadism, while acknowledging the safety warnings from North America.[103] However, our preference is to follow the guidance from the EMA stating that when hypogonadism is properly diagnosed and managed, there is currently no consistent evidence of an increased risk of CV disease during TRT.[104]

5.2.4 | Remarks

It should be important to recognize that the proposed criteria related to Hct thresholds are derived from the general population not living at high altitudes.

5.3 | Fertility

5.3.1 | Recommendations

Recommendation #28. We recommend against TRT in hypogonadal men who desire fertility (1⊕⊕⊕⊕).

5.3.2 | Evidence

TRT suppresses gonadotrophins and endogenous T secretion as well as spermatogenesis. Data derived from the use of anabolic steroids indicated that such suppression may even persist many months (up to 12 months usually but sometimes more) after treatment discontinuation.[105]

5.3.3 | Values

TRT is contraindicated in men with function hypogonadism who desire fertility [106] (see Section 7.8).

6 | MONITORING

The follow-up of T treatment in patients with functional hypogonadism, in general, should be no different from organic hypogonadism. The EAA guidelines, therefore, largely agrees with the recent US and Australian Endocrine Society guidelines.[5,20]

6.1 | Monitoring TRT for functional hypogonadism

6.1.1 | Recommendations

Recommendation #29. We recommend assessing the clinical response as well as adverse effects to TRT at 3 and 12 months after initiation of treatment. Thereafter, clinical review should be scheduled at least yearly (1⊕⊕⊕⊕).

Recommendation #30. We suggest that on-treatment total T concentrations should be measured at each clinic visit to ensure that average total T concentrations achieve the targeted mid-normal range for young men (2 ⊕⊕○○).

Recommendation #31. We suggest performing digital rectal examination and checking PSA at 3 to 12 months for men > 40 years of age after initiating T treatment. After the first 12 months, local guidelines for prostate cancer screening for the general population should be followed (2⊕○○○).

Recommendation #32. We suggest further evaluation and/or urological consultation, if there is: (a) an increase in serum PSA concentration >1.4 ng/mL within 12 months of initiating T treatment, (b) a confirmed PSA > 4 ng/mL at any time and (c) detection of a prostatic abnormality on DRE or a substantial worsening of LUTS (2⊕○○○).

Recommendation #33. We recommend measuring the haematocrit (Hct) 3-6 months after initiation of TRT and then annually. If Hct is >54%, TRT should be discontinued, until Hct decreases to a safe level; evaluate the patient for hypoxia and sleep apnoea; reinitiate therapy with a reduced dose (1 ⊕⊕⊕⊕).

6.1.2 | Evidence

At each clinic review, serum T concentration should be checked to ensure that the normal range for young men 9.6-30 nmol/L (280-873 ng/dL)[6] is attained (Figure 1; see Recommendation #29, above).There is a general consensus that Hct > 54% requires TRT withdrawal (and sometimes phlebotomy) to minimize the risks of VTE and CV events.[93]

6.1.3 | Values

We place a high value on minimizing the risk of unnecessary prostate biopsy (resulting in over-diagnosis of clinical inconsequential prostate cancer in situ or high-grade prostatic intraepithelial neoplasia, infection, cost, etc) as a consequence of prostate safety monitoring.

In view of the conflicting evidence and continuing controversies,[90] patients should be counselled about the potential benefits and risks of prostate cancer screening for on-treatment monitoring. These discussions should also take account of local guidelines (when available) for prostate cancer screening for the general population. In line with the European Association of Urology (EAU) guidelines,[90] in men >40 years, who have initiated TRT, we *suggest* (after discussing potential benefits and risks of prostate screening) engaging the patient in shared decision-making regarding continued monitoring after the first 12 months of treatment. In men >40 years at increased risk of prostate cancer (eg men of African descent and those with a first-degree relative with diagnosed prostate cancer or previously positive prostate biopsy, and in those with baseline PSA concentrations >1 ng/mL at age 40 years or >2 ng/mL at age 60 years), having initiated TRT, we *suggest* (after discussing prostate cancer risk with the patient) offering continued monitoring options after the first 12 months of treatment. The risk of prostate cancer in men younger of 40 years is very low, whereas the risk of dying from prostate cancer (as opposed to other co-morbidities) in men diagnosed when they are 70 years of age or older has been not considered high enough to warrant monitoring in the general population.[90]The use of cancer risk calculators [107] can allow clinicians to identify patients at higher risk for prostate cancer.[90]

6.1.4 | Remarks

The exact timing for T evaluation depends on the T preparation used.[5] Dose adjustment, switching to alternate T preparations or (dis) continuation of treatment can be guided by the clinical response and the on-treatment T concentration. It is important to be reminded that many cases of functional hypogonadism are potentially reversible. Thus, TRT withdrawal may be considered following weight reduction or if medications such as opiates can be stopped or substituted. If TRT does not result in significant clinical improvement after 6 months, treatment should be discontinued, and alternate diagnosis sought. Temporary treatment 'holidays' will allow the HPT axis function to be reassessed and the requirement for continuation of TRT determined.

7 | CONCLUSIONS

Functional hypogonadism is a relatively new clinical diagnosis that is still not universally recognized or accepted. T concentrations decline gradually with age, but the clinical significance of low T in ageing men remains unclear. This presents a difficult challenge to clinicians who are charged with confirming a genuine diagnosis of (functional) hypogonadism amongst a plethora of relatively non-specific symptoms (of which sexual symptoms show the strongest association with T deficiency). This is compounded by the fact that T concentrations in functional hypogonadism are commonly found in the borderline (8-12 nmol/L) rather than the unequivocally pathological range (<6 nmol/L). In this situation, fT measurement can be helpful in resolving borderline cases. It is important to recognize the roles of obesity and co-morbidity as well as medications in aggravating the natural age-related T decline, with the important implication of potential reversibility. Thus, TRT, more often than not, initiated as a therapeutic trial, should not be continued if there is no clinical improvement. Moreover, the diagnosis and changing requirements/priorities of the patient should be reviewed regularly, especially of those in advanced age whose risk and benefit balance may shift with time. The present recommendations for or against treatment are substantially influenced by the fact that real clinical benefits and safety (especially in the longer term) of TRT have not been fully documented. Furthermore, due to its potential reversibility, no data are currently available to recommend the appropriate duration of TRT in individual patients with functional hypogonadism. It is clear that this is an evolving area of clinical practice that requires much more clinical research efforts. The relative abundance of negative rather than positive recommendations (which may not always be definitive) in these guidelines reflects a dearth of high-level evidence. In the meantime, clinicians dealing with individual patients with possible functional hypogonadism should be prepared to explicitly discuss the uncertainties of the potential risks and benefits of TRT from current evidence and engage them in shared management decision-making.

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APPENDIX

The manuscript has been approved by the European Academy of Andrology (EAA) Guidelines Committee members (G. Corona, D.G. Goulis, G. Forti, H.M. Behre, M. Punab, J. Toppari, C. Krausz), EAA Executive Council (C. Krausz, Ewa Rajpert-De Meyts, Frank Tüttelmann, A.M. Isidori, Eduard Ruiz-Castane, Davor Jezek, Zsolt Kopa, J. Toppari, M. Simoni), EAA Center Directors and the Co-Editor-in-chief (M. Simoni).

In addition, the manuscript has been revised and approved by Andrea Isidori and Mario Maggi on behalf of the European Society of Endocrinology.

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REVIEW ARTICLE

ANDROLOGY WILEY

European academy of andrology guidelines on Klinefelter Syndrome: Endorsing Organization: European Society of Endocrinology

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Abstract

Background: Knowledge about Klinefelter syndrome (KS) has increased substantially since its first description almost 80 years ago. A variety of treatment options concerning the spectrum of symptoms associated with KS exists, also regarding aspects beyond testicular dysfunction. Nevertheless, the diagnostic rate is still low in relation to prevalence and no international guidelines are available for KS.

Objective: To create the first European Academy of Andrology (EAA) guidelines on KS.

Methods: An expert group of academicians appointed by the EAA generated a consensus guideline according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

Results: Clinical features are highly variable among patients with KS, although common characteristics are severely attenuated spermatogenesis and Leydig cell impairment, resulting in azoospermia and hypergonadotropic hypogonadism. In addition, various manifestations of neurocognitive and psychosocial phenotypes have been described as well as an increased prevalence of adverse cardiovascular, metabolic and bone-related conditions which might explain the increased morbidity/mortality

in KS. Moreover, compared to the general male population, a higher prevalence of dental, coagulation and autoimmune disorders is likely to exist in patients with KS. Both genetic and epigenetic effects due to the supernumerary X chromosome as well as testosterone deficiency contribute to this pathological pattern. The majority of patients with KS is diagnosed during adulthood, but symptoms can already become obvious during infancy, childhood or adolescence. The paediatric and juvenile patients with KS require specific attention regarding their development and fertility.

Conclusion: These guidelines provide recommendations and suggestions to care for patients with KS in various developmental stages ranging from childhood and adolescence to adulthood. This advice is based on recent research data and respective evaluations as well as validations performed by a group of experts.

1 | INTRODUCTION

Klinefelter syndrome (KS) is the most frequent chromosome disorder in men, exhibiting a karyotype of 47,XXY. Symptoms in KS are highly variable. Nevertheless, frequent characteristics are small testes, azoospermia and hypergonadotropic hypogonadism. Also neurocognitive and psychosocial manifestations can be seen as well as cardiovascular, metabolic and bone-related conditions of adverse nature. Generally, morbidity and mortality are increased in KS compared to men with a karyotype of 46,XY. Both hypogonadism and genetic effects seem to contribute to this clinical spectrum. Among physicians, knowledge about KS regarding diagnosis and treatment is distributed unevenly. KS is not fully known to many physicians and there is a marked need for a respective improvement of medical curricula.

Whereas KS is usually considered in all guidelines dealing with the management of hypogonadism, no specific guideline and recommendation have ever been published to care for patients with KS in various developmental stages. The aim of the present study is summarize available evidence on KS providing a list of suggestions and recommendations on behalf of European Academy of Andrology (EAA) and endorsed by the European Society of Endocrinology in order to correctly manage patients with KS from pre-natal period to adulthood.

2 | METHODOLOGY OF THE GUIDELINE COMPOSITION

2.1 | Data identification

The EAA guidelines committee commissioned an expert task force of academicians with clinical expertise in the field to create new guidelines for the management of KS. All experts involved are andrologists with a various background (urology, genetics, paediatrics and endocrinology). PubMed was searched for articles in English with the search term 'Klinefelter' (the search period involved all literature regarding KS starting from 1942 to June 2020). The text was drafted in a group effort following scrutiny and discussion of the best evidence from published literature. Thus, a series of consensus recommendations and suggestions according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system was generated.[1]

2.2 | Levels of evidence and grades of recommendation

The GRADE system is a method of developing evidence-based guidelines, involving key recommendations and the use of a consistent language and graphical descriptions for standardizing the grading of both the strength of recommendation and the quality of the evidence.[1] widely used from scientific societies including the EAA. According to GRADE, the task force used the following internationally shared coding system: [1] 'we recommend' indicates a strong recommendation; [2] 'we suggest' denotes a weak recommendation. As far as the evidence grading is concerned: ⊕◯◯◯ denotes 'very low-quality evidence'; ⊕⊕◯◯ 'low quality', ⊕⊕⊕◯ 'moderate quality' and ⊕⊕⊕⊕ 'high quality'.

Largely, a '⊕⊕⊕⊕' score is awarded to evidence that is based on randomized controlled trials (RCTs) and meta-analyses, and a '⊕⊕◯◯' score to evidence that is based on observational studies. Specific methodological characteristics (quality, consistency, directness and effect size) increase or decrease this score.

Statements on AETIOLOGY AND PREVALENCE.

I Klinefelter syndrome (KS) is the most frequent sex chromosomal anomaly in males, described by a karyotype with one or more extra X Chromosome (most frequently 47,XXY) in men.

II KS is associated with testicular malfunction resulting very often in hypogonadism and/or infertility

III The classical description of the adult male with KS includes primary testicular failure with small testes (1-5 mL), hypergonadotropic hypogonadism, gynaecomastia, infertility (mostly

KS are afflicted with a higher risk of having cardiovascular, metabolic, psychiatric and other comorbidities. Providing the patient with KS and, if deemed adequate, his parents with suitable and balanced information as well as assistance for various aspects of his life after receiving the diagnosis is suggested. Prevention and treatment of the medical complications and comorbidities associated with KS should be standardized as far as possible. Also minimizing neurodevelopmental dysfunction, that is verbal deficits, learning difficulties, behavioural problems should be aimed at. These measures are likely to promote the patients' self-esteem, assure quality of life and improve his social adaption. Finally, preservation of the fertility potential, that is cryopreservation of spermatozoa from ejaculate or testicular tissue is an option now widely available.

The pathological conditions in patients with KS are most likely of a combined endocrine, genetic and epigenetic origin. Further research in a coordinated fashion is needed. KS is vastly underdiagnosed and an increment of general knowledge as well as establishment of standard care in multidisciplinary networks is mandatory. These are the first guidelines to take a step towards this goal.

6 | LIST OF RECOMMENDATIONS AND SUGGESTIONS

6.1 | Genetic issues

1. We recommend that a pre-natal diagnosis of KS is confirmed on a chromosome analysis on peripheral blood postnatally (1, ⊕⊕⊕◯).
2. We recommend conventional karyotyping on peripheral blood cells for diagnosis of KS (1, ⊕⊕⊕◯).
3. We recommend that patients with KS and/or their parents are offered genetic counselling; pre-natal counselling should be non-directive (1, ⊕⊕⊕◯).
4. We recommend karyotype analysis for detecting KS in men with non-obstructive azoospermia and (severe) oligozoospermia (total sperm count < 10 x 10^6/ejaculate or sperm concentration < 5 x 10^6/ml (1, ⊕⊕⊕◯).
5. We recommend karyotype analysis for detecting KS in men with primary hypogonadism (low serum levels of testosterone) and elevated serum levels of gonadotropins (LH and FSH) combined with small testicular volumes (<5 ml per testis) (1, ⊕⊕⊕◯).

6.2 | CHILDREN AND PRE-PUBERTAL BOYS WITH KS

6. We suggest karyotype analysis for detecting KS in boys born with cryptorchidism, especially the bilateral forms, who do not experience spontaneous descent of the testes at the first year (2, ⊕⊕◯◯).
7. We recommend to treat cryptorchidism in children with KS according to the current treatment guidelines in children without KS (1, ⊕⊕⊕◯).
8. We recommend general physical examinations in pre-pubertal children with KS including a testicular evaluation. These should be performed biennially or as deemed as appropriate. Suspected neurological or psychiatric deficits should be examined by respective specialists (1, ⊕⊕⊕◯).
9. We suggest determination of LH and testosterone during the first 2-3 months after birth in children with pre-natal diagnosis of KS when it might have a therapeutic consequence (ie diagnosis of micro-penis) (2, ⊕◯◯◯).
10. We recommend against testicular tissue cryopreservation or spermatogonial stem cell retrieval in pre-pubertal children with KS (1, ⊕⊕⊕◯).
11. We recommend against testosterone supplementation during early childhood in all patients with KS except in cases of micro-penis (1, ⊕⊕⊕◯).
12. We suggest measurement of height according to centiles or standard deviation scores as well as body proportions and determinations of bone age in pre-pubertal children with KS depending on individual growth patterns (2, ⊕⊕◯◯).
13. We suggest determination of vitamin D blood levels and adequate vitamin D and calcium supplementation in pre-pubertal children with KS (2, ⊕◯◯◯).
14. We suggest assessment of bone mineral status during childhood in case of vitamin D deficiency biennially in patients with KS (DXA scan, size-corrected determinations using a three-step-method are required) (2, ⊕◯◯◯).
15. We recommend measurement of weight using centiles or standard deviation scores in pre- pubertal children with KS (1, ⊕⊕⊕◯).
16. We recommend against testosterone treatment in infants and pre-pubertal boys with KS (1, ⊕⊕⊕◯).
17. We recommend speech therapist control and therapy, monitoring learning disabilities, social training and psychological support, in pre-pubertal children with KS if needed (1, ⊕⊕⊕◯).

6.3 | ADOLESCENTS WITH KS

18. We recommend that information on fertility issues is given to adolescent patients with KS and, if deemed adequate, his parents. There is no level of recommendation, as this can be considered good clinical practice.
19. We suggest testicular ultrasound during puberty of patients with KS and regularly at follow-up visits (2, ⊕◯◯◯).
20. We suggest semen collection in adolescents with KS after careful information and assessment of the wish of the patient and cryopreservation if motile spermatozoa are present (2, ⊕⊕◯◯).
21. We suggest that adolescents with KS might undergo a testicular biopsy for testicular sperm extraction (TESE) either using multifocal (standard TESE) or microdissection-TESE (mTESE) and consequent sperm cryopreservation in selected cases requiring

specific counselling, provided their physical and mental maturity is apt for this decision (2, ⊕⊕◯◯).

22. We recommend assessment of Tanner stages, pubertal development, measurement of testosterone and gonadotropins, signs and symptoms of hypogonadism, height, weight, waist circumference and body proportions starting prior to the predicted start of puberty in patients with KS and at individually determined intervals thereafter (the time-window for the start of puberty does not differ from boys with a karyotype of 46,XY) (1, ⊕⊕⊕◯).

23. We recommend testosterone supplementation in case of delayed puberty and/or signs and symptoms of hypogonadism associated with low-normal testosterone and supra-normal LH serum concentrations (LH> 2 SD according to age-related references), after the fertility issues have been addressed (see above) (1, ⊕⊕⊕◯).

24. We suggest against testosterone therapy in adolescents with KS with compensated hypergonadotropic hypogonadism (2, ⊕⊕◯◯).

25. We recommend speech therapist control, monitoring educational problems, social training and psychological support in adolescents with KS, if needed (1 ⊕⊕⊕◯).

6.4 | ADULTS WITH KS

26. We recommend initiation of testosterone substitution in patients with KS with hypogonadism as diagnosed according to established guidelines on hypogonadism, if possible once fertility issues have been addressed (1, ⊕⊕⊕◯).

27. We recommend that testosterone substitution in patients with KS should follow the established guidelines on hypogonadism using the usually suggested monitoring intervals for clinical assessment, safety parameters (haematocrit, PSA, other) and dose titration (1, ⊕⊕⊕◯).

28. We recommend endocrine evaluation every 12 months in adult patients with KS who are not on testosterone substitution (1,⊕⊕◯◯).

29. We recommend semen analysis and sperm cryopreservation in all adult patients with KS and a wish for paternity (1, ⊕⊕⊕◯).

30. We recommend that all adult patients with KS and confirmed azoospermia and a current or putative future wish for paternity undergo a testicular biopsy for testicular sperm extraction (TESE) either using multifocal (standard TESE) or microdissection-TESE (mTESE) and consequent sperm cryopreservation (1, ⊕⊕⊕◯).

31. We suggest against starting testosterone replacement therapy in patients with KS when a TESE is planned, due to the possible suppression of gonadotropins and further suppression of remnant spermatogenesis (2, ⊕⊕◯◯)

32. We recommend education on lifestyle and yearly assessment of weight, waist circumference, blood pressure, fasting glucose, HbA1c and lipid profile and adequate treatment in all patients with KS (1, ⊕⊕⊕◯).

33. We suggest thrombosis prophylaxis prior to long-term flights or exposure to other risks in patients with KS to attenuate the increased risk for deep vein thrombosis and/or pulmonary embolism (2, ⊕⊕⊕◯).

34. We suggest assessment of 12-lead ECG QTc time at least once in patients with KS (2, ⊕⊕⊕◯)

35. We recommend following the EAA clinical guidelines on management of bone health in the andrological outpatient clinic, bearing in mind that patients with KS are at risk of low bone mineral density (BMD) and fractures independently of their serum levels of testosterone (1, ⊕⊕⊕◯).

36. We recommend DXA analysis at the lumbar and femoral levels and fracture risk assessment at the first visit of adult patients with KS and then on an individual basis (1, ⊕⊕◯◯).

37. We suggest determination of vitamin D plasma levels in all adult patients with KS at the first visit and then on an individual basis, independently from their BMD, and proper vitamin D and calcium supplementation when needed (2, ⊕⊕◯◯).

38. We recommend considering psychosexual and psychiatric issues in all adult patients with KS and to induce consultation by a specialist if required (1, ⊕⊕◯◯).

39. We suggest attention to the putative existence of gender incongruence in patients with KS. The patient should then attend a respective specialist within a multidisciplinary setting (2, ⊕◯◯◯) (2, ⊕◯◯◯).

40. We recommend breast examination for patients with KS (including mammary gland ultrasonography if necessary) for detecting gynaecomastia at the first visit and then on an individual basis and eventual treatment as per guidelines (1, ⊕⊕⊕◯).

41. We suggest clinical breast and axilla examinations every two years in adult patients with KS and eventual mammography and/or mammary gland ultrasonography especially in those patients with a family history of breast cancer or other reasons for suspicion thereof (1, ⊕⊕◯◯).

42. We suggest ophthalmological assessments in patients with KS if the history points towards visual complaints (2, ⊕◯◯◯).

43. We suggest examination of the dental status in patients with KS (2, ⊕◯◯◯).

44. We suggest attention to possible autoimmune dysfunctions in patients with KS (2, ⊕◯◯◯).

6.5 | GENERAL DEMANDS

45. We recommend the set-up of multidisciplinary centres or structures to care for patients with KS (1, ⊕⊕⊕◯).

46. We recommend improving the transitional care for patients with KS from paediatric to adult endocrinologists/andrologists (1, ⊕⊕⊕◯).

47. We recommend improving knowledge about KS among doctors and society, especially by structured graduate and postgraduate education (1, ⊕⊕⊕◯).

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Biomarkers and Noncalcified Coronary Artery Plaque Progression in Older Men Treated With Testosterone

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Abstract

Objective: Recent results from the Cardiovascular Trial of the Testosterone Trials showed that testosterone treatment of older men with low testosterone was associated with greater progression of noncalcified plaque (NCP). We evaluated the effect of anthropometric measures and cardiovascular biomarkers on plaque progression in individuals in the Testosterone Trial.

Methods: The Cardiovascular part of the trial included 170 men aged 65 years or older with low testosterone. Participants received testosterone gel or placebo gel for 12 months. The primary outcome was change in NCP volume from baseline to 12 months, as determined by coronary computed tomography angiography (CCTA). We assayed several markers of cardiovascular risk and analyzed each marker individually in a model as predictive variables and change in NCP as the dependent variable.

Results: Of 170 enrollees, 138 (73 testosterone, 65 placebo) completed the study and were available for the primary analysis. Of 10 markers evaluated, none showed a significant association with the change in NCP volume, but a significant interaction between treatment assignment and waist-hip ratio (WHR) (P = 0.0014) indicated that this variable impacted the testosterone effect on NCP volume. The statistical model indicated that for every 0.1 change in the WHR, the testosterone-induced 12-month change in NCP volume increased by 26.96 mm3 (95% confidence interval, 7.72-46.20).

Conclusion: Among older men with low testosterone treated for 1 year, greater WHR was associated with greater NCP progression, as measured by CCTA. Other biomarkers and anthropometric measures did not show statistically significant association with plaque progression.

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ORIGINAL ARTICLE

ANDROLOGY WILEY

Testicular ultrasound score: A new proposal for a scoring system to predict testicular function

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Funding information
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Abstract

Background: Testicular ultrasound (US) is routinely employed in the evaluation of reproductive and sexual function. However, its use for characteristics other than testicular volume is hampered by a lack of information on the prognostic value of its findings, which to date have only been incorporated in a score proposed by Lenz et al in 1993.

Objectives: We sought to explore whether testicular US examination can predict the quality of spermatogenesis and provide information on testicular endocrine function.

Materials and methods: We retrospectively reviewed 6210 testicular US examinations, finally selecting examinations from 2230 unique men. The following variables were considered: bitesticular volume and testicular asymmetry, parenchymal echotexture, echogenicity and presence of microlithiasis, solid lesions and varicocoele. Concurrent fasting hormonal data were available for 1160 men, while 979 had a semen sample available from the same day as the US examination.

Results: We derived a new US score, termed TU score, that can predict both impaired spermatogenesis (AUC 0.73, sensitivity 72%, specificity 61%, $P < .001$) and hypogonadism (AUC 0.71, sensitivity 71%, specificity 53%, $P < .001$) more accurately than the Lenz's score. In a multivariate analysis, a reduced sperm *composite index* (defined as total spermatozoa × total motility × normal forms) was independently predicted by bitesticular volume and by inhomogeneous echotexture, while hypogonadism was independently predicted also by reduced echogenicity and presence of microlithiasis.

Discussion and conclusions: We describe the testicular US characteristics that are independently associated with impaired spermatogenesis and hypogonadism and propose the TU score as a simple screening method for use in subjects referred for testicular US.

KEYWORDS
hypogonadism, infertility, spermatogenesis, testicular endocrine function, testicular ultrasound, testosterone

Pozza and Kanakis contributed equally to this work.

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REVIEW ARTICLE

The effects of postnatal exposure of endocrine disruptors on testicular function: a systematic review and a meta-analysis

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Abstract

Background Despite many epidemiological studies having been conducted, the impact of postnatal exposure of endocrine disruptors (EDs) on testicular function remains a controversial issue.

Aim To systematically review the literature and perform a quantitative synthesis to evaluate the effect of EDs on testicular function.

Materials and methods A comprehensive search was conducted in the MEDLINE, Scopus, and CENTRAL databases. Eligible for the systematic review were observational (cross-sectional and cohort) studies with (i) adult men who had a high probability of postnatal exposure to EDs ("exposed"), (ii) adult men who had a low probability of postnatal exposure to EDs ("non-exposed"), and (iii) an outcome of interest [seminal parameters and reproductive hormone concentrations]. The continuous outcomes in each of the studies were synthesized by the random effects model and expressed as standardized mean difference (SMD) with 95% confidence interval (CI).

Results Thirteen studies, including 959 exposed and 907 non-exposed men, fulfilled the inclusion criteria. Exposure to EDs was associated with decreased LH [SMD − 0.17, 95% CI − 0.33 to − 0.02, 10 studies (616 exposed, 563 non-exposed), I^2 40%, p = 0.09], progressive motility [SMD − 0.45, 95% CI − 0.77 to − 0.13, three studies (133 cases, 153 controls), I^2 38%, p = 0.20], and normal morphology [SMD − 0.50, 95% CI − 0.85 to − 0.14, eight studies (562 cases, 540 controls), I^2 87%, p < 0.01] compared with non-exposure. No difference was observed between the other study groups.

Conclusions Postnatal exposure to EDs is associated with decreased semen quality. Nevertheless, there is no evidence that a disruption of testicular function mediates the deterioration in semen quality.

Keywords Endocrine disruptors · Hormone disruption · Male infertility · Sperm parameters

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ORIGINAL ARTICLE

ANDROLOGY WILEY

Pantoprazole, a proton-pump inhibitor, impairs human sperm motility and capacitation in vitro

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Funding information
INSERM; Applied Human Toxicology – SCAHT

Abstract

Background: The effects of PPIs on human sperm fertilizing capacity were poorly investigated although these drugs are widely over-used. Two publications retrospectively studied relationships between any PPI intake and sperm parameters from patients consulting at infertility clinics, but the conclusions of these reports were contradictory. Only two reports investigated the effects of lansoprazole and omeprazole on sperm motility and found lansoprazole to be deleterious and omeprazole to be neutral for sperm motility. The inconsistency of the PPI effect in the previous reports emphasizes the need for more basic research on human spermatozoa, taking into account the hypothesis that the different PPI drugs may have different effects on sperm physiology.

Objectives: Do PPIs, which are among the most widely sold drug in the word, impact negatively human sperm capacitation and sperm motility?

Materials and methods: The effects of PPIs on human sperm maturation and motility were analyzed by CASA, flow cytometry, and Western blot.

Results: We tested the impact of 6 different PPIs on human sperm motility and capacitation. We showed that pantoprazole, but not the other PPIs, decreased sperm progressive motility and capacitation-induced sperm hyperactivation. We therefore investigated further the effects of pantoprazole on sperm capacitation, and we observed that it had a significant deleterious effect on the capacitation-induced hyperpolarization of the membrane potential and capacitation-associated protein phosphorylation.

Discussion and Conclusion: Our results indicate that exposure to pantoprazole has an adverse effect on the physiological competence of human spermatozoa. As the capacitation process takes place within the female tract, our results suggest that PPIs intake by the female partner may impair in vivo sperm maturation and possibly fertilization. Moreover, the absence of adverse effect by PPIs on mouse sperm emphasizes the need to develop reprotox assays using human material to better assess the effects of medication intake on sperm physiology.

KEYWORDS
capacitation, fertility, flow cytometry, human spermatozoa, proton-pump inhibitor

ORIGINAL ARTICLES: ANDROLOGY

Check for updates

The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial

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Objective: To determine whether antioxidants improve male fertility, as measured by semen parameters and DNA fragmentation at 3 months and pregnancy resulting in live birth after up to 6 months of treatment, among couples with male factor infertility.
Design: Multicenter, double-blind, randomized, placebo-controlled trial with an internal pilot study.
Setting: Nine fertility centers in the United States from December 2015 to December 2018.
Patient(s): Men (N = 174) with sperm concentration ≤15 million/mL, motility ≤40%, normal morphology ≤4%, or DNA fragmentation >25%, and female partners who were ovulatory, ≤40 years old, and had documented tubal patency.
Intervention(s): Males randomly assigned to receive an antioxidant formulation (n = 85) containing 500 mg of vitamin C, 400 mg of vitamin E, 0.20 mg of selenium, 1,000 mg of L-carnitine, 20 mg of zinc, 1,000 μg of folic acid, 10 mg of lycopene daily, or placebo (n = 86). Treatment lasted for a minimum of 3 months and maximum of 6 months, and couples attempted to conceive naturally during the first 3 months and with clomiphene citrate with intrauterine insemination of the female partner in months 4 through 6.

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Supported by the National Institutes of Health (NIH)/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Grants U10HD077844 (to A.Z.S.), U10HD077680 (to K.R.H., V.L.B.), U10HD077841 (to M.I.C.), U10HD027049 (to C.C.); U10HD038992 (to R.S.L.); U10HD039005 (to M.P.D, R.U., S.K.); and UL1 TR001863 (to H.Z.). This work was funded through cooperative agreements with the awardee institutions. All authors had financial support from NICHD/NIH for the submitted work, had no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and had no other relationships or activities that could appear to have influenced the submitted work.
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Main Outcome Measure(s): Primary outcome was live birth; secondary outcomes included pregnancy within 6 months of treatment. For the internal pilot, the primary outcomes were semen parameters and sperm DNA fragmentation index after 3 months of treatment.
Result(s): In the Males, Antioxidants, and Infertility (MOXI) study, after 3 months of treatment, the change in sperm concentration differed between the antioxidant group (median −4.0 [interquartile range −12.0, 5.7] million/mL) and placebo group (+2.4 [−9.0, 15.5] million/mL). However, there were no statistically significant differences between the two groups for changes in sperm morphology, motility, or DNA fragmentation. Among the 66 oligospermic men at randomization, sperm concentration did not differ at 3 months between the antioxidant and control groups: 8.5 (4.8, 15.0) million/mL versus 15.0 (6.0, 24.0) million/mL. Of the 75 asthenospermic men, motility did not differ at 3 months: 34% ± 16.3% versus 36.4% ± 15.8%. Among the 44 men with high DNA fragmentation, DNA fragmentation did not differ at 3 months: 29.5% (21.6%, 36.5%) versus 28.0% (20.6%, 36.4%). In the entire cohort, cumulative live birth did not differ at 6 months between the antioxidant and placebo groups: 15% versus 24%.
Conclusion(s): Antioxidants do not improve semen parameters or DNA integrity among men with male factor infertility. Although limited by sample size, this study suggests that antioxidant treatment of the male partner does not improve in vivo pregnancy or live-birth rates.
Clinical Trial Registration Number: NCT02421887 (Fertil Steril® 2020;113:552–60. ©2019 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Antioxidants, male factor infertility, randomized controlled trial

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ORIGINAL ARTICLE

ANDROLOGY WILEY

Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients

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Abstract

Background: The pandemic of new severe acute respiratory syndrome (SARS) due to coronavirus (CoV) 2 (SARS-CoV-2) has stressed the importance of effective diagnostic and prognostic biomarkers of clinical worsening and mortality. Epidemiological data showing a differential impact of SARS-CoV-2 infection on women and men have suggested a potential role for testosterone (T) in determining gender disparity in the SARS-CoV-2 clinical outcomes.

Objectives: To estimate the association between T level and SARS-CoV-2 clinical outcomes (defined as conditions requiring transfer to higher or lower intensity of care or death) in a cohort of patients admitted in the respiratory intensive care unit (RICU).

Materials and methods: A consecutive series of 31 male patients affected by SARS-CoV-2 pneumonia and recovered in the respiratory intensive care unit (RICU) of the "Carlo Poma" Hospital in Mantua were analyzed. Several biochemical risk factors (ie, blood count and leukocyte formula, C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH), ferritin, D-dimer, fibrinogen, interleukin 6 (IL-6)) as well as total testosterone (TT), calculated free T (cFT), sex hormone–binding globulin (SHBG), and luteinizing hormone (LH) were determined.

Results: Lower TT and cFT were found in the transferred to ICU/deceased in RICU group vs groups of patients transferred to IM or maintained in the RICU in stable condition. Both TT and cFT showed a negative significant correlation with biochemical risk factors (ie, the neutrophil count, LDH, and PCT) but a positive association with the lymphocyte count. Likewise, TT was also negatively associated with CRP and ferritin levels. A steep increase in both ICU transfer and mortality risk was observed in men with TT < 5 nmol/L or cFT < 100 pmol/L.

Discussion and conclusion: Our study demonstrates for the first time that lower baseline levels of TT and cFT levels predict poor prognosis and mortality in SARS-CoV-2-infected men admitted to RICU.

KEYWORDS
COVID-19, inflammatory markers, mortality, prognosis, sex hormones

Giulia Rastrelli and Vincenza Di Stasi equally contributed to this study.

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www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Male Infertility

FSH dosage effect on conventional sperm parameters: a meta-analysis of randomized controlled studies

Rossella Cannarella, Sandro La Vignera, Rosita A Condorelli, Laura M Mongioì, Aldo E Calogero

Follicle-stimulating hormone (FSH) represents a therapeutic option in normogonadotropic patients with idiopathic oligozoospermia. The aim of this review was to evaluate the possible dose- and drug-dependent efficacy of FSH treatment on conventional sperm parameters. We performed a comprehensive systematic review via a meta-analysis of all available randomized controlled trials, in which FSH administration was compared with placebo or no treatment when administered to normogonadotropic patients with idiopathic oligozoospermia. Of the 971 articles that were retrieved, 5 were finally included, including a total of 372 patients and 294 controls. Overall, FSH treatment was effective in ameliorating the sperm concentration, total count, progressive motility, but not normal forms. On the basis of the weekly dosage, the studies were classified into those using low (175–262.5 IU per week), intermediate (350–525 IU per week), and high (700–1050 IU per week) doses. At low doses, FSH improved only sperm motility. At intermediate doses, FSH ameliorated sperm concentration and morphology. Total sperm count and progressive motility showed a trend toward the increase. At high doses, FSH increased sperm concentration, total sperm count, and progressive motility. Sperm morphology showed a trend toward the increase. Finally, both highly purified FSH (hpFSH) and recombinant human FSH (rhFSH) improved sperm concentration, total sperm count, progressive motility, but not morphology. No different efficacy was observed between these two preparations. This meta-analysis provides evidence in favor of high FSH doses. The FSH efficacy was not related to the preparation type (recombinant *vs* highly purified). Further studies are needed to evaluate the effectiveness of long-standing treatment regimes.

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Keywords: follicle-stimulating hormone; male infertility; oligozoospermia; sperm concentration; sperm count

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Open Access

ORIGINAL ARTICLE

Male Infertility

A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility

Francesco Del Giudice[1], Gian Maria Busetto[1], Ettore De Berardinis[1], Isabella Sperduti[2], Matteo Ferro[3], Martina Maggi[1], Martin S Gross[4], Alessandro Sciarra[1], Michael L Eisenberg[5]

Aromatase activity has commonly been associated with male infertility characterized by testicular dysfunction with low serum testosterone and/or testosterone to estradiol ratio. In this subset of patients, and particularly in those with hypogonadism, elevated levels of circulating estradiol may establish a negative feedback on the hypothalamic–pituitary–testicular axis by suppressing follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production and impaired spermatogenesis. Hormonal manipulation via different agents such as selective estrogen modulators or aromatase inhibitors to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility is an off-label option for treatment. We carried out a systematic review and meta-analysis of the literature of the past 30 years in order to evaluate the benefits of the use of aromatase inhibitors in the medical management of infertile/hypoandrogenic males. Overall, eight original articles were included and critically evaluated. Either steroidal (Testolactone) or nonsteroidal (Anastrozole and Letrozole) aromatase inhibitors were found to statistically improve all the evaluated hormonal and seminal outcomes with a safe tolerability profile. While the evidence is promising, future prospective randomized placebo-controlled multicenter trials are necessary to better define the efficacy of these medications.

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Keywords: aromatase inhibitor; hypogonadism; male infertility; meta-analysis; systematic review

Λιπίδια

ΠΡΟΕΔΡΟΣ: Βασίλης Τσιμιχόδημος
ΟΜΙΛΗΤΗΣ: Χαράλαμπος Μηλιώνης

Research

JAMA | Original Investigation

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; A. Michael Lincoff, MD; Michelle Garcia, RN, BSN, CCRC; Dianna Bash, BSN; Christie M. Ballantyne, MD; Philip J. Barter, MBBS, PhD; Michael H. Davidson, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Darren K. McGuire, MD, MHSc; Dariush Mozaffarian, MD, DrPH; Paul M Ridker, MD; Kausik K. Ray, MBChB, MD, MPhil; Brian G. Katona, PharmD; Anders Himmelmann, MD, PhD; Larrye E. Loss, PharmD, MBA; Martin Rensfeldt; Torbjörn Lundström, MD, PhD; Rahul Agrawal, MD; Venu Menon, MD; Kathy Wolski, MPH; Steven E. Nissen, MD

JAMA Network

QUESTION In statin-treated patients with high cardiovascular risk, high triglycerides, and low HDL cholesterol, does adding a carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) to ongoing treatment improve cardiovascular outcomes?

CONCLUSION The findings from this randomized trial do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in patients at high cardiovascular risk.

POPULATION

8510 Men
4568 Women

Adults with high triglycerides and low HDL levels, treated with statins, and at high risk of adverse cardiovascular outcomes

Mean age: 62.5 years

LOCATIONS

675 Hospitals in 22 countries

INTERVENTION

13 078 Patients randomized

6539
Omega-3
4 g/d of omega-3 CA (carboxylic acid) capsules containing EPA and DHA for up to 5 years

6539
Corn oil
Comparator capsules for up to 5 years

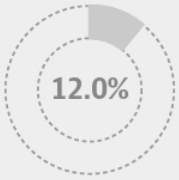
PRIMARY OUTCOME

Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization

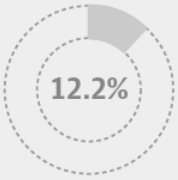
FINDINGS

Occurrence of composite outcome events

Omega-3
785 of 6539 patients



Corn oil
795 of 6539 patients



At early trial termination, there was no significant difference between groups in the primary outcome:

HR, **0.99** (95% CI, 0.90-1.09); *P* = .84

Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. Published online November 15, 2020. doi:10.1001/jama.2020.22258

JAMA | Original Investigation

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

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IMPORTANCE It remains uncertain whether the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce cardiovascular risk.

OBJECTIVE To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, randomized, multicenter trial (enrollment October 30, 2014, to June 14, 2017; study termination January 8, 2020; last patient visit May 14, 2020) comparing omega-3 CA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized at 675 academic and community hospitals in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa.

INTERVENTIONS Participants were randomized to receive 4 g/d of omega-3 CA (n = 6539) or corn oil, which was intended to serve as an inert comparator (n = 6539), in addition to usual background therapies, including statins.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

RESULTS When 1384 patients had experienced a primary end point event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs the corn oil comparator. Among the 13 078 treated patients (mean [SD] age, 62.5 [9.0] years; 35% women; 70% with diabetes; median low-density lipoprotein [LDL] cholesterol level, 75.0 mg/dL; median triglycerides level, 240 mg/dL; median HDL-C level, 36 mg/dL; and median high-sensitivity C-reactive protein level, 2.1 mg/L), 12 633 (96.6%) completed the trial with ascertainment of primary end point status. The primary end point occurred in 785 patients (12.0%) treated with omega-3 CA vs 795 (12.2%) treated with corn oil (hazard ratio, 0.99 [95% CI, 0.90-1.09]; *P* = .84). A greater rate of gastrointestinal adverse events was observed in the omega-3 CA group (24.7%) compared with corn oil–treated patients (14.7%).

CONCLUSIONS AND RELEVANCE Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

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Visual Abstract

Editorial and Editor's Note

Supplemental content

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Considerable interest has focused on the potential cardiovascular benefits of omega-3 fatty acids. Observational studies have demonstrated an inverse association between dietary consumption of either fatty fish or omega-3 fatty acids and incident cardiovascular events[1,2] and that circulating concentrations of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) inversely correlate with cardiovascular risk.[3,4] Omega-3 fatty acid supplementation exerts favorable effects on lipoprotein metabolism and inflammatory, oxidative, thrombotic, vascular, and arrhythmogenic factors implicated in cardiovascular disease.[5,6] One study, prior to routine clinical use of statins, demonstrated cardiovascular benefit with 1 g/d of an EPA and DHA supplement,[7] but subsequent larger trials failed to replicate these findings.[8,9]

Most trials recruited a broad cohort of patients and administered low doses of omega-3 fatty acids that did not produce substantial increases in EPA or DHA concentrations. Recent trials have studied higher dosages of omega-3 fatty acids, reporting a cardiovascular benefit in 2 trials of purified EPA.[10,11] However, other recent trials studying lower doses of omega-3 fatty acids in a broader range of patients failed to demonstrate significant reductions of total cardiovascular events.[12,13]

Omega-3 CA (Epanova; AstraZeneca) is a carboxylic acid formulation of omega-3 fatty acids (EPA and DHA) that does not require hydrolysis by pancreatic lipase during intestinal absorption, eliminating the need for consumption with a high-fat meal, resulting in greater bioavailability compared with standard omega-3 ethyl ester formulations. Administration of 4 g/d of omega-3 CA produces similar increases in plasma EPA levels as doses of purified EPA approved for clinical use, and also increases DHA concentrations.[14,15] Initial trials of omega-3 CA demonstrated dose-dependent lowering of plasma triglyceride levels up to 31%.[14,15]

This trial, the Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH), evaluated the effects of omega-3 CA on clinical outcomes in patients at high cardiovascular risk.

Key Points

Question In statin-treated patients with high cardiovascular risk, high triglycerides, and low HDL cholesterol levels, does adding a carboxylic acid formulation of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) to background therapy improve cardiovascular outcomes?

Findings In this randomized clinical trial of 13 078 patients that was stopped early, daily supplementation with omega-3 fatty acids, compared with corn oil, resulted in no significant difference in a composite outcome of major adverse cardiovascular events (hazard ratio, 0.99)

Meaning These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in patients with high cardiovascular risk.

Methods

Study Organization and Oversight

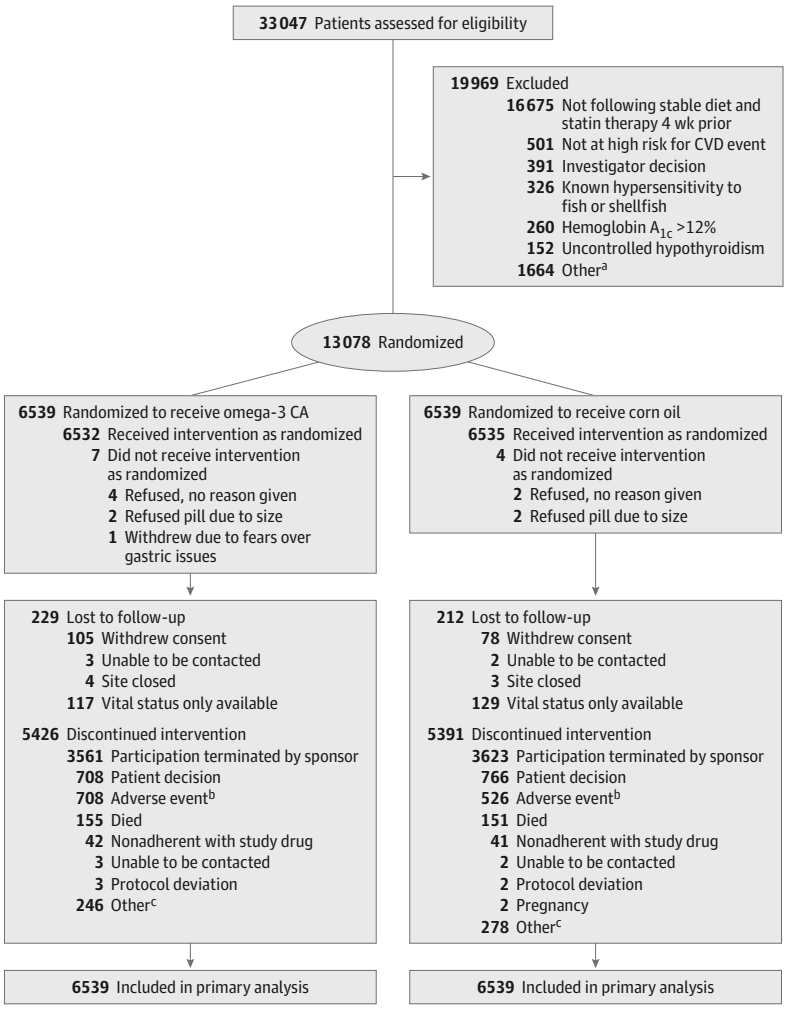
The trial was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research). The protocol was developed by members of the independent academic executive steering committee in conjunction with the sponsor. The study protocol and statistical analysis plan are available in Supplement 1 and Supplement 2. The study design was approved by responsible regulatory agencies and ethics committees or institutional review boards at each site prior to commencing patient enrollment. All potential patients provided written informed consent prior to study entry. IQVIA provided operational management of sites and collected the data. A data monitoring committee (DMC) that was independent from the executive steering committee and sponsor monitored the trial and performed analyses of unblinded data supported by an independent data analysis center at Statistics Collaborative Inc.

Study Population

Details of the study design have been published previously.[16] Adult patients (≥18 years) considered at high risk for a future cardiovascular event were eligible to participate. High cardiovascular risk was defined as (1) the presence of established atherosclerotic cardiovascular disease involving the coronary, peripheral, carotid, or aortic territories (secondary prevention); (2) type 1 or 2 diabetes with age 40 years or older for men and 50 years or older for women with at least 1 additional risk factor including chronic smoking, hypertension, high-sensitivity C-reactive protein (hs-CRP) level of 2 mg/L or higher, or moderately increased albuminuria; or (3) high-risk primary prevention patients aged at least 50 years for men or at least 60 years for women with at least 1 additional risk factor, including a family history of premature coronary artery disease, chronic smoking, hs-CRP level of 2 mg/L or higher, impaired kidney function, or coronary calcium score greater than 300 Agatston units.

At least 50% of randomized patients were required to satisfy criteria for secondary cardiovascular prevention. All eligible patients were also required to be treated with a statin for at least 4 weeks; have a low-density lipoprotein (LDL) cholesterol level lower than 100 mg/dL or be treated with maximally tolerated statin therapy; and have atherogenic dyslipidemia, defined as triglyceride levels of 180 to less than 500 mg/dL and high-density lipoprotein (HDL) cholesterol levels lower than 42 mg/dL for men or lower than 47 mg/dL for women. Patients were excluded from enrollment if they had a prior ischemic cardiovascular event within the preceding 30 days or consumed more than one capsule (1 g) per day of omega-3 dietary supplements or any prescription medication containing EPA or DHA. Use of fibrates or weight loss drugs was also prohibited. Patient race and ethnicity were reported by participants using an open-ended question to account for ethnic variability in baseline systemic omega-3 fatty acid concentrations.

Figure 1. Recruitment, Randomization, and Patient Flow in the STRENGTH Clinical Trial



CA indicates carboxylic acid formulation; CVD, cardiovascular disease.

[a] Other reasons for not meeting inclusion/exclusion criteria include not meeting age requirement; elevated liver enzymes; use of fibrates, bile acid sequestrants, or niacin within 4 weeks of randomization; not following a stable diet; poorly controlled hypertension; and occurrence of myocardial infarction or coronary bypass graft surgery within 30 days of randomization.

[b] Adverse events leading to study drug discontinuation by system organ class (omega-3 CA/corn oil; multiple events are possible): gastrointestinal (403/202), neoplasms (81/78), cardiac (39/46), nervous system (36/42), infections (32/30), skin (24/20), kidney/urinary (16/25), investigations (21/14), metabolic disorders (18/17), musculoskeletal (14/18), hepatobiliary (13/14), injury (11/13), vascular (13/11), respiratory (13/10), and psychiatric (11/7).

[c] Other reasons abstracted from free text (omega-3 CA/corn oil): investigator decision (22/22), patient decision (26/33), potential lost to follow-up (113/129), reached end point (18/18), moved (31/36), social reasons (7/13), comorbid condition (11/8), pill burden (5/10), study terminated (9/4), and site closed (4/5).

Study Procedures

The protocol specified that enrolled patients receive treatment with a stable dose of statin therapy for at least 4 weeks and lifestyle advice for the prevention of cardiovascular disease. Patients who met all inclusion criteria and volunteered to participate were randomized in a 1:1 ratio to treatment with omega-3 CA, 4 g/d, or a matching corn oil comparator for a maximum duration of 5 years (**Figure 1**). Randomization was performed using a computer-generated random number with a blocking size of 6. Corn oil was selected because it was considered an inert comparator without effects on biochemical parameters associated with cardiovascular risk.[17,18] Patients reported for study visits at 3, 6, and 12 months following randomization and then every 6 months thereafter. Additional telephone calls were made on a 3-month basis commencing at month 9. A visit for assessment of any adverse events was performed 3 weeks after the last dose of study medication. Plasma and red blood cell concentrations of EPA and DHA were determined by OmegaQuant.

Study End Points

The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. Secondary efficacy end points included the following: (1) composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina in patients with established cardiovascular disease at baseline, (2) composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in the whole cohort and in patients with established cardiovascular disease at baseline, (3) composite of cardiac death, nonfatal myocardial infarction, coronary revascularization, and hospitalization for unstable angina in the whole cohort and in patients with established cardiovascular disease at baseline, (4) cardiovascular death in the whole cohort and in patients with established cardiovascular disease at baseline, and (5) all-cause death in the whole cohort and in patients with established cardiovascular disease at baseline.

The primary end point and key secondary end points (1) through (5) were evaluated in a hierarchical manner (see eAppendix in Supplement 3). Prespecified tertiary efficacy end points included new-onset atrial fibrillation, thrombotic events, and new-onset heart failure. Changes in lipid levels, inflammatory markers, and levels of both EPA and DHA were also prespecified efficacy parameters. A post hoc analysis investigated the association between both plasma and red blood cell concentrations of EPA and DHA with cardiovascular event rates. All investigator-reported primary and secondary events, as well as heart failure events, were adjudicated by a core laboratory at C5Research.

Sample Size Calculation and Power

The primary efficacy analysis was based on time to first occurrence of any positively adjudicated primary end point including all randomized patients regardless of treatment adherence. Time-to-event analysis was calculated from randomization date to the date of the event, or censored at the last known follow-up for each patient. The trial was designed to enroll 13 000 patients and study completion required positive adjudication of 1600 primary events to provide 90% power to detect a 15% reduction in relative risk in the omega-3 CA group. A 15% reduction in the risk of cardiovascular events was selected because it was deemed the minimally important difference of clinical significance by consensus among the trial executive committee.

Assuming a 4% annual primary end point event rate in the corn oil group, a trial duration of 4.5 years was projected. Interim analyses for superiority or futility were specified at 50% and 75% of the required primary end point events. A group sequential design was used with superiority boundaries for both interim analyses set at an absolute value for a z score of 3.719 and futility boundaries set at a z score of 0.3085 at the first interim analysis and 1.2375 for the second interim analysis.

Statistical Analysis

The full analysis set included all patients according to their randomization group. A safety analysis population was defined as any patient who took at least 1 dose of study drug. The efficacy objectives were evaluated in all randomized patients using analysis of time from randomization to the first event. Censoring rules are described in Supplement 1. Estimates of hazard ratios (HRs) and 95% CIs for omega-3 CA compared with corn oil were calculated using Cox proportional hazards models with covariates for established cardiovascular disease at baseline (yes/no) and region. The proportionality assumption was assessed by including a time-dependent covariate (treatment × time interaction) to the model. Biochemical parameters are presented as median with first (Q1) and third (Q3) quartiles.

The differences in percentage change from baseline between the omega-3 CA and corn oil groups were estimated from an analysis of covariance model (ANCOVA) with treatment group as a main effect and natural log of the baseline as a covariate. The dependent variable was calculated as the natural log of the ratio of the follow-up visit to the baseline visit: log[100 × log(follow-up/baseline)]. The least-squares estimates for differences between treatment groups were then back-transformed from the log scale and expressed as the geometric mean ratio. A sensitivity analysis was conducted using multiple imputation methods to assess the effect of missing biomarker data.

Significance testing was performed using 2-sided tests (α= .05). Primary and key secondary efficacy end points were evaluated sequentially to control the type I error rate. Other end points were not adjusted for multiplicity, and findings for analyses of these end points should be interpreted as exploratory. The statistical analysis plan (Supplement 1) prespecified that a hierarchical testing strategy was to be used, and that once an end point was not statistically significant at an α of .05, all subsequent comparisons will be considered exploratory and nominal P values will be reported. Subgroup analyses of the primary end point were conducted as prespecified, with any potential difference determined by the presence of a nominally significant P value on formal interaction testing.

All analyses were conducted using SAS version 9.4. Additional analytic methods are described in the study protocol and statistical analysis plan (Supplement 1 and Supplement 2).

Early Trial Termination

On January 8, 2020, when 1384 primary end points had been recorded in 13 078 randomized patients, the independent DMC recommended termination of the trial due to a low probability of demonstrating a clinical benefit of omega-3 CA compared with corn oil. This decision was based on the data crossing the futility boundary prespecified in the group sequential monitoring plan in conjunction with an increased risk of atrial fibrillation (oral communication, DMC chair Mark Pfeffer, MD, PhD, to executive committee chair Steven E. Nissen, MD, August 2020). The executive steering committee and sponsor accepted this recommendation and terminated the trial on this date, and patients were recommended to stop study medication. End-of-study visits were scheduled for all patients, with the last patient visit completed by May 14, 2020. The executive steering committee and others involved in the conduct of the trial remained blinded to treatment allocation and results until the conclusion of the trial and finalization of the database.

Study drug was stopped as soon as feasible following the termination of the trial. Because the study was terminated during the early phases of the coronavirus disease 2019 (COVID-19) pandemic, the end-of-treatment visit was permitted to be completed by telephone to allow the study to close in a timely and orderly manner, with the least possible effect on study integrity.

Results

Study Population

A total of 33 047 patients were assessed for eligibility; after exclusions, 13 078 patients were enrolled at 675 sites in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa between October

30, 2014, and June 14, 2017, and entered into the primary analysis. The disposition of patients during the study is summarized in Figure 1. At study closure the median patient follow-up was 42.0 months (interquartile range [IQR], 37.5-48.3). Patients were treated with study drug for a median of 38.2 months (IQR, 30.5-44.9).

Vital status was recorded in 99.8% of patients and 96.6% of patients had complete follow-up for assessment of the primary end point. Baseline characteristics of patients at randomization were similar in the 2 treatment groups (**Table 1**). Patients (mean age, 62.5 years; men, 65%; White race, 82%) demonstrated a high rate of cardiovascular risk factors, including diabetes (70%) and established atherosclerotic disease (56%), in both groups. All patients were treated with statins (50% high-intensity) at randomization. A high rate of use of other evidence-based preventive therapies was observed in both groups.

Clinical End Points

At the completion of the study, 1580 patients had experienced an adjudicated first primary end point event. The primary end point of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization occurred in 785 patients (12.0%) treated with omega-3 CA and 795 (12.2%) treated with corn oil (HR, 0.99 [95% CI, 0.90-1.09]; *P* = .84) (**Table 2**, **Figure 2**).

Similarly, the secondary end point of cardiovascular death, myocardial infarction, or stroke occurred in 541 patients (8.3%) treated with omega-3 CA and 517 (7.9%) treated with corn oil (HR, 1.05 [95% CI, 0.93-1.19]; nominal *P* = .40). An additional secondary end point—cardiac death, myocardial infarction, coronary revascularization, or hospitalization for unstable angina—occurred in 556 patients (8.5%) treated with omega-3 CA and 616 (9.4%) treated with corn oil (HR, 0.91 [95% CI, 0.81-1.02]; nominal *P* = .09).

There were no significant differences between the treatment groups with regard to the risk of individual components of the primary end point (Table 2). Survival curves for the primary end point in patients with and without established cardiovascular disease are shown in eFigure 1 in Supplement 3.

Prespecified subgroup analyses (**Figure 3**) revealed an HR for the primary end point of 0.94 (95% CI, 0.84-1.05) in the secondary prevention population and 1.16 (95% CI, 0.95-1.41) in the primary prevention population, with a nominal interaction *P* value for these 2 subgroups of .07. There were numerically fewer cardiovascular events in the omega-3 CA group among patients treated with ezetimibe (nominal interaction *P* = .008). There was a nominally significant reduction in the risk of cardiac death, myocardial infarction, coronary revascularization, and hospitalization for unstable angina in patients with established cardiovascular disease at baseline, although this finding was unadjusted for multiplicity (Table 2). All-cause mortality occurred in 373 patients (5.7%) in the omega-3 CA group and 333 (5.1%) in the corn oil group (nominal *P* = .11).

With regard to prespecified tertiary end points, an increased rate of investigator-reported new-onset atrial fibrillation was observed in the omega-3 CA group (2.2% vs 1.3%; HR, 1.69 [95% CI, 1.29-2.21]; nominal *P* < .001) compared with corn oil (number needed to harm, 114) (eFigure 2 in Supplement 3). There were no significant differences between the groups with regard to new-onset heart failure (2.2% vs 2.0%; HR, 1.12 [95% CI, 0.88-1.42]; nominal *P* = .35) or venous thromboembolic events (0.41% vs 0.26%; HR, 1.62 [95% CI, 0.88-2.97]; nominal *P* = .12).

In a post hoc exploratory analysis, no association was observed between either plasma or red blood cell EPA or DHA concentrations after 12 months of treatment and subsequent cardiovascular event rates (**Table 3**).

Table 1. Patient Characteristics and Medication Use in a Trial of Omega-3 Fatty Acids to Reduce Major Adverse Cardiovascular Events

	No. (%)	
	Omega-3 CA (n = 6539)	Corn oil (n = 6539)
Age, mean (SD), y	62.5 (9.0)	62.5 (9.0)
Sex		
Male	4250 (65.0)	4260 (65.1)
Female	2289 (35.0)	2279 (34.9)
Body mass index, mean (SD)	32.2 (5.7)	32.2 (5.6)
Race		
White	5341 (81.7)	5382 (82.3)
Asian	698 (10.7)	657 (10.0)
Black	180 (2.8)	166 (2.5)
Other[a]	320 (4.9)	334 (5.1)
Ethnicity: Hispanic or Latino	264/4647 (5.7)	268/4675 (5.7)
Comorbidities		
Established CVD at baseline	3638 (55.6)	3678 (56.2)
Coronary disease	3009 (46.0)	3026 (46.3)
Cerebrovascular disease	536 (8.2)	512 (7.8)
Peripheral vascular disease	227 (3.5)	257 (3.9)
Aortic disease	214 (3.3)	244 (3.7)
Diabetes at baseline[b]	4608 (70.5)	4562 (69.8)
Hypertension	5732 (87.7)	5688 (87.0)
eGFR,[c] mean (SD), mL/min/1.73 m^2	77.2 (19.9)	77.5 (19.7)
Medication use		
RAAS blockers	5315 (81.3)	5310 (81.2)
Antiplatelet agents	4623 (70.7)	4700 (71.9)
β-Blockers	4347 (66.5)	4348 (66.5)
High-intensity statin	3255 (49.8)	3273 (50.1)
Other statin	3284 (50.2)	3266 (49.9)
Ezetimibe	234 (3.6)	245 (3.7)

Abbreviations: CA, carboxylic acid formulation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin aldosterone system.

[a] The "other" category included American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; multiple races; and unknown.

[b] Diabetes on or before the first dose of study medication, defined by patient self-report, chart review, or use of diabetes medications.

[c] Estimated glomerular filtration rate was estimated using the CKD-EPI formula: eGFR = 141 × min(SCr/κ, 1)α × max(SCr /κ, 1) − 1.209 × 0.993Age × 1.018 [if female] × 1.159 [if Black]; where k = 0.7 for females or 0.9 for males and α = −0.329 for females or −0.411 for males.

Table 2. Incidence of Adjudicated Clinical Events in a Trial of Omega-3 Fatty Acids to Reduce Major Adverse Cardiovascular Events[a]

	Omega-3 CA (n = 6539)			Corn oil (n = 6539)			Omega 3 CA vs corn oil		
	Person-years	IR per 100 person-years	No. of patients with events (% of total)	Person-years	IR per 100 person-years	No. of patients with events (% of total)	Difference in IR (95% CI)	HR (95% CI)	*P* value
Primary end point									
MACE[b]	21 908	3.58	785 (12.0)	21 920	3.63	795 (12.2)	−0.04 (−0.40 to 0.31)	0.99 (0.90-1.09)	.84
Components of the composite outcome									
Cardiovascular death	23 500	0.97	228 (3.5)	23 575	0.90	211 (3.2)	0.07 (−0.10 to 0.25)	1.09 (0.90-1.31)	.37
Nonfatal MI	22 650	0.96	218 (3.3)	22 725	0.99	226 (3.5)	−0.03 (−0.21 to 0.15)	0.97 (0.81-1.17)	.77
Nonfatal stroke	22 786	0.62	142 (2.2)	22 871	0.55	125 (1.9)	0.08 (−0.06 to 0.22)	1.14 (0.90-1.45)	.28
Revascularization	22 236	1.86	414 (6.3)	22 270	1.98	441 (6.7)	−0.12 (−0.38,0.14)	0.94 (0.83-1.08)	.41
Hospitalization for unstable angina	22 854	0.38	87 (1.3)	22 895	0.45	104 (1.6)	−0.07 (−0.19 to 0.04)	0.84 (0.63-1.12)	.23
Secondary end points[c]									
MACE in patients with established CVD at baseline	11 695	4.87	569 (15.6)	11 751	5.19	610 (16.6)	−0.32 (−0.90 to 0.25)	0.94 (0.84-1.05)	.27
Cardiovascular events[d]	22 425	2.41	541 (8.3)	22 507	2.30	517 (7.9)	0.11 (−0.17 to 0.40)	1.05 (0.93-1.19)	.40
Cardiovascular events in patients with established CVD at baseline	12 091	3.17	383 (10.5)	12 223	3.15	385 (10.5)	0.02 (−0.43 to 0.46)	1.01 (0.87-1.16)	.94
Coronary events[e]	22 121	2.51	556 (8.5)	22 127	2.78	616 (9.4)	−0.27 (−0.57 to 0.03)	0.91 (0.81-1.02)	.09
Coronary events in patients with established CVD at baseline	11 826	3.53	417 (11.5)	11 892	4.15	493 (13.4)	−0.62 (−1.12 to −0.12)	0.85 (0.75-0.97)	.02
Cardiovascular death in patients with established CVD at baseline	12 722	1.19	152 (4.2)	12 927	1.07	138 (3.8)	0.13 (−0.13 to 0.39)	1.12 (0.89-1.41)	.34
All-cause death	23 500	1.59	373 (5.7)	23 575	1.41	333 (5.1)	0.17 (−0.05 to 0.40)	1.13 (0.97-1.31)	.11
All-cause death in patients with established CVD at baseline	12 722	1.84	234 (6.4)	12 927	1.56	202 (5.5)	0.28 (−0.04 to 0.60)	1.18 (0.97-1.42)	.09
Tertiary end points									
Heart failure event: hospitalization or urgent outpatient visit for heart failure	22 830	0.62	142 (2.2)	22 899	0.56	128 (2.0)	0.06 (−0.01 to 0.20)	1.12 (0.88-1.42)	.35
Atrial fibrillation[f]	22 740	0.63	144 (2.2)	22 916	0.38	86 (1.3)	0.26 (0.13 to 0.39)	1.69 (1.29-2.21)	<.001
Stent thrombosis[f]	23 009	0.05	12 (0.18)	23 063	0.07	17 (0.26)	−0.02 (−0.07 to 0.02)	0.71 (0.34-1.48)	.36
Venous thromboembolism or pulmonary embolism[f]	22 987	0.12	27 (0.41)	23 061	0.07	17 (0.26)	0.04 (−0.01 to 0.10)	1.62 (0.88-2.97)	.12

Abbreviations: CA, carboxylic acid formulation; CVD, cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction.

[a] *P* values were generated from the Wald test using a Cox proportional hazards model containing factors for randomized treatment group, established cardiovascular disease at baseline, and region. Estimates for the subgroup of patients with established cardiovascular disease at baseline adjusted only for treatment group and region. The proportionality assumptions were met for all adjudicated end points.

[b] MACE: first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergent/elective coronary revascularization, and hospitalization for unstable angina.

[c] The statistical analysis plan (Supplement 1) prespecified that a hierarchical testing strategy was to be used and that once an end point was not statistically significant at α = .05 all subsequent comparisons would be considered exploratory and nominal *P* values reported.

[d] Cardiovascular event: defined as the first occurrence of any of the components of cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

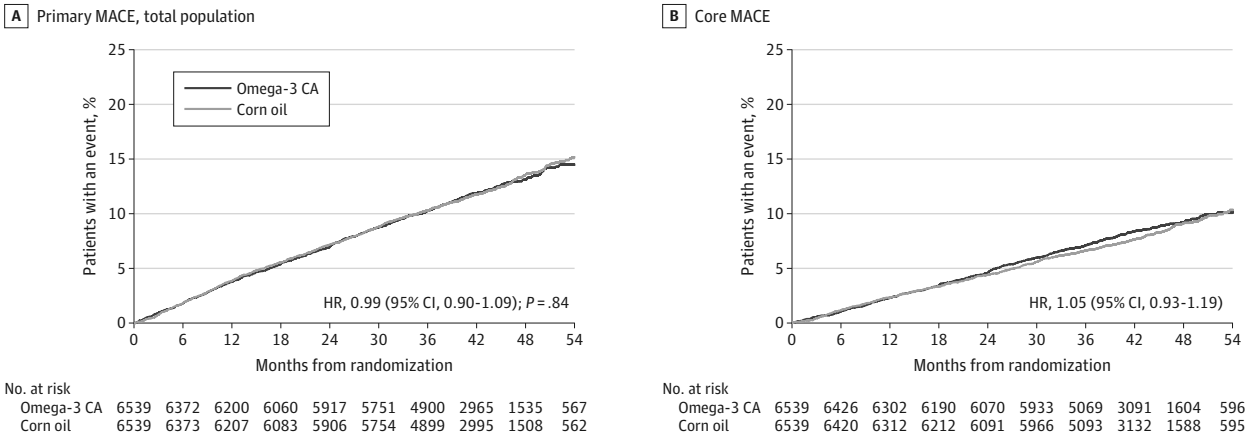
[e] Coronary events: defined as the first occurrence of any of the components of coronary events, including cardiac death, nonfatal myocardial infarction, emergent/elective coronary revascularization, or hospitalization for unstable angina.

[f] Not adjudicated.

Biochemical Parameters

Prespecified exploratory biochemical parameters at baseline, follow-up, and their percentage change during the course of the study are summarized in **Table 4**. At randomization, median levels of LDL cholesterol were 75 mg/dL; HDL cholesterol, 36 mg/dL; triglycerides, 240 mg/dL; and hs-CRP, 2.1 mg/L. During the course of the study, greater reductions in triglycerides (−19.0% vs −0.9%; geometric mean ratio [GMR], 0.82 [95% CI, 0.81-0.83]; *P* < .001), non-HDL cholesterol (−6.1% vs −1.1%; GMR, 0.95

Figure 2. Time to First Incidence of Any Component of the Primary Composite End Point and Time to Core MACE



A, The primary composite end point consisted of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. Median (Q1-Q3) observation time was 41.3 (36.0-47.5) months for patients receiving omega-3 CA and 41.4 (35.9-47.4) months for patients receiving corn oil. B, Core major adverse cardiovascular events (MACE) included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Median (Q1-Q3) observation time of 41.5 (36.6-47.8) months for patients receiving omega-3 CA and 41.6 (36.8-47.4) months for patients receiving corn oil.

[95% CI, 0.94-0.96]; $P < .001$), and hs-CRP (−20.0% vs −6.3%; GMR, 0.89 [95% CI, 0.84-0.95]; $P < .001$) were observed in the omega-3 CA treatment group compared with corn oil group, respectively.

LDL cholesterol levels increased in the omega-3 CA group but not in the corn oil group (1.2% vs −1.1%; GMR, 1.03 [95% CI, 1.01-1.04]; $P < .001$), while greater increases in HDL cholesterol were observed in the omega-3 CA group (5.0% vs 3.2%; GMR, 1.01 [95% CI, 1.00-1.02]; $P = .002$). Apolipoprotein CIII levels decreased in the omega-3 CA group but not in the corn oil group (−7.0% vs 5.9%; GMR, 0.88 [95% CI, 0.87-0.89]; $P < .001$). In contrast, no significant difference was observed with regard to percentage change in apolipoprotein B levels (−2.0% vs −1.0%; GMR, 0.99 [95% CI, 0.98-1.01]; $P = .34$) between the omega-3 and corn oil treatment groups, respectively.

Administration of omega-3 CA resulted in greater increases in concentrations of EPA as compared with corn oil (Table 4). Concentrations of DHA in plasma and in red blood cells were also increased by omega-3 CA administration, compared with corn oil (Table 4).

Adverse Events

The number of adverse events and serious adverse events are summarized in **Table 5**. Drug-related adverse events were more commonly observed in the omega-3 CA group than the comparator group (22.2% vs 12.9%, respectively). Discontinuation of study drug treatment (10.8% vs 8.0%) and dose reduction (12.0% vs 6.1%) for adverse events occurred more frequently in patients treated with omega-3 CA compared with those treated with corn oil. There were more gastrointestinal adverse events in the omega-3 CA group (24.7%) compared with corn oil–treated patients (14.7%).

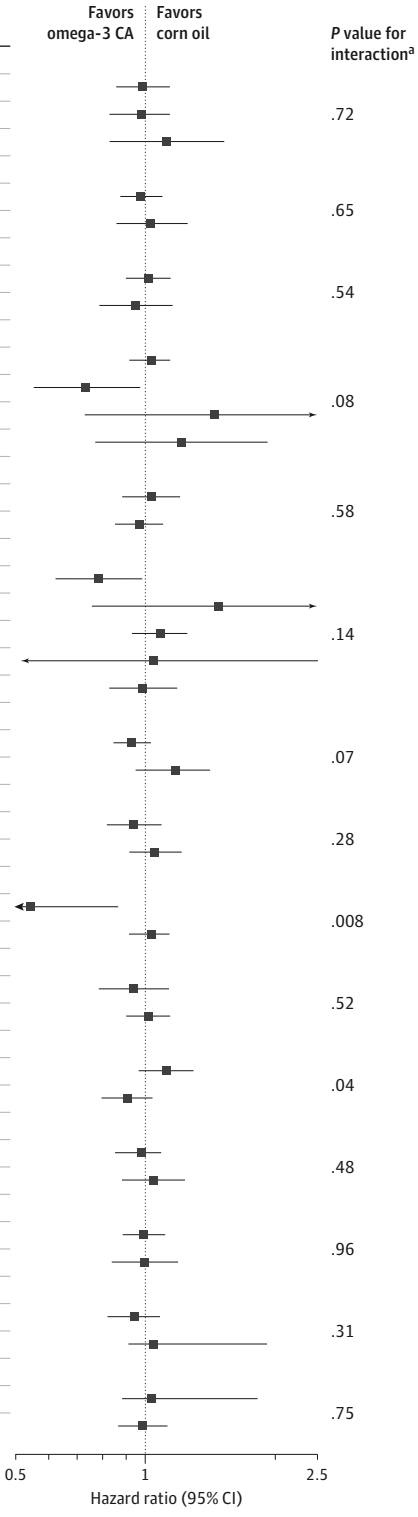
Discussion

In this randomized clinical trial, administration of omega-3 CA did not result in a significant reduction in the composite end point of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina compared with use of corn oil. The findings of this trial contribute to a large body of clinical research that has investigated whether administration of omega-3 fatty acids has a role in the prevention of cardiovascular disease. The origins of this research were based on observations that dietary consumption of fatty fish or omega-3 fatty acids were associated with lower rates of incident cardiovascular events in large cohort studies.[1,2,19,20] The potential value of omega-3 fatty acids was supported by epidemiological studies demonstrating an inverse relationship between circulating concentrations of omega-3 fatty acids and cardiovascular risk.[3,4] Preclinical studies demonstrated favorable effects of EPA and DHA on lipoprotein metabolism and a range of other biological factors implicated in atherosclerosis,[5] but several large clinical trials failed to demonstrate any cardiovascular benefit with administration of low doses of omega-3 fatty acids.[8,12,13] Despite these findings, over-the-counter use of low-dose omega-3 fatty acids is widespread.[21,22]

Two large clinical trials have suggested potential benefit of purified formulations of EPA alone. The Japan EPA Lipid Intervention Study (JELIS), an open-label trial that administered EPA, 1.8 g/d, in combination with a statin for a median of 4.6 years in 18 645 Japanese patients with hypercholesterolemia, resulted in fewer major coronary events compared with statin therapy alone (2.8% vs 3.5%; HR, 0.81 [95% CI, 0.69-0.95]).[10] The JELIS trial was not conducted using

Figure 3. Effect of Omega-3 CA on the Primary Composite Cardiovascular End Point in Prespecified Subgroups

Subgroup	Omega-3 CA			Corn oil			Absolute rate difference	Hazard ratio (95% CI)	*P* value for interaction[a]
	No. of events	Total person-years	Events per 100 person-years	No. of events	Total person-years	Events per 100 person-years			
Age at baseline, y									
<65	391	12721	3.07	390	12493	3.12	-0.05	0.98 (0.85-1.13)	.72
65-75	305	7642	3.99	327	7964	4.11	-0.12	0.97 (0.83-1.14)	
>75	89	1545	5.76	78	1463	5.33	0.43	1.12 (0.82-1.51)	
Diabetes on or before the first dose of study medication									
Yes	565	15452	3.67	576	15345	3.75	-0.08	0.97 (0.87-1.09)	.65
No	220	6456	3.41	219	6576	3.33	0.08	1.02 (0.85-1.24)	
Sex									
Men	583	14132	4.13	579	14163	4.09	0.04	1.01 (0.90-1.13)	.54
Women	202	7776	2.60	216	7758	2.78	-0.18	0.94 (0.78-1.14)	
Race									
White	644	18085	3.56	644	18246	3.53	0.03	1.02 (0.91-1.13)	.08
Asian	81	2234	3.63	103	2028	5.08	-1.45	0.72 (0.54-0.96)	
Black	22	579	3.80	14	540	2.59	1.21	1.44 (0.73-2.81)	
Other	38	996	3.81	33	1073	3.08	0.73	1.20 (0.76-1.91)	
BMI at baseline									
<30	309	8341	3.70	297	8126	3.66	0.04	1.03 (0.88-1.20)	.58
≥30	475	13552	3.51	496	13780	3.60	-0.09	0.97 (0.85-1.10)	
Region									
Asia	134	3457	3.88	166	3364	4.93	-1.05	0.78 (0.62-0.98)	.14
Australia and New Zealand	21	441	4.76	14	442	3.17	1.59	1.48 (0.75-2.90)	
Europe	384	11755	3.27	359	11771	3.05	0.22	1.07 (0.93-1.24)	
Latin America	11	474	2.32	11	506	2.17	0.15	1.03 (0.45-2.37)	
North America	235	5781	4.06	245	5838	4.20	-0.14	0.98 (0.82-1.18)	
Established CVD at baseline									
Yes	569	11695	4.87	610	11751	5.19	-0.32	0.94 (0.84-1.05)	.07
No	216	10214	2.11	185	10169	1.82	0.29	1.16 (0.95-1.41)	
Statin use at baseline									
High intensity	371	10905	3.40	393	10944	3.59	-0.19	0.94 (0.81-1.08)	.28
Other	414	11003	3.76	402	10976	3.66	0.10	1.04 (0.91-1.20)	
Ezetimibe at baseline									
Yes	29	795	3.65	49	768	6.38	-2.73	0.54 (0.34-0.86)	.008
No	756	21114	3.58	746	21152	3.53	0.05	1.02 (0.92-1.13)	
eGFR at baseline, mL/min BSA									
<60	223	4185	5.33	231	4047	5.71	-0.38	0.94 (0.78-1.13)	.52
≥60	562	17716	3.17	564	17869	3.16	0.01	1.01 (0.90-1.13)	
hsCRP at baseline, mg/dL									
<0.2	381	10483	3.63	348	10702	3.25	0.38	1.11 (0.96-1.28)	.04
≥0.2	404	11425	3.54	447	11218	3.98	-0.44	0.90 (0.79-1.03)	
Non-HDL-C at baseline, mg/dL									
<140	505	14394	3.51	516	14169	3.64	-0.13	0.97 (0.85-1.09)	.48
≥140	280	7515	3.73	279	7752	3.60	0.13	1.04 (0.88-1.23)	
Triglycerides at baseline, mg/dL									
<300	562	15905	3.53	566	15794	3.58	-0.05	0.99 (0.88-1.11)	.96
≥300	223	6003	3.71	229	6127	3.74	-0.03	0.99 (0.83-1.19)	
VLDL									
<46	347	10373	3.35	368	10283	3.58	-0.23	0.94 (0.81-1.08)	.31
≥46	414	10844	3.82	403	10934	3.69	0.13	1.04 (0.91-1.91)	
Apolipoprotein CIII									
<16	346	9980	3.47	338	9890	3.42	0.05	1.02 (0.88-1.81)	.75
≥16	433	11634	3.72	446	11802	3.78	-0.06	0.98 (0.86-1.12)	



BSA, body surface area; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and VLDL, very low-density lipoprotein. SI conversion factors are in Table 4.

[a] *P* value estimated using a Cox proportional hazards model with factors for treatment, established cardiovascular status at baseline, region, subgroup (only if not one of the covariates), and treatment × subgroup interaction in the model.

Table 3. Primary Event Rate by Tertile of Percent Change in Fatty Acid From Baseline to Month 12[a]

	Tertile 1[b]		Tertile 2			Tertile 3		
	No./No. (%)	Person-years	No./No. (%)	Person-years	HR (95% CI)	No./No. (%)	Person-years	HR (95% CI)
Plasma EPA								
Omega-3 CA (<144%, 144% to 435%, >435%)	180/1725 (10.4)	5933	191/1725 (11.1)	6035	1.04 (0.85-1.28)	204/1725 (11.8)	5951	1.13 (0.92-1.38)
Corn oil (<−28%, −28% to 10%, >10%)	195/1735 (11.2)	6005	194/1736 (11.2)	6059	0.99 (0.81-1.20)	185/1736 (10.7)	5956	0.96 (0.78-1.17)
RBC EPA								
Omega-3 CA (<117%, 117% to 450%, >450%)	185/1716 (10.8)	5887	182/1717 (10.6)	6011	0.96 (0.78-1.18)	202/1716 (11.8)	5945	1.08 (0.89-1.32)
Corn oil (<−20%, −20% to 3%, >3%)	193/1728 (11.2)	5980	194/1728 (11.2)	6015	0.99 (0.82-1.22)	186/1729 (10.8)	5945	0.97 (0.79-1.19)
Plasma DHA								
Omega-3 CA (<16%, 16%-68%, >68%)	178/1725 (10.3)	5992	192/1725 (11.1)	5989	1.08 (0.88-1.32)	205/1725 (11.9)	5937	1.16 (0.95-1.42)
Corn oil (<−17%, −17% to 6%, >6%)	198/1735 (11.4)	6067	187/1736 (10.8)	6052	0.95 (0.78-1.16)	189/1736 (10.9)	5901	0.98 (0.80-1.20)
RBC DHA								
Omega-3 CA (<12%, 12%-41%, >41%)	186/1716 (10.8)	5960	189/1717 (11.0)	5949	1.02 (0.83-1.25)	194/1716 (11.3)	5935	1.05 (0.86-1.28)
Corn oil (<−9%, −9% to 3%, >3%)	191/1728 (11.1)	6024	191/1729 (11.1)	6052	1.00 (0.82-1.22)	191/1728 (11.1)	5864	1.03 (0.84-1.26)

Abbreviations: CA, carboxylic acid formulation; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; RBC, red blood cell.

[a] Primary cardiovascular end point rate and hazard ratio estimated using a Cox proportional hazards regression model in patients treated with omega-3 CA and corn oil, according to tertiles of percentage change in either plasma or red blood cell EPA and DHA concentrations in a post hoc exploratory analysis. Tertile range for percentage change provided for individual fatty acid species.

[b] The first tertile is the reference category.

contemporary standards of care: patients were enrolled with mean LDL-C levels of 180 mg/dL, but treated with very low doses of statins (pravastatin 10 mg or simvastatin 5 mg), and elective revascularization was included in a broad composite clinical end point.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) trial reported that administration of EPA, 4 g/d, compared with mineral oil for a median duration of 4.9 years in 8179 statin-treated patients with a fasting triglyceride level between 135 and 499 mg/dL (median, 216 mg/dL) resulted in fewer cardiovascular events (17.2% vs 22.0%; HR, 0.75 [95% CI, 0.68-0.83]).[11] Concerns emerged in the scientific community and during hearings by the US Food and Drug Administration (FDA) whether mineral oil represented a neutral comparator, particularly in the context of a greater than 30% increase in CRP in the mineral oil treatment group.[23] Additional analyses of both EPA studies suggested an inverse association between plasma EPA concentration during treatment and the rate of cardiovascular events.[24,25]

The current trial similarly administered a 4-g dose of omega-3 fatty acids in high-risk patients with evidence of atherogenic dyslipidemia treated with a statin. In contrast to the trials of purified EPA, this trial administered an omega-3 CA formulation composed of both EPA and DHA. While the administered EPA content of omega-3 CA was less than that dispensed with icosapent, the carboxylic acid formulation has greater bioavailability, permitting substantial elevations in EPA concentrations, confirmed in phase 2 studies.[14,15] Although the achieved EPA levels in plasma and red blood cells were higher with icosapent in REDUCE-IT compared with this trial,[11] it is uncertain whether these differences would be sufficient to explain the completely different results observed. This uncertainty is heightened by the observation of no significant reduction in the risk of cardiovascular events in those patients with greater, compared with those with lesser, increases in EPA levels in the current trial. Furthermore, triglyceride levels were reduced 18% in both trials after 12 months, which also suggests similar biochemical effects of these treatments. It remains unknown whether administration of omega-3 fatty acids in a carboxylic acid formulation, as opposed to an ethyl ester, might have differential cardiovascular effects.

This trial was stopped prematurely when it became apparent that the probability of clinical benefit was likely to be low and there was evidence of risk, including a higher, albeit small, incidence of investigator-reported atrial fibrillation in the omega-3 CA treatment group. A number of potential factors may have contributed to the differences in outcomes of these clinical trials. While the duration of follow-up was longer in both studies of purified EPA, there was no separation of event curves in this trial in patients treated for a median of more than 3 years (Figure 2). There were differences in the patient populations, with this trial recruiting a greater percentage of patients with diabetes and somewhat fewer with clinically manifest cardiovascular disease. Although the study was terminated

Table 4. Baseline, Follow-up, and Percentage Change in Biochemical Measures

	Median (Q1-Q3)							
	Omega-3 CA			Corn oil			Between groups	
	Baseline (n = 6539)	12-mo Follow-up (n = 5821)[a]	% Change (n = 5821)	Baseline (n = 6539)	12-mo Follow-up (n = 5907)[a]	% Change (n = 5907)	Geometric mean ratio[b]	*P* value[b]
Total cholesterol, mg/dL	160.0 (139.0 to 188.0)	154.0 (131.0 to 185.0)	−3.4 (−14.6 to 9.0)	160.0 (138.0 to 188.0)	161.0 (137.0 to 191.0)	0 (−10.9 to 12.5)	0.97 (0.96 to 0.97)	<.001
LDL cholesterol, mg/dL	75.0 (56.0 to 99.0)	76.0 (56.0 to 102.0)	1.2 (−18.2 to 25.7)	75.0 (56.0 to 99.0)	75.0 (55.0 to 100.0)	−1.1 (−19.7 to 21.8)	1.03 (1.01 to 1.04)	<.001
HDL cholesterol, mg/dL	36.0 (31.0 to 40.0)	37.0 (32.0 to 43.0)	5.0 (−4.9 to 15.8)	36.0 (31.0 to 40.0)	37.0 (32.0 to 42.0)	3.2 (−5.7 to 14.3)	1.01 (1.00 to 1.02)	.002
Triglycerides, mg/dL	239.0 (192.0 to 307.0)	191.0 (146.0 to 255.0)	−19.0 (−39.2 to 6.4)	240.0 (191.0 to 309.0)	235.0 (178.0 to 315.0)	−0.9 (−25.2 to 27.8)	0.82 (0.81 to 0.83)	<.001
Non-HDL cholesterol, mg/dL	125.0 (104.0 to 152.0)	116.0 (94.0 to 146.0)	−6.1 (−20.3 to 9.6)	125.0 (103.0 to 152.0)	123.0 (100.0 to 152.0)	−1.1 (−14.9 to 14.5)	0.95 (0.94 to 0.96)	<.001
Apolipoprotein B, mg/dL	56.2 (43.8 to 72.3)	54.9 (43.8 to 69.7)	−2.0 (−24.5 to 27.6)	55.6 (43.6 to 71.7)	55.3 (44.3 to 69.4)	−1.0 (−23.5 to 27.1)	0.99 (0.98 to 1.01)	.34
Apolipoprotein CIII, mg/dL	17.0 (14.0 to 21.0)	16.0 (13.0 to 20.0)	−7.0 (−25.0 to 15.0)	17.0 (14.0 to 21.0)	18.0 (14.0 to 23.0)	5.9 (−14.3 to 30.0)	0.88 (0.87 to 0.89)	<.001
hs-CRP, mg/L[a]	2.1 (1.1 to 4.2)	1.7 (0.8 to 3.6)	−20.0 (−53.2 to 36.5)	2.1 (1.1 to 4.2)	1.8 (0.9 to 4.0)	−6.3 (−45.3 to 55.9)	0.89 (0.84 to 0.95)	<.001
EPA, μg/mL								
Plasma	21.0 (12.7 to 33.9)	89.6 (46.7 to 131.5)	268.8 (85.7 to 549.1)	21.3 (13.3 to 33.7)	19.0 (11.6 to 30.7)	−10.5 (−36.9 to 26.3)	3.75 (3.65,3.86)	<.001
RBC	0.60 (0.39 to 0.96)	2.81 (1.50 to 3.96)	298.6 (112.9 to 558.0)	0.61 (0.40 to 0.95)	0.55 (0.36 to 0.86)	−8.7 (−26.2 to 11.1)	4.02 (3.92 to 4.12)	<.001
DHA, μg/mL								
Plasma	61.9 (46.3 to 83.8)	90.7 (71.4 to 114.0)	39.7 (5.4 to 86.1)	62.5 (46.9 to 84.4)	58.1 (43.4 to 79.9)	−6.9 (−23.7 to 13.8)	1.50 (1.48 to 1.52)	<.001
RBC	5.0 (3.9 to 6.2)	6.6 (5.7 to 7.3)	23.9 (5.7 to 52.0)	5.0 (3.9 to 6.1)	4.8 (3.8 to 6.0)	−3.3 (−11.9 to 6.3)	1.33 (1.32 to 1.34)	<.001

Abbreviations: CA, carboxylic acid formulation; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

SI conversion factors: To convert cholesterol to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.

[a] All follow-up measures were at 12 months, except for hs-CRP, which was measured at 60 months (n = 1499 in corn oil placebo and n = 1467 in omega-3 CA).

[b] Geometric mean ratios >1.0 represent an x-fold increase in omega-3 CA compared with corn oil, while values <1.0 represent an x-fold decrease. *P* values were generated from the analysis of covariance model.

Table 5. Key Adverse Events in the Safety Population[a]

	No. (%)	
	Omega-3 CA (n = 6532)	Corn oil (n = 6535)
Drug-related adverse event	1451 (22.2)	843 (12.9)
Adverse event leading to drug discontinuation	708 (10.8)	525 (8.0)
Gastrointestinal disorders[b]	1616 (24.7)	959 (14.7)
Diarrhea	780 (11.9)	323 (4.9)
Nausea	207 (3.2)	113 (1.7)
Dyspepsia	90 (1.4)	42 (0.6)
Abdominal discomfort	87 (1.3)	36 (0.6)
New onset of diabetes[c]	286/1929 (14.8)	280/1975 (14.2)
Syncope	35 (0.5)	17 (0.3)
Any bleeding event	322 (4.9)	322 (4.9)
TIMI criteria major bleeding event	52 (0.8)	46 (0.7)

Abbreviations: CA, carboxylic acid formulation; TIMI, Thrombolysis in Myocardial Infarction.

[a] The safety population includes all randomized patients who received at least one dose of study drug.

[b] Gastrointestinal disorders reported by the patient.

[c] In those without diabetes on or before first dose of study medication.

prematurely, the number of adjudicated primary end point events was consistent with the original sample size assumptions (1580 vs 1600 events), reducing concerns that the trial may have been underpowered. A high level of follow-up of patients was achieved despite the challenges imposed by closing a large, multinational clinical trial during the COVID-19 pandemic.

A possible explanation for the different outcomes relates to the comparators used. The decision was made with the design of this trial to administer corn oil because it was considered to be a neutral comparator with the least effects on a range of biochemical parameters associated with cardiovascular risk.[17,18] In contrast, the cardiovascular effects of icosapent were compared with mineral oil, with adverse effects, compared with baseline, on apolipoprotein B, LDL cholesterol, and hs-CRP levels.[11] These effects were not observed with the corn oil group in this trial, highlighting differences between the comparator used in the studies. Given that these parameters are well-established risk factors associated with differences in cardiovascular event rates in clinical trials,[26-28] the adverse biochemical effects in the mineral oil group may have contributed to the apparent cardiovascular benefit observed with icosapent. However, the FDA subsequently awarded a label claim for cardiovascular event reduction for icosapent ethyl based on analyses that concluded that the effects of mineral oil could not entirely explain the observed differences in outcome.

The omega-3 fatty acid formulations differed in terms of their composition. While cardiovascular benefit has been reported with administration of purified formulations of EPA, omega-3 CA is a combination of EPA and DHA, with the potential to achieve similar tissue EPA concentrations. Theoretically, the lack of cardiovascular benefit with omega-3 CA could reflect adverse effects from coadministration of DHA. Although preclinical studies have reported potentially differential biological effects of EPA and DHA in studies of endothelial cells and vascular reactivity,[29-31] DHA has not demonstrated an adverse effect on atherosclerosis[32,33] and DHA levels have been reported to associate with cardiovascular protection.[34] Furthermore, while the increases in plasma and red blood cell concentrations of EPA were substantial, the percentage increases in DHA concentrations were modest (Table 2) and did not correlate with event rates (Table 3). Accordingly, it seems unlikely that the DHA component of the omega-3 CA formulation caused harm.

Administration of omega-3 CA was associated with a greater rate of both gastrointestinal adverse events and study drug discontinuation (Table 5). Investigator-reported new-onset atrial fibrillation was more common in patients receiving omega-3 CA, a finding also reported with purified EPA administration in REDUCE-IT (5.3% vs 3.9% with icosapent vs mineral oil).[11] These are potentially important findings that must be considered in the context of the possibility that the observed benefit of purified EPA may have been related to an increase in event rates in the mineral oil placebo treatment group. Accordingly, there is some uncertainty whether there is net benefit or harm with administration of any omega-3 fatty acid formulation. Given that 2 large clinical trials have now demonstrated a higher incidence rate, albeit small, of atrial fibrillation with high-dose omega-3 fatty acid administration, the mechanisms underscoring this observation require additional investigation. In contrast, it was reassuring to observe no excess bleeding with omega-3 CA, despite the high rate of use of background antiplatelet agents in the study.

Limitations

This study has several limitations. First, all patients were at high risk of future cardiovascular events, and background statin therapy was required. Whether benefits might be observed in a lower-risk primary prevention population remains uncertain. Second, this trial evaluated the effect of administration of 4-g/d of a combination of EPA and DHA in fixed proportion. While different doses and proportions were not evaluated, elevations in plasma concentrations of both EPA and DHA were achieved, yet no cardiovascular benefit was observed. Third, no large clinical trial has evaluated the effect of purified DHA at any dose on cardiovascular outcomes.

Conclusions

Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

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Author Contributions: Drs Nicholls and Nissen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Nicholls and Lincoff contributed equally to this article.
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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

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ABSTRACT

BACKGROUND

Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin–kexin type 9. Previous studies suggest that inclisiran might provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing.

METHODS

We enrolled patients with atherosclerotic cardiovascular disease (ORION-10 trial) and patients with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11 trial) who had elevated LDL cholesterol levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540.

RESULTS

A total of 1561 and 1617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [CI], 48.8 to 55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6 to 53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3 to 56.2) and 49.2% (95% CI, 46.8 to 51.6) ($P<0.001$ for all comparisons vs. placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent.

CONCLUSIONS

Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo. (Funded by the Medicines Company; ORION-10 and ORION-11 ClinicalTrials.gov numbers, NCT03399370 and NCT03400800.)

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The binding of proprotein convertase subtilisin–kexin type 9 (PCSK9) in the circulation by monoclonal antibodies reduces both low-density lipoprotein (LDL) cholesterol levels and the incidence of cardiovascular events.[1,2] Inclisiran, a small interfering RNA (siRNA) therapeutic agent, reduces hepatic synthesis of PCSK9. In one trial, the LDL cholesterol level was lowered by 52.6% at 180 days after two doses of 284 mg of inclisiran (equivalent to 300 mg of inclisiran sodium) administered on day 1 and day 90.[3] Data from the same trial following the same patients over a period of 360 days suggested that inclisiran might provide sustained reductions in LDL cholesterol levels, with the potential for a dosing schedule of once every 6 months.[4]

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted two randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials. The objectives of the ORION-10 and ORION-11 trials were to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for cardiovascular disease in whom LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy. The maximum tolerated dose was defined as the maximum dose of a statin that could be taken by the patient on a regular basis without unacceptable adverse events. Inability to receive statins required documentation of historical adverse events that were attributable to more than one statin and that were recorded in source documents and the trial case-report form.

The trial protocols (available with the full text of this article at NEJM.org) were identical and were approved by an institutional review board or independent ethics committee at each participating institution. All the patients provided written informed consent. The first two authors and the steering committee in collaboration with the sponsor (the Medicines Company) designed each trial protocol (with subsequent review and approval by regulators) and selected participating countries and sites. Monitoring and site supervision were performed by a contract research organization (PPD) with oversight by the sponsor. The first two authors wrote the first draft of the manuscript. All the authors participated in its revision, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols.

PATIENTS

The ORION-10 trial was conducted in the United States and included adults with atherosclerotic cardiovascular disease. Patients were eligible for enrollment if their LDL cholesterol levels at screening were 70 mg per deciliter (1.8 mmol per liter) or higher. The ORION-11 trial was conducted in Europe and South Africa and included adults with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent). The LDL cholesterol eligibility criteria for patients with atherosclerotic cardiovascular disease were identical in the two trials, but in the ORION-11 trial, patients with an atherosclerotic cardiovascular disease risk equivalent were required to have an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher.[5] Entry criteria required stable doses of background lipid-lowering therapies for at least 30 days before screening. Patients receiving treatment with monoclonal antibodies directed toward PCSK9 within 90 days before screening were excluded. Detailed inclusion and exclusion criteria for each trial are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Randomization was stratified according to background use of statins in both trials and also according to country in the ORION-11 trial, with patients assigned (in a 1:1 ratio) to receive either inclisiran (284 mg) or matching placebo — both administered as a 1.5-ml subcutaneous injection under blinded conditions. Each patient received four injections of inclisiran or placebo. After the first injection (day 1), patients returned on day 90, day 270, and day 450 to receive subsequent doses of inclisiran or placebo (Fig. S1 in the Supplementary Appendix). Patients also attended the clinic on days 30, 150, 330, and 510 for follow-up and limited laboratory assessments. The end-of-trial visit was conducted on day 540.

END POINTS

The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540. The latter end point is the mean percentage change in LDL cholesterol level from baseline over the period after day 90 and up to day 540 and takes into account peak and trough measurements within that time window (samples recorded on days 150, 270, 330, 450, 510, and 540). Key secondary end points for each trial were the absolute change in LDL cholesterol level from baseline to day 510, the time-adjusted absolute change in LDL cholesterol level from baseline after day 90 and up to day 540, and the percentage change from baseline to day 510 in levels of PCSK9, total cholesterol, apoliprotein B, and non–high-density lipoprotein (HDL) cholesterol. Full details of other prespecified secondary end points are listed in the Supplementary Appendix. Finally, the incidence of a *Medical Dictionary for Regulatory Activities* (MedDRA)–defined cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke was a prespecified exploratory end point.

We recorded adverse events and clinical laboratory values at all visits through the end-of-trial visit (day 540). Investigators classified adverse events according to organ class and as mild, moderate, or severe using standard MedDRA nomenclature. Antidrug antibodies were measured in plasma with the use of highly sensitive screening methods and, if needed, confirmatory assays in accordance with the most recent regulatory guidance, developed and validated to minimize the risk of false negative results.[6,7]

STATISTICAL ANALYSIS

The detailed statistical analysis plans for both trials are available with the protocols at NEJM.org. In brief, under the assumption of a 5% dropout rate, a mean reduction in LDL cholesterol level of no less than 30 mg per deciliter (0.8 mmol per liter), and a standard deviation of 20 mg per deciliter (0.5 mmol per liter), a sample of approximately 1425 patients who could be evaluated would provide more than 90% power to detect a 30% lower level of LDL cholesterol in the inclisiran group than in the placebo group with a two-sided significance level of 0.05 in each trial.

In each trial, the first primary efficacy end point was analyzed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analyzed with the use of a mixed model for repeated measures, both with multiple imputation of data. A nested procedure was specified for the two primary end points, with the requirement that significance must be shown for the first primary end point before the second primary end point could be tested. For the key secondary end points, there were six different tests (two absolute-change measures and four percentage-change measures). With an alpha of 0.05 overall, the Hochberg procedure was applied, in which the highest P value was tested at $0.05 \div 1$, the next one was tested at $0.05 \div 2$, and continuing until the final (lowest) P value was tested at $0.05 \div 6$ (0.008). All primary and secondary end points used multiple imputation to account for missing data (see the Supplementary Appendix). The planned sample size of approximately 1425 in each trial was also expected to contribute safety data from more than 6000 injections per trial. Analyses were performed with the use of SAS software, version 9.2 or higher (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

The ORION-10 and ORION-11 trials screened 2329 and 2381 patients, respectively, with 1561 and 1617 subsequently undergoing randomization. The intention-to-treat populations comprised 781 patients assigned to inclisiran and 780 to placebo in the ORION 10 trial and 810 assigned to inclisiran and 807 to placebo in the ORION 11 trial. A large majority of those enrolled completed the trial activities (90.6% and 95.2%, respectively) through the end-of-trial visit on day 540 (Fig. S2). Thus, these two trials provide 2166 person-years of exposure to inclisiran.

The characteristics of the populations in each trial were similar with respect to age and the proportion of men enrolled (Table 1), but there were differences between the trials, with the ORION-10 trial enrolling fewer white patients but a higher proportion of patients with diabetes, hypertension, and heterozygous familial hypercholesterolemia. Although both trials enrolled

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	ORION-10 Trial		ORION-11 Trial	
	Inclisiran (N=781)	Placebo (N=780)	Inclisiran (N=810)	Placebo (N=807)
Age — yr	66.4±8.9	65.7±8.9	64.8±8.3	64.8±8.7
Male sex — no. (%)	535 (68.5)	548 (70.3)	579 (71.5)	581 (72.0)
White race — no. (%)†	653 (83.6)	685 (87.8)	791 (97.7)	796 (98.6)
Cardiovascular risk factors — no. (%)				
ASCVD	781 (100)	780 (100)	712 (87.9)	702 (87.0)
ASCVD risk equivalent‡	0	0	98 (12.1)	105 (13.0)
Current smoker§	123 (15.7)	111 (14.2)	160 (19.8)	132 (16.4)
Hypertension§	714 (91.4)	701 (89.9)	640 (79.0)	661 (81.9)
Diabetes§	371 (47.5)	331 (42.4)	296 (36.5)	272 (33.7)
Heterozygous familial hypercholesterolemia§	8 (1.0)	12 (1.5)	14 (1.7)	14 (1.7)
Concomitant lipid-modifying therapy — no. (%)				
Statin	701 (89.8)	692 (88.7)	766 (94.6)	766 (94.9)
High-intensity statin	525 (67.2)	537 (68.8)	640 (79.0)	631 (78.2)
Ezetimibe	80 (10.2)	74 (9.5)	52 (6.3)	62 (7.7)
Lipid measures — mg/dl				
LDL cholesterol	104.5±39.6	104.8±37.0	107.2±41.8	103.7±36.4
Total cholesterol	180.6±46.1	180.6±43.6	187.3±48.2	183.3±42.8
Non-HDL cholesterol	134.0±44.5	134.7±43.5	137.6±46.9	133.9±41.0
HDL cholesterol	46.6±14.3	45.9±14.4	49.7±15.5	49.3±13.8
Apolipoprotein B	94.1±25.6	94.6±25.1	97.1±28.0	95.1±5.2
Lipoprotein(a) — nmol/liter				
Median	57	56	42	35
IQR	18–181	20–189	18–178	18–181
Triglycerides — mg/dl				
Median	127	129	135	135
IQR	92–181	96–182	99–181	102–185
PCSK9 — μg/liter	422.1±176.9	414.9±145.7	355±98.9	353±97.4

* Plus–minus values are means ±SD. For the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides, and total cholesterol, the baseline value was defined as the mean of the values at screening and before receipt of the dose of inclisiran or placebo on day 1; for other variables, the baseline value was defined as the last value before the first dose of inclisiran or placebo. In a post hoc analysis to provide descriptive statistical comparisons, there were no significant differences between the two groups in the baseline characteristics. To convert values for cholesterol and apolipoprotein B to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ASCVD denotes atherosclerotic cardiovascular disease, IQR interquartile range, and PCSK9 proprotein convertase subtilisin–kexin type 9.

† Race was reported by the patient.

‡ Patients in this category had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.

§ Percentages are reported as a proportion of the overall cohort, including patients in the risk-equivalent category.

patients with atherosclerotic cardiovascular disease, in the ORION-11 trial there were also 203 patients (12.6%) enrolled in the risk-equivalent category, of whom 132 (65.0%) had diabetes, 30 (14.8%) had heterozygous familial hypercholesterolemia, and 41 (20.2%) had a 10-year predicted risk of cardiovascular disease of 20% or greater.

The use of stable doses of statin treatment was high (89.2% in the ORION-10 trial and 94.7% in

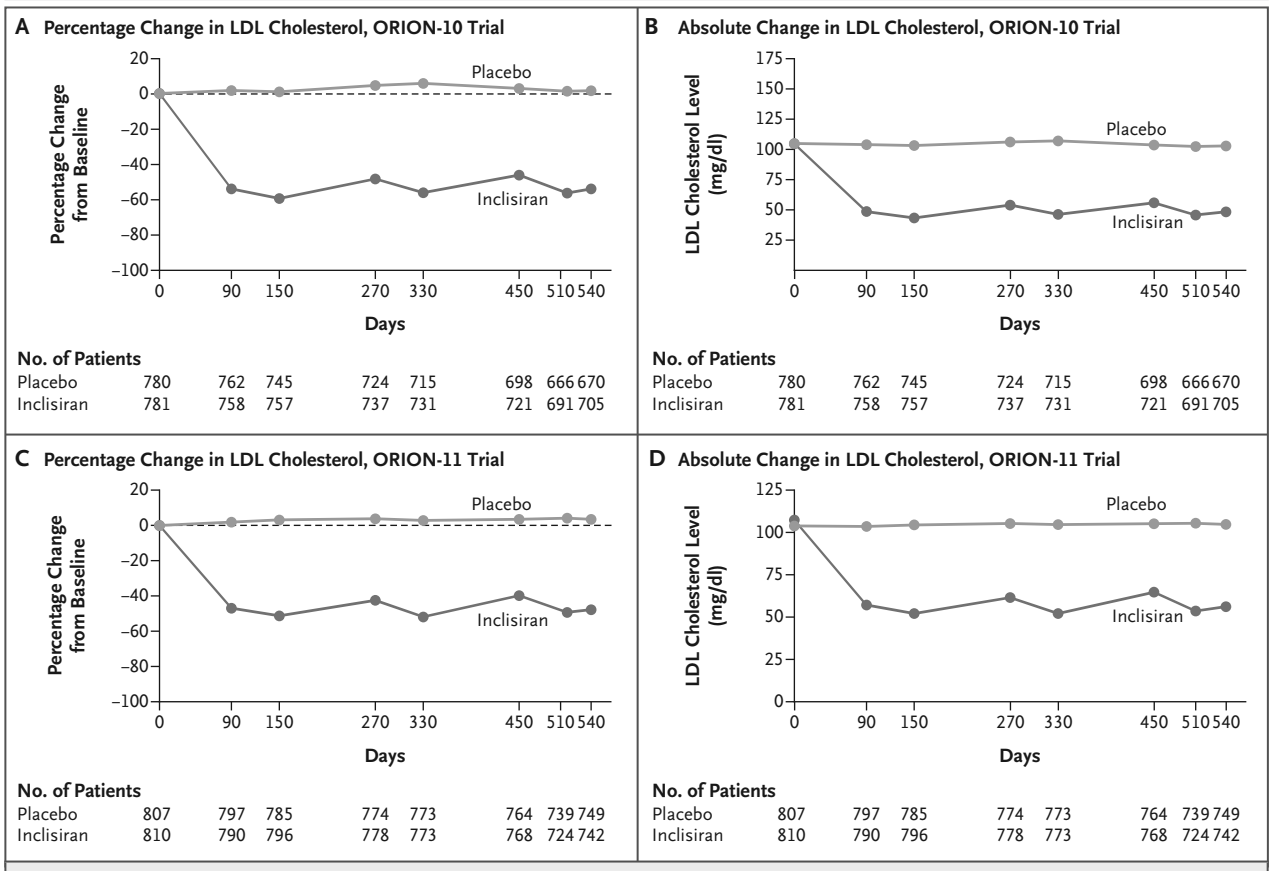

Figure 1. Efficacy of Inclisiran or Placebo in Lowering LDL Cholesterol over the 540-Day Trial Period (Intention-to-Treat Population).

The graphs use observed data. The numbers of patients with missing data at each time point are shown in Table S1 in the Supplementary Appendix. Least-squares means are shown for inclisiran and placebo over time. Panels A and B show the percentage change and the absolute change in low-density lipoprotein (LDL) cholesterol level over time in the ORION-10 trial. Panels C and D show the percentage change and the absolute change in LDL cholesterol level over time in the ORION-11 trial. The primary end point of percentage change in LDL cholesterol level from baseline to day 510 and a key secondary end point of absolute change at day 510 were analyzed with the use of an analysis-of-covariance model and a mixed model for repeated measures, respectively, with multiple imputation for missing values. P values for the comparison of inclisiran with placebo for the percentage and absolute change from baseline were less than 0.001 for all four comparisons at day 510.

the ORION-11 trial), with the majority of patients receiving high-intensity statins (68.0% and 78.6%, respectively). Use of ezetimibe either alone or in combination with statins was low (9.9% in the ORION-10 trial and 7.1% in the ORION-11 trial). The mean (±SD) LDL cholesterol level at baseline was 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter) in the respective trials (Table 1).

EFFICACY

Primary End Points

The percentage and absolute changes in LDL cholesterol level from baseline with inclisiran or placebo in each trial are shown in Figure 1. In the ORION-10 trial, the percentage change in LDL cholesterol level at day 510 was 1.0% in the placebo group and −51.3% in the inclisiran group, resulting in a between-group difference of −52.3% (95% confidence interval [CI], −55.7 to −48.8; P<0.001). The time-adjusted change in LDL cholesterol level after day 90 and up to day 540 (coprimary end point) as compared with baseline was 2.5% with placebo and −51.3% with inclisiran, representing a between-group difference of −53.8% (95% CI, −56.2 to −51.3; P<0.001). In the ORION-11 trial, the corresponding percentage change in LDL cholesterol level at day 510 was 4.0% in the placebo group and −45.8% in the inclisiran group, resulting in a between-group difference of −49.9% (95%

CI, −53.1 to −46.6; P<0.001). The corresponding time-adjusted change in LDL cholesterol level was 3.4% with placebo and −45.8% with inclisiran, representing a between-group difference of −49.2% (95% CI, −51.6 to −46.8; P<0.001).

Key Secondary End Points

In the ORION-10 trial, the absolute change in LDL cholesterol level at day 510 was −2.1 mg per deciliter (−0.05 mmol per liter) in the placebo group and −56.2 mg per deciliter (−1.45 mmol per liter) in the inclisiran group, with a between-group difference of −54.1 mg per deciliter (−1.40 mmol per liter) (95% CI, −57.4 to −50.9 mg per deciliter [−1.48 to −1.32 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 was −0.4 mg per deciliter (−0.01 mmol per liter) in the placebo group and −53.7 mg per deciliter (−1.39 mmol per liter) in the inclisiran group, with a difference of −53.3 mg per deciliter (−1.38 mmol per liter) (95% CI, −55.8 to −50.8 mg per deciliter [−1.44 to −1.31 mmol per liter]; P<0.001).

In the ORION-11 trial, the corresponding absolute change in LDL cholesterol level at day 510 was 1.0 mg per deciliter (0.03 mmol per liter) in the placebo group and −50.9 mg per deciliter (−1.32 mmol per liter) in the inclisiran group, with a between-group difference of −51.9 mg per deciliter (−1.34 mmol per liter) (95% CI, −55.0 to −48.7 mg per deciliter [−1.42 to −1.26 mmol per liter]; P<0.001). The time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 was 0.3 mg per deciliter (0.01 mmol per liter) in the placebo group and −48.6 mg per deciliter (−1.26 mmol per liter) in the inclisiran group, with a difference of −48.9 mg per deciliter (−1.26 mmol per liter) (95% CI, −51.4 to −46.5 mg per deciliter [−1.33 to −1.20 mmol per liter]; P<0.001).

The percentage and absolute changes in PCSK9 levels from baseline with inclisiran or placebo in each trial are shown in Figure 2. In the ORION-10 trial, the percentage change at day 510 (key secondary end point) was 13.5% with placebo and −69.8% with inclisiran, representing a between-group difference of −83.3% (95% CI, −89.3 to −77.3; P<0.001). Similarly, in the ORION-11 trial, the percentage change at day 510 was 15.6% with placebo and −63.6% with inclisiran, representing a between-group difference of −79.3% (95% CI, −82.0 to −76.6; P<0.001). In each trial, inclisiran resulted in improvement in other key secondary end points at day 510 as compared with placebo, including lower levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B (P<0.001 for all three comparisons) (Table S4A and S4B). The effect of inclisiran on LDL cholesterol levels at day 510 appeared consistent within each trial across a range of subgroups (Figs. 3 and 4).

Other End Points

Inclisiran lowered levels of triglycerides and lipoprotein(a) and increased HDL cholesterol levels at day 510 (Table S4A and S4B). In each trial, the proportion of patients likely to have a 50% reduction in LDL cholesterol level was higher in the inclisiran group than in the placebo group (Table S5), as were the proportions of patients in whom an LDL cholesterol level of less than 25, 50, 70, and 100 mg per deciliter (0.65, 1.3, 1.8, and 2.6 mmol per liter, respectively) was achieved. Although the placebo group showed considerable variation in changes in PCSK9 and LDL cholesterol levels at day 510, the inclisiran group showed very little (Fig. S3).

SAFETY

In the ORION-10 trial, 2 patients who were assigned to the placebo group did not receive placebo; therefore, the safety population comprises 781 patients in the inclisiran group and 778 patients in the placebo group. In the ORION-11 trial, 2 patients who were assigned to the placebo group did not receive placebo, and 1 patient who was assigned to placebo was given a dose of inclisiran in error and is included in the inclisiran group for safety reporting; therefore, the safety population of the latter trial comprises 811 patients exposed to inclisiran and 804 patients exposed to placebo.

The incidence of adverse events is shown in Table 2. Adverse events that occurred during the trial period, regardless of causality, were reported in 574 of 781 patients (73.5%) receiving inclisiran and 582 of 778 (74.8%) receiving placebo in the ORION-10 trial and in 671 of 811 patients (82.7%) receiving inclisiran and 655 of 804 (81.5%) receiving placebo in the ORION-11 trial. The majority of events in each trial were reported to be mild or moderate, with the most common adverse events occurring with similar frequency in the inclisiran and placebo groups. Laboratory results with respect to liver and kidney function, levels of creatine kinase and high-

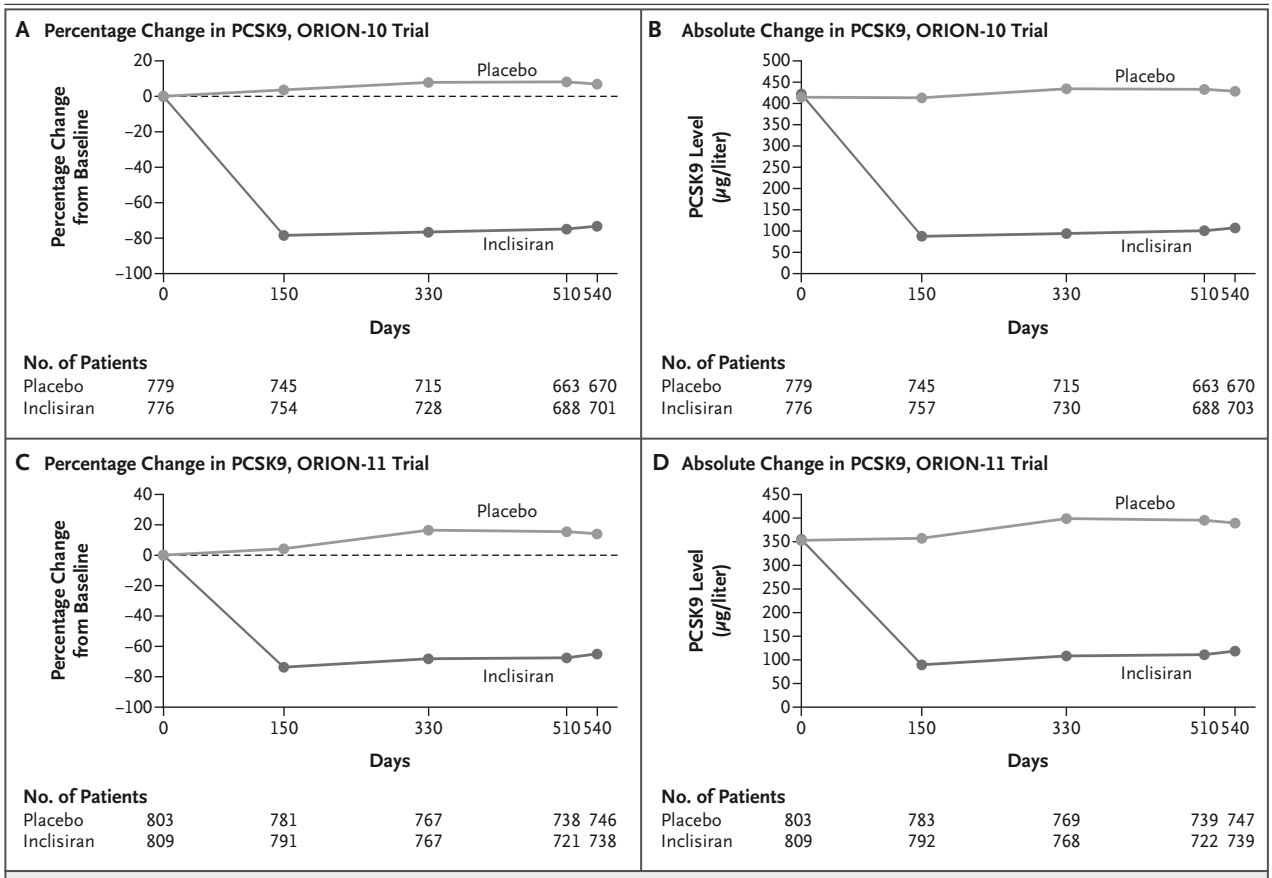

Figure 2. Efficacy of Inclisiran or Placebo in Lowering PCSK9 Levels over the 540-Day Trial Period (Intention-to-Treat Population).

The graphs use observed data. The numbers of patients with missing data at each time point are shown in Table S2. Least-squares means are shown for inclisiran and placebo over time. Panels A and B show the percentage change and the absolute change in proprotein convertase subtilisin–kexin type 9 (PCSK9) level over time in the ORION-10 trial. Panels C and D show the percentage change and the absolute change in PCSK9 level over time in the ORION-11 trial. The key secondary end point of percentage change in PCSK9 level from baseline to day 510 and the secondary end point of absolute change at day 510 were analyzed with the use of separate mixed models for repeated measures, with multiple imputation for missing values. P values for the comparison of inclisiran with placebo for the percentage and absolute change from baseline were less than 0.001 for all four comparisons at day 510.

sensitivity C-reactive protein, and platelet count were also similar in the inclisiran and placebo groups in each trial (Table 2 and Tables S6, S7A, and S7B). Injection-site adverse events were more frequent with inclisiran than with placebo in both trials, with between-group differences of 1.7 percentage points in the ORION-10 trial and 4.2 percentage points in the ORION-11 trial; the majority of reactions were mild (between-group differences in mild reactions, 0.8 percentage points and 2.4 percentage points, respectively), with none being severe or persistent.

Antidrug antibodies were detected in 2.0% and 2.5% of the samples from inclisiran-treated patients in the ORION-10 and ORION-11 trials, respectively, findings consistent with assay specifications but not drug induction. The frequency of positive samples was similar in pretreatment and post-treatment samples. The presence of antidrug antibodies in post-treatment samples was low titer, often transient, and not associated with changes in any pharmacologic or clinical variables. In addition, there were no treatment-boosted antidrug antibodies.

Serious adverse events were reported in 175 patients (22.4%) receiving inclisiran and 205 (26.3%) receiving placebo in the ORION-10 trial and in 181 patients (22.3%) receiving inclisiran and 181 (22.5%) receiving placebo in the ORION-11 trial. These included 12 deaths (1.5%) in the inclisiran group and 11 (1.4%) in the placebo group in the ORION-10 trial and 14 deaths (1.7%) in

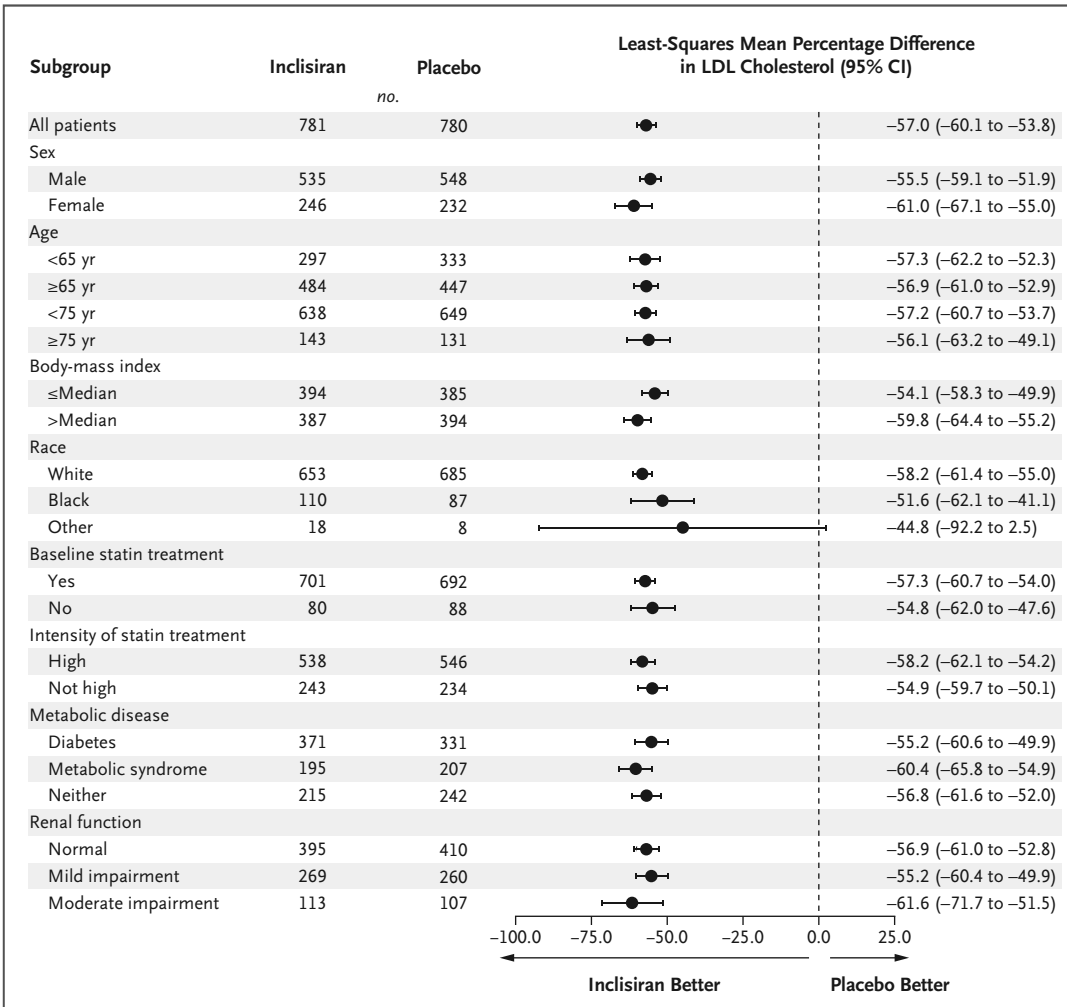

Figure 3. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-10 Trial (Intention-to-Treat Population).

Data are least-squares mean differences and 95% confidence intervals. The difference in the percentage change from baseline between inclisiran and placebo was analyzed for each subgroup with the use of a mixed model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points. The median body-mass index (the weight in kilograms divided by the square of the height in meters) was 30.8. High-intensity statins are defined in the Methods section in the Supplementary Appendix. Renal function was divided into normal (estimated glomerular filtration rate, ≥90 ml per minute per 1.73 m^2), mild impairment (60 to 89 ml per minute per 1.73 m^2), and moderate impairment (30 to 59 ml per minute per 1.73 m^2).

the inclisiran group and 15 (1.9%) in the placebo group in the ORION-11 trial. The incidences of cancer-related deaths and new, worsening, or recurrent cancer were low and were similar among patients receiving inclisiran and those receiving placebo.

EXPLORATORY ANALYSIS

The prespecified exploratory cardiovascular end point occurred in 58 patients (7.4%) in the inclisiran group and 79 (10.2%) in the placebo group in the ORION-10 trial and in 63 patients (7.8%) in the inclisiran group and 83 (10.3%) in the placebo group in the ORION-11 trial.

DISCUSSION

In our trials, a regimen of subcutaneous inclisiran injections on day 1, day 90, and then every 6 months reduced LDL cholesterol levels by

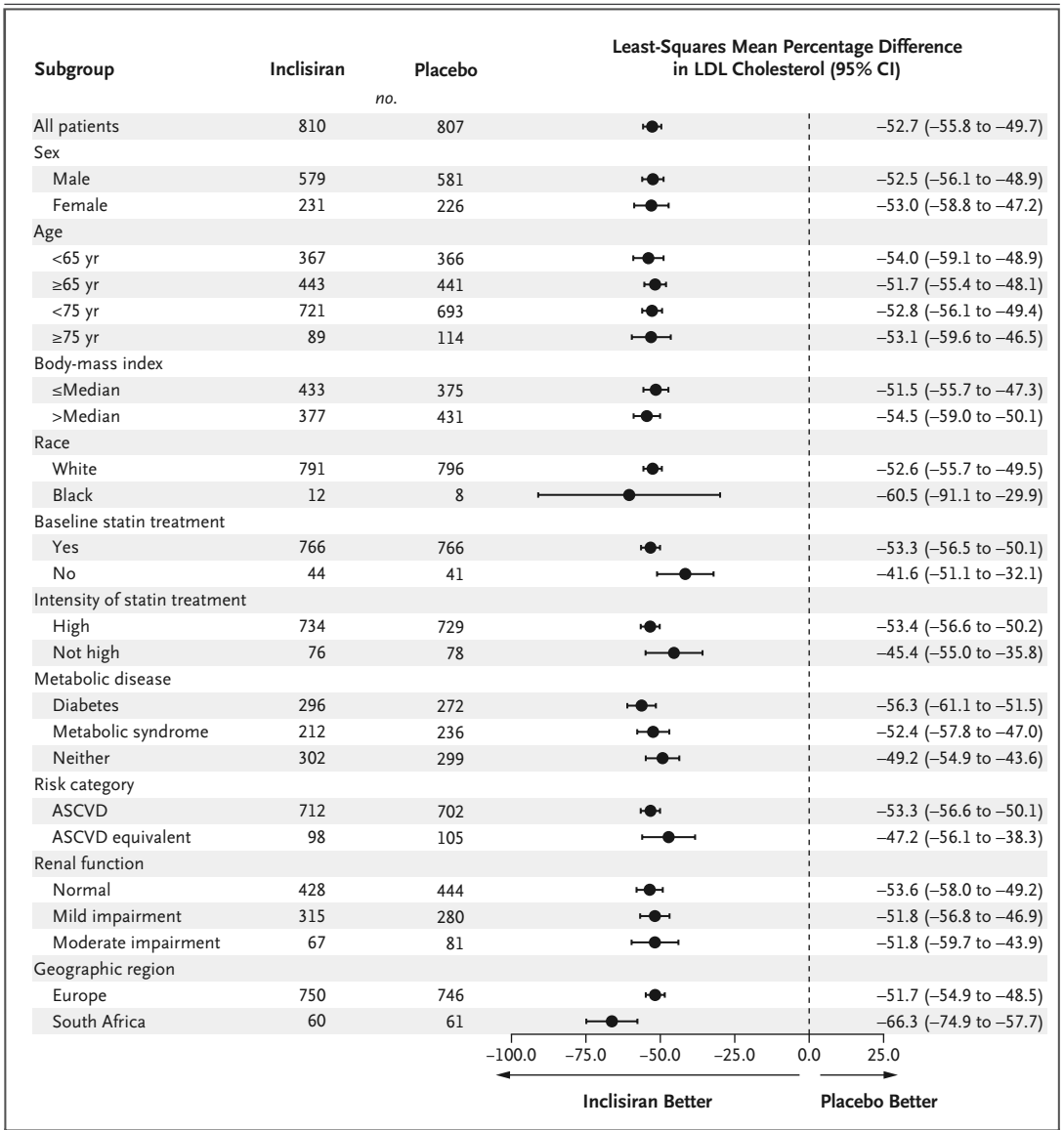

Figure 4. Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-11 Trial (Intention-to-Treat Population).

Data are least-squares mean differences and 95% confidence intervals. The difference in the percentage change from baseline between inclisiran and placebo was analyzed for each subgroup with the use of a mixed-effects model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points. The median body-mass index was 29.4. Patients with an atherosclerotic cardiovascular disease (ASCVD) risk equivalent had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.

49.9% to 52.2% at month 17 and lowered time-adjusted LDL cholesterol levels between months 3 and 18 by 49.2% to 53.8% as compared with placebo in two separate populations at high risk for cardiovascular disease. These reductions were achieved on top of maximum tolerated, guideline-recommended statin treatment. The results for the percentage change in LDL cholesterol levels at month 17 were consistent across subgroups. Among patients given placebo, PCSK9 levels generally increased, whereas PCSK9 levels decreased in nearly all the patients given inclisiran.

Peak plasma levels of inclisiran occur approximately 4 hours after dosing, and most is excreted through the kidney.[8] Triantennary N-acetylgalactosamine (GalNAc) modification of the double-stranded inclisiran molecule ensures rapid hepatic uptake through the asialoglycoprotein receptors expressed exclusively on liver cells; after uptake, inclisiran is bound to the RNA-induced silencing complex in liver-cell cytoplasm.[9,10] Inclisiran is no longer detectable in plasma within 24 to 48 hours after dosing.[9,10] A theoretical concern for therapies with a long duration of action is the potential for irreversible adverse events. Without further injections, the

Table 2. Adverse Events and Key Safety Laboratory Findings.*

Variable	ORION-10 Trial			ORION-11 Trial		
	Inclisiran (N=781)	Placebo (N=778)	Risk Ratio (95% CI)	Inclisiran (N=811)	Placebo (N=804)	Risk Ratio (95% CI)
	no. of patients (%)			*no. of patients (%)*		
Adverse events						
≥1 Adverse event	574 (73.5)	582 (74.8)	1.0 (0.9–1.0)	671 (82.7)	655 (81.5)	1.0 (0.9–1.1)
≥1 Event leading to discontinuation of inclisiran or placebo	19 (2.4)	17 (2.2)	1.1 (0.6–2.1)	23 (2.8)	18 (2.2)	1.3 (0.7–2.3)
Serious adverse events						
≥1 Serious adverse event	175 (22.4)	205 (26.3)	0.9 (0.7–1.0)	181 (22.3)	181 (22.5)	1.0 (0.8–1.2)
Death	12 (1.5)	11 (1.4)	1.1 (0.5–2.4)	14 (1.7)	15 (1.9)	0.9 (0.4–1.9)
Death from cardiovascular causes	7 (0.9)	5 (0.6)	1.4 (0.4–4.4)	9 (1.1)	10 (1.2)	0.9 (0.4–2.2)
Cancer-related death	1 (0.1)	3 (0.4)	0.3 (0.0–3.2)	3 (0.4)	3 (0.4)	1.0 (0.2–4.9)
New, worsening, or recurrent cancer	26 (3.3)	26 (3.3)	1.0 (0.6–1.7)	16 (2.0)	20 (2.5)	0.8 (0.1–1.5)
Other cardiovascular adverse events						
Prespecified exploratory cardiovascular end point†	58 (7.4)	79 (10.2)	0.7 (0.5–1.0)	63 (7.8)	83 (10.3)	0.8 (0.6–1.0)
Fatal or nonfatal myocardial infarction	20 (2.6)	18 (2.3)	1.1 (0.6–2.1)	10 (1.2)	22 (2.7)	0.5 (0.2–0.9)
Fatal or nonfatal stroke	11 (1.4)	7 (0.9)	1.6 (0.6–4.0)	2 (0.2)	8 (1.0)	0.2 (0.1–1.2)
Injection-site adverse events‡						
Any reaction	20 (2.6)	7 (0.9)	2.9 (1.2–6.7)	38 (4.7)	4 (0.5)	9.4 (3.4–26.3)
Mild	13 (1.7)	7 (0.9)	1.9 (0.7–4.6)	23 (2.8)	3 (0.4)	7.6 (2.3–25.2)
Moderate	7 (0.9)	0	—	15 (1.8)	1 (0.1)	14.9 (2.0–112.3)
Severe	0	0	—	0	0	—
Persistent	0	0	—	0	0	—
Frequent adverse events§						
Diabetes mellitus	120 (15.4)	108 (13.9)	1.1 (0.9–1.4)	88 (10.9)	94 (11.7)	0.9 (0.7–1.2)
Nasopharyngitis	—	—	—	91 (11.2)	90 (11.2)	1.0 (0.8–1.3)
Bronchitis	46 (5.9)	30 (3.9)	1.5 (1.0–2.4)	—	—	—
Dyspnea	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	—	—	—
Hypertension	42 (5.4)	42 (5.4)	1.0 (0.7–1.5)	53 (6.5)	54 (6.7)	1.0 (0.7–1.4)
Upper respiratory tract infection	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	52 (6.4)	49 (6.1)	1.1 (0.7–1.5)
Arthralgia	—	—	—	47 (5.8)	32 (4.0)	1.5 (0.9–2.3)
Osteoarthritis	—	—	—	32 (3.9)	40 (5.0)	0.8 (0.5–1.2)
Back pain	39 (5.0)	39 (5.0)	1.0 (0.6–1.5)	—	—	—

Table 2. (Continued.)

Variable	ORION-10 Trial			ORION-11 Trial		
	Inclisiran (N=781)	Placebo (N=778)	Risk Ratio (95% CI)	Inclisiran (N=811)	Placebo (N=804)	Risk Ratio (95% CI)
	no. of patients (%)			*no. of patients (%)*		
Laboratory results						
Liver function						
Alanine aminotransferase >3× ULN	2 (0.3)	2 (0.3)	1.0 (0.1–7.1)	4 (0.5)	4 (0.5)	1.0 (0.2–4.0)
Aspartate aminotransferase >3× ULN	4 (0.5)	5 (0.6)	0.8 (0.2–3.0)	2 (0.2)	4 (0.5)	0.5 (0.1–2.7)
Alkaline phosphatase >3× ULN	5 (0.6)	3 (0.4)	1.7 (0.4–6.9)	1 (0.1)	2 (0.2)	0.5 (0.0–5.5)
Bilirubin >2× ULN	4 (0.5)	3 (0.4)	1.3 (0.3–5.9)	6 (0.7)	8 (1.0)	0.7 (0.3–2.1)
Kidney function: creatinine >2 mg/dl	30 (3.8)	30 (3.9)	1.0 (0.6–1.6)	5 (0.6)	11 (1.4)	0.5 (0.2–1.3)
Muscle: creatine kinase >5× ULN	10 (1.3)	8 (1.0)	1.2 (0.5–3.1)	10 (1.2)	9 (1.1)	1.1 (0.5–2.7)
Hematology: platelet count <75×10^9/liter	1 (0.1)	0	—	0	1 (0.1)	—

* The safety population included all the patients who received at least one dose of inclisiran or placebo. Adverse events were recorded over the trial period of 540 days. ULN denotes the upper limit of the normal range.
† The exploratory cardiovascular end point comprised a *Medical Dictionary for Regulatory Activities*–defined cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke.
‡ Injection-site adverse events included the preferred terms injection-site erythema, injection-site hypersensitivity, injection-site pruritus, injection-site rash, and injection-site reaction.
§ Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. Some events occurred with a frequency of less than 5% in one trial but not the other; a dash indicates that the frequency was less than 5% in that trial.

LDL cholesterol–lowering effects of inclisiran are reversed at the rate of approximately 2% per month,[3,4] which means that these effects can persist for up to approximately 2 years. It is therefore reassuring that in the present trials with 6075 injections of inclisiran and 2166 person-years of exposure, the adverse-event profile of inclisiran was similar to that of placebo. Injection-site adverse events were more frequent with inclisiran than with placebo, but most were mild or moderate, did not require intervention, and were not persistent. Ongoing open-label extension studies will provide additional longer-term safety follow-up information.[8]

Overall deaths were similar in the inclisiran and placebo groups in each trial. The prespecified cardiovascular composite end point was reported with lower frequency in the inclisiran group (7.4 to 7.8%, as compared with 10.2 to 10.3% in the placebo group). However, the total number of nonadjudicated cardiovascular events observed was too small to draw meaningful conclusions about any potential benefits of inclisiran on cardiovascular outcomes, a question that is being tested in an ongoing cardiovascular outcomes trial.[8]

The potential for siRNA-based therapies has already reached fruition in rare-disease areas such as transthyretin amyloidosis and porphyria.[11,12] This therapeutic approach harnesses the intrinsic natural and highly conserved process of RNA interference present in all mammalian cells. Therapies that are based on RNAi seem to require less frequent dosing than other RNA-based therapies, such as antisense oligonucleotides.[13] The results of our trials have the potential to move RNAi-based therapies from the realm of rare to common diseases.[10]

The aim of any cholesterol-lowering therapeutic regimen is to maintain consistent, long-term reductions in the exposure to LDL cholesterol and to do so safely. Statins are first-line pharmacotherapy for LDL cholesterol lowering, but many patients require additional LDL cholesterol lowering.[14,15] The convenience of a treatment regimen and the medication burden that is placed on the patient may influence long-term adherence.[16,17] Poor adherence to statins is associated with less

favorable reductions in LDL cholesterol levels and in turn a higher risk of cardiovascular events as compared with good adherence.[18,19] Furthermore, at a population level, poor adherence attenuates the benefit of LDL cholesterol reduction that is achievable through proper adherence.[18] Our trials suggest that sustained reductions in LDL cholesterol levels are achievable with an infrequent dosing schedule of inclisiran. Complete adherence might be feasible if this therapy were administered by a health care professional,[20] thus potentially helping address an existing challenge to contemporary prevention strategies — namely, how to maintain reductions to adverse exposures such as LDL cholesterol over the long term.

We found that a regimen of inclisiran every 6 months was feasible and significantly reduced LDL cholesterol levels by approximately 50%. More injection-site adverse events occurred with inclisiran than with placebo.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

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ABSTRACT

BACKGROUND

Evidence from a recent trial has shown that the antiinflammatory effects of colchicine reduce the risk of cardiovascular events in patients with recent myocardial infarction, but evidence of such a risk reduction in patients with chronic coronary disease is limited.

METHODS

In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of colchicine once daily or matching placebo. The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary end point was a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke.

RESULTS

A total of 5522 patients underwent randomization; 2762 were assigned to the colchicine group and 2760 to the placebo group. The median duration of follow-up was 28.6 months. A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001). A key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group (incidence, 1.5 vs. 2.1 events per 100 person-years; hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P=0.007). The incidence rates of spontaneous myocardial infarction or ischemia-driven coronary revascularization (composite end point), cardiovascular death or spontaneous myocardial infarction (composite end point), ischemia-driven coronary revascularization, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).

CONCLUSIONS

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.)

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*A complete list of the investigators in the LoDoCo2 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Nidorf and Fiolet and Drs. Mosterd, Cornel, and Thompson contributed equally to this article.

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Despite lifestyle changes and risk-factor reduction, patients with chronic coronary disease remain at high risk for acute cardiovascular events.[1-3] The central role of inflammation in the progression of coronary disease is well recognized.[4,5] The possibility that antiinflammatory therapy may improve cardiovascular outcomes was first highlighted in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) involving patients with a history of myocardial infarction and an elevated baseline level of C-reactive protein; the results showed that the risk of recurrent cardiovascular events was lower among those who received canakinumab than among those who received placebo.[6] However, in another trial, a clinical benefit with methotrexate was not observed in patients with chronic coronary disease.[7]

Colchicine is an antiinflammatory drug originally extracted from the autumn crocus (*Colchicum autumnale*) and was used by the ancient Greeks and Egyptians. In contrast to selective inhibition of interleukin-1β by canakinumab, colchicine has broad cellular effects that include inhibition of tubulin polymerization and alteration of leukocyte responsiveness.[8-10] In the Colchicine Cardiovascular Outcomes Trial (COLCOT) involving patients who had a myocardial infarction within 30 days before enrollment, the percentage of those who had the composite end point of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization was lower among those who received 0.5 mg of colchicine once daily than among those who received placebo.[11]

In an earlier trial of low-dose colchicine (LoDoCo) involving patients with chronic coronary disease, we found that the risk of acute cardiovascular events was lower among those who received 0.5 mg of colchicine once daily than among those who did not receive colchicine.[12] This was an open-label trial involving only 532 patients, and the results required confirmation. Accordingly, we conducted an investigator-initiated, randomized, controlled, double-blind, event-driven trial of low-dose colchicine (LoDoCo2) to determine whether 0.5 mg of colchicine once daily, as compared with placebo, prevents cardiovascular events in patients with chronic coronary disease.

Methods

Trial Design and Oversight

Patient recruitment in the LoDoCo2 trial commenced on August 4, 2014, at 13 centers affiliated with GenesisCare and the Heart and Vascular Research Institute of Sir Charles Gairdner Hospital in Western Australia. On October 27, 2016, patient recruitment was expanded with the inclusion of 30 centers of the Dutch Network for Cardiovascular Research in the Netherlands. Enrollment was completed by December 3, 2018. The design of the trial has been published previously.[13] The trial protocol, available with the full text of this article at NEJM.org, was approved by a centralized institutional review board in each participating country. An independent data and safety monitoring board reviewed cumulative safety data to safeguard the well-being of the patients. Full details of the trial organization and a list of the trial sites and investigators are provided in the Supplementary Appendix, also available at NEJM.org.

The academic and clinical investigators designed the study, collected and managed the data, performed the statistical analyses, and drafted the manuscript. The funders had no role in the design or writing of the protocol and statistical analysis plan; in the selection or monitoring of the participating sites; in the enrollment or follow-up of patients; in the distribution or administration of the trial drug or placebo; in the collection, storage, analysis, and interpretation of the data; in the drafting of the manuscript; or in the decision to submit the manuscript for publication. The trial drug and matching placebo were donated by Aspen Pharmacare in Australia and by Tiofarma in the Netherlands. The members of the steering committee and the trial statisticians had unrestricted access to the data and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Trial Population

Patients 35 to 82 years of age were eligible if they had any evidence of coronary disease on invasive coronary angiography or computed tomography angiography or a coronary-artery calcium score of at least 400 Agatston units on a coronary-artery calcium scan. Patients were required to have been

in a clinically stable condition for at least 6 months before enrollment. Patients were not eligible if they had moderate-to-severe renal impairment, severe heart failure, severe valvular heart disease, or known side effects from colchicine. Renal function was defined on the basis of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.[14] A full list of the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. All the patients provided written informed consent to participate.

RUN-IN, RANDOMIZATION, AND FOLLOW-UP

After signing the informed-consent form, eligible patients entered an open-label run-in phase for 1 month, during which time they received 0.5 mg of colchicine once daily. At the end of the open-label run-in phase, the patients who were in stable condition and had no unacceptable side effects, had adhered to the open-label colchicine regimen, and remained willing to continue participation were randomly assigned in a 1:1 ratio to receive 0.5 mg of colchicine once daily or matching placebo. Randomization was performed in a double-blind manner with the use of a computerized algorithm, with stratification according to country. Clinical evaluations were scheduled before the run-in phase, at the time of randomization, and at 6-month intervals until the completion of the trial. All follow-up assessments were performed in person, if possible, or by telephone. The trial regimens were continued until the completion of the trial. Moreover, clinical follow-up was continued until the date of trial completion regardless of premature discontinuation of colchicine or placebo.

END POINTS

The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. Secondary end points, which were tested in hierarchical fashion, were ranked in the following order: the composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke (key secondary end point); the composite of spontaneous myocardial infarction or ischemia-driven coronary revascularization; the composite of cardiovascular death or spontaneous myocardial infarction; ischemia-driven coronary revascularization; spontaneous myocardial infarction; ischemic stroke; death from any cause; and cardiovascular death. The list of end points, including the primary end point, was revised several times during the trial; the latest and final revision took place in January 2020 before the data were unblinded. End points were adjudicated by a committee whose members were unaware of the trial-group assignments. Additional end points and definitions are provided in Table S2.

STATISTICAL ANALYSIS

The trial was designed to accrue a minimum of 331 primary end-point events and to have a minimum follow-up of 1 year. On the basis of a target enrollment of 6053 patients in the open-label run-in phase, with 5447 undergoing randomization after screening, we estimated that the trial would have more than 90% power, at a two-sided alpha level of 0.05, to detect a 30% lower rate (i.e., a hazard ratio of 0.70) of a primary composite end-point event in the colchicine group than in the placebo group, assuming a 10% rate of discontinuation of colchicine or placebo and an annual rate of the primary end point in the control group of 2.6%. Details of the statistical methods are provided in the Supplementary Appendix.

The main analysis was based on the time from randomization to the first occurrence of any component of the primary composite end point. If the incidence of the primary end point was significantly lower in the colchicine group than in the placebo group ($P<0.05$), then the ranked secondary end points were tested in a hierarchical fashion at a significance level of 0.05 in order to preserve the alpha level. The original protocol did not include a plan to adjust for multiple testing; hierarchical testing was included in the protocol in January 2020 before the data were unblinded to be consistent with the new guidelines for statistical reporting in the *Journal*.[15]

The main analysis was performed according to the intention-to-treat principle and included all adjudicated end-point events that occurred between randomization and the end-of-trial date in all patients who had undergone randomization, regardless of whether they adhered to their assigned regimen. Cause-specific hazard ratios in the colchicine group, as compared with the placebo group, and 95% confidence intervals were

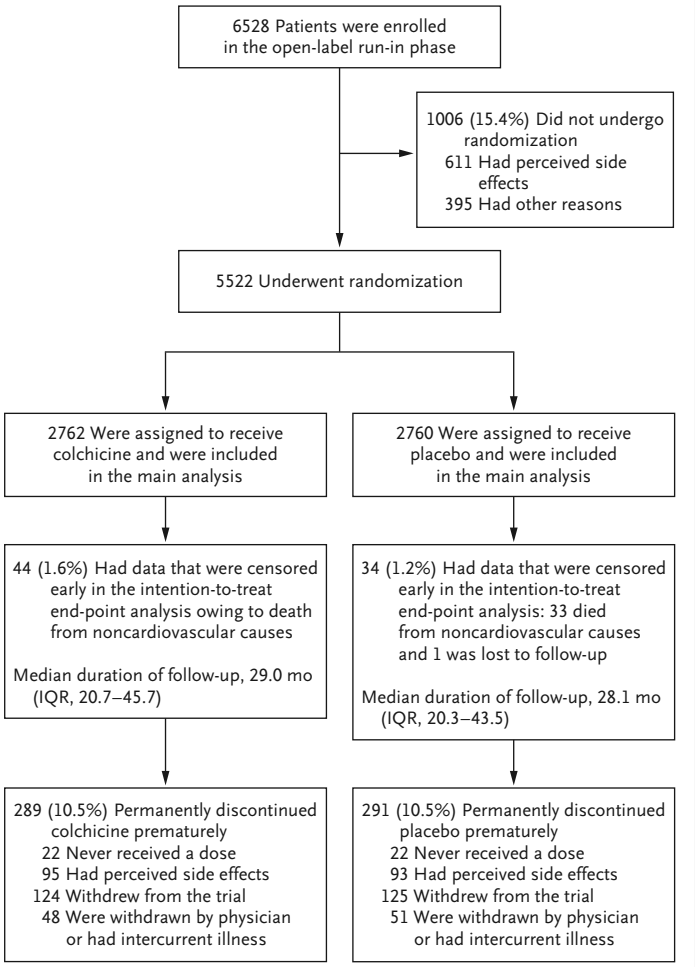

Figure 1. Enrollment, Randomization, and Follow-up.

Premature permanent discontinuation of colchicine or placebo was determined to have occurred if colchicine or placebo was permanently discontinued more than 30 days before the occurrence of a primary end-point event, the occurrence of noncardiovascular death, or the regular end-of-trial date, whichever came first.

determined with the use of Cox proportional-hazards models, stratified according to country. If an end-point event had not occurred, follow-up data were censored at the time of the competing risk event (death from noncardiovascular causes or death from any cause, as appropriate) or at the end of the trial. Two-sided P values for superiority were calculated with the use of log-rank tests, as governed by the rules of hierarchical testing. The prespecified subgroup analyses were performed with the use of the Cox proportional-hazards method.

An exploratory sensitivity analysis of the primary end point in the on-treatment data set was also performed. The on-treatment analysis was performed in patients who had received at least one dose of colchicine or placebo, with additional censoring of data 30 days after the last dose was received (in addition to the data that were censored according to the rules for the main intention-to-treat analysis). Analyses of the primary and secondary end points were also performed with the use of Fine and Gray subdistribution hazard models to account for competing risks.

RESULTS

PATIENTS

Among the 6528 patients who provided written informed consent and started the open-label run-in period, 5522 underwent randomization and 5478 received at least one dose of colchicine or placebo (Fig. 1 and Table S3). Among the 1006 patients (15.4%) who had started the run-in period but did not undergo randomization, the most common reason was gastrointestinal upset (in 437 patients).

The baseline characteristics of the patients were well balanced between the trial groups (Table 1). The mean (±SD) age of the patients was 66±8.6 years, and 846 (15.3%) were female; 11.7% of the patients were current smokers, and 18.2% had diabetes. Most patients (4658 [84.4%]) had a history of acute coronary syndrome; in 68.2% of the patients, the acute event had occurred more than 24 months before randomization. At baseline, the patients were well treated with respect to chronic coronary disease, with 99.7% taking an antiplatelet agent or an anticoagulant, 96.6% a lipid-lowering agent, 62.1% a beta-blocker, and 71.7% an inhibitor of the renin–angiotensin system. Distribution of baseline characteristics according to country is provided in Table S4.

ADHERENCE AND FOLLOW-UP

The date of the last follow-up contact with a patient was February 17, 2020. The database was locked on May 22, 2020. The primary end-point status was available for all but one patient. The median duration of follow-up was 28.6 months (interquartile range, 20.5 to 44.4). In each trial group, 10.5% of the patients permanently discontinued colchicine or placebo prematurely (Fig. 1).

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Colchicine (N = 2762)	Placebo (N = 2760)
Age — yr	65.8±8.4	65.9±8.7
Female sex — no. (%)	457 (16.5)	389 (14.1)
Country — no. (%)		
Australia	951 (34.4)	953 (34.5)
The Netherlands	1811 (65.6)	1807 (65.5)
Current smoker — no. (%)†	318 (11.5)	330 (12.0)
Hypertension — no. (%)	1421 (51.4)	1387 (50.3)
Diabetes — no. (%)		
Patients receiving any treatment for diabetes	492 (17.8)	515 (18.7)
Patients dependent on insulin	140 (5.1)	147 (5.3)
Renal function — no. (%)‡		
Stage 1 or 2	2614 (94.6)	2602 (94.3)
Stage 3a	148 (5.4)	158 (5.7)
Prior acute coronary syndrome — no. (%)	2323 (84.1)	2335 (84.6)
Time since last acute coronary syndrome — no. (%)		
≤24 mo	753 (27.3)	726 (26.3)
>24 mo	1570 (56.8)	1609 (58.3)
Prior coronary revascularization — no. (%)	2301 (83.3)	2320 (84.1)
Coronary-artery bypass grafting	319 (11.5)	391 (14.2)
Percutaneous coronary intervention	2100 (76.0)	2077 (75.3)
History of atrial fibrillation — no. (%)	332 (12.0)	317 (11.5)
History of gout — no. (%)	220 (8.0)	226 (8.2)
Medication use — no. (%)		
Single antiplatelet therapy	1849 (66.9)	1852 (67.1)
Dual antiplatelet therapy	638 (23.1)	642 (23.3)
Anticoagulant	342 (12.4)	330 (12.0)
No antiplatelet agent or anticoagulant	4 (0.1)	11 (0.4)
Statin	2594 (93.9)	2594 (94.0)
Ezetimibe	551 (19.9)	522 (18.9)
Any lipid-lowering agent	2670 (96.7)	2665 (96.6)
Renin–angiotensin inhibitor	1995 (72.2)	1965 (71.2)
Beta-blocker	1692 (61.3)	1735 (62.9)
Calcium-channel blocker	633 (22.9)	611 (22.1)

* Plus–minus values are means ±SD.
† Information on smoking was missing for 21 patients.
‡ Stage 1 refers to an estimated glomerular filtration rate of at least 90 ml per minute per 1.73 m^2 of body-surface area (normal or high), stage 2 to a rate of 60 to 89 ml per minute per 1.73 m^2 (mildly decreased), and stage 3a to a rate of 45 to 59 ml per minute per 1.73 m^2 (mildly to moderately decreased). Stages are based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.[14]

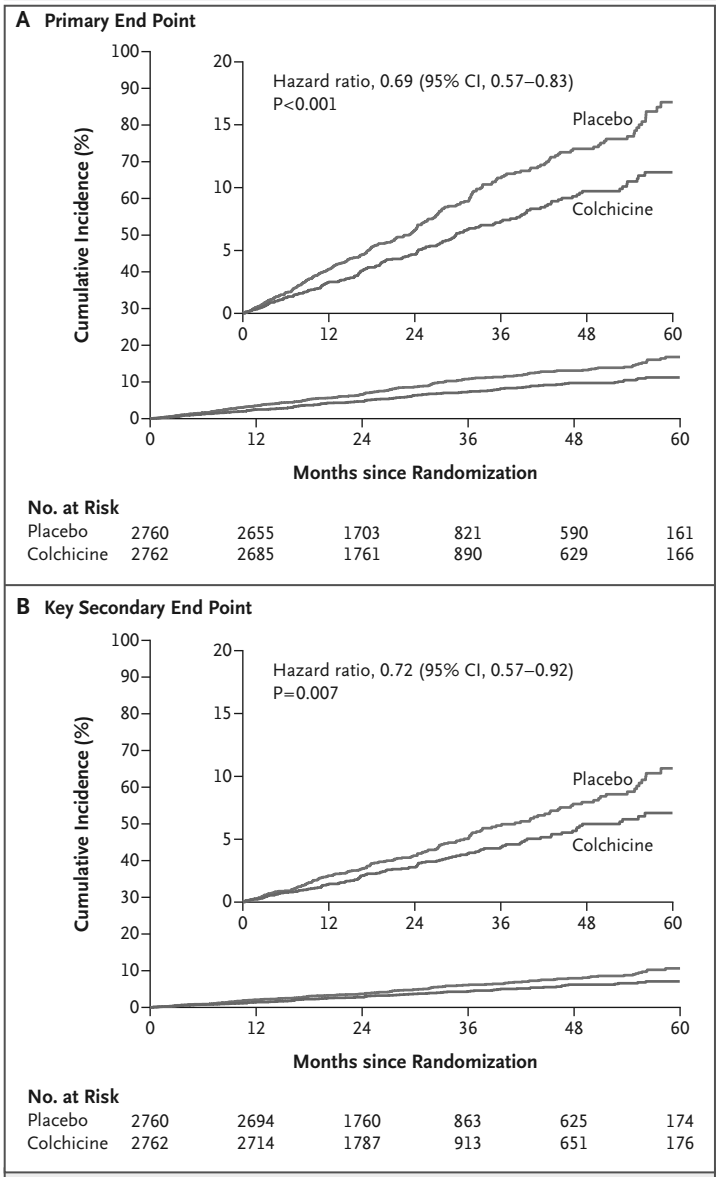

Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary End Point.

Panel A shows the cumulative incidence of the primary composite end point of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization, and Panel B shows the cumulative incidence of the key secondary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke. The inset in each panel shows the same data on an enlarged y axis.

PRIMARY AND SECONDARY END POINTS

The primary composite end-point event of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group, with incidence rates of 2.5 and 3.6 events, respectively, per 100 person-years (hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001) (Figs. 2 and 3). This treatment effect was consistent in the on-treatment analysis (Fig. S1 and Table S5).

A key secondary composite end-point event of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group, with incidence rates of 1.5 and 2.1 events, respectively, per 100 person-years (hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P=0.007) (Figs. 2 and 3). In the prespecified hierarchical testing of the ranked secondary end points, the rates of the first five secondary end points, including spontaneous myocardial infarction, were significantly lower in the colchicine group than in the placebo group (Fig. 3). Colchicine did not result in a lower incidence of death from any cause than placebo (73 vs. 60 fatalities; incidence, 0.9 vs. 0.8 events, respectively, per 100 person-years; hazard ratio, 1.21; 95% CI, 0.86 to 1.71). Fine and Gray subdistribution hazard ratios were virtually identical to the cause-specific hazard ratios (Table S6).

ADDITIONAL END POINTS

A primary composite end-point event as defined in the first LoDoCo trial (sudden cardiac death, nonfatal out-of-hospital cardiac arrest, acute coronary syndrome [myocardial infarction or unstable angina irrespective of revascularization], or atherosclerotic ischemic stroke) occurred in 201 patients in the colchicine group and in 290 patients in the placebo group, with incidence rates of 2.7 and 4.0 events, respectively, per 100 person-years (hazard ratio, 0.67; 95% CI, 0.56 to 0.81) (Fig. 3). The results with respect to the occurrence of new onset or first recurrence of atrial fibrillation, deep-venous thrombosis or pulmonary embolism or both, and new-onset diabetes did not differ significantly between the trial groups.

ADVERSE EVENTS

Noncardiovascular deaths occurred more frequently among the patients who received colchicine than among those who received placebo, with incidence rates of 0.7 and 0.5 events, respectively, per 100 person-years (hazard ratio, 1.51; 95% CI, 0.99 to 2.31) (Table 2 and Table S7). We observed similar rates of cancer diagnosis, hos-

pitalization for infection, hospitalization for pneumonia, and hospitalization for a gastrointestinal reason in the two trial groups, in both the intention-to-treat analysis and the on-treatment analysis (Table 2 and Table S8). Gout occurred in 38 patients (1.4%) in the colchicine group and in 95 patients (3.4%) in the placebo group (cumulative incidence ratio, 0.40; 95% CI, 0.28 to 0.58). Neutropenia and myotoxic effects were uncommon in both trial groups. Among the patients from the Netherlands, myalgia was reported in 384 (21.2%) in the colchicine group and 334 (18.5%) in the placebo group (cumulative incidence ratio, 1.15; 95% CI, 1.01 to 1.31). Dysesthesia was reported in 143 patients (7.9%) in the colchicine group and in 150 patients (8.3%) in the placebo group (cumulative incidence ratio, 0.95; 95% CI, 0.76 to 1.18).

SUBGROUP ANALYSES

The effects of colchicine, as compared with placebo, on the primary end point were consistent in the prespecified subgroups defined according to sex, age (>65 years vs. ≤65 years), smoking status (current vs. former or never), hypertension (yes vs. no), diabetes (yes vs. no), renal function (stage 1 or 2 vs. stage 3a [stages are based on the KDIGO

End Point	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Primary end point						
Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	2.5	264 (9.6)	3.6	0.69 (0.57–0.83)	<0.001
Secondary end points in ranked order						
Cardiovascular death, myocardial infarction, or ischemic stroke	115 (4.2)	1.5	157 (5.7)	2.1	0.72 (0.57–0.92)	0.007
Myocardial infarction or ischemia-driven coronary revascularization	155 (5.6)	2.1	224 (8.1)	3.0	0.67 (0.55–0.83)	<0.001
Cardiovascular death or myocardial infarction	100 (3.6)	1.3	138 (5.0)	1.8	0.71 (0.55–0.92)	0.01
Ischemia-driven coronary revascularization	135 (4.9)	1.8	177 (6.4)	2.4	0.75 (0.60–0.94)	0.01
Myocardial infarction	83 (3.0)	1.1	116 (4.2)	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	16 (0.6)	0.2	24 (0.9)	0.3	0.66 (0.35–1.25)	0.20
Death from any cause	73 (2.6)	0.9	60 (2.2)	0.8	1.21 (0.86–1.71)	
Cardiovascular death	20 (0.7)	0.3	25 (0.9)	0.3	0.80 (0.44–1.44)	
Additional end points						
The primary end point in the first LoDoCo trial	201 (7.3)	2.7	290 (10.5)	4.0	0.67 (0.56–0.81)	
New onset or first recurrence in atrial fibrillation or atrial flutter	126 (4.6)	1.7	148 (5.4)	2.0	0.84 (0.66–1.07)	
Deep-vein thrombosis or pulmonary embolism or both	17 (0.6)	0.2	16 (0.6)	0.2	1.06 (0.53–2.10)	
Any myocardial infarctions	85 (3.1)	1.1	117 (4.2)	1.5	0.72 (0.54–0.95)	
New-onset diabetes	34 (1.2)	—	49 (1.8)	—	0.69 (0.44–1.06)	

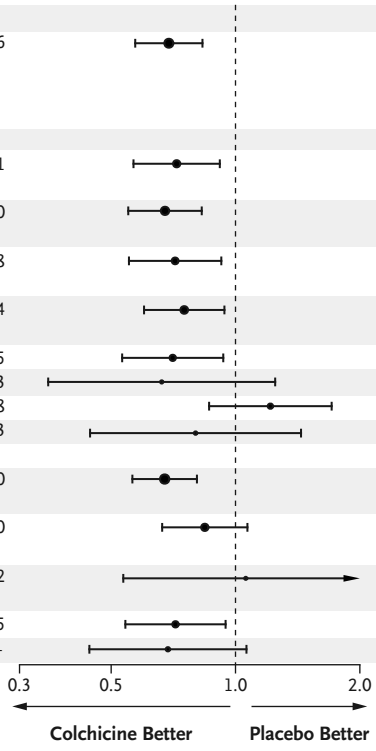

Figure 3. Key End Points and their Components.

The cause-specific hazard ratios were estimated from Cox proportional-hazard regression analysis with death from noncardiovascular causes or death from any cause as a competing risk event. Myocardial infarction refers to spontaneous (nonprocedural) myocardial infarction. The primary end point in the first low-dose colchicine (LoDoCo) trial was a composite of sudden cardiac death, nonfatal out-of-hospital cardiac arrest, acute coronary syndrome (myocardial infarction or unstable angina irrespective of revascularization), or atherosclerotic ischemic stroke. Any myocardial infarctions refers to either spontaneous or procedural myocardial infarctions. The ratio for new-onset diabetes is presented as a cumulative incidence ratio because time-to-event data were not collected. The size of the data points is inversely proportional to the precision (the standard error of the log of the hazard ratios or cumulative incidence ratio) of the estimates, with larger data points representing more precise estimates. The testing hierarchy for statistical significance was broken at the end point of ischemic stroke.

Table 2. Adverse Events in the Intention-to-Treat Population.*

Event	Colchicine (N = 2762)		Placebo (N = 2760)		Hazard Ratio or Cumulative Incidence Ratio (95% CI)
	no. of patients/ total no. (%)	*no. of events/100 person-yrs*	*no. of patients/ total no. (%)*	*no. of events/100 person-yrs*	
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)
Diagnosis of cancer	120/2762 (4.3)	1.6	122/2760 (4.4)	1.6	0.98 (0.76–1.26)
Hospitalization for infection	137/2762 (5.0)	1.8	144/2760 (5.2)	1.9	0.95 (0.75–1.20)
Hospitalization for pneumonia	46/2762 (1.7)	0.6	55/2760 (2.0)	0.7	0.84 (0.56–1.24)
Hospitalization for gastrointestinal reason	53/2762 (1.9)	0.7	50/2760 (1.8)	0.7	1.06 (0.72–1.56)
Gout	38/2762 (1.4)	—	95/2760 (3.4)	—	0.40 (0.28–0.58)
Neutropenia	4/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myotoxic effects†	3/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myalgia‡	384/1811 (21.2)	—	334/1807 (18.5)	—	1.15 (1.01–1.31)
Dysesthesia: numbness or tingling‡	143/1811 (7.9)	—	150/1807 (8.3)	—	0.95 (0.76–1.18)

* Hazard ratios are reported for noncardiovascular death, diagnosis of cancer, hospitalization for infection, hospitalization for pneumonia, and hospitalization for gastrointestinal reason; cumulative incidence ratios are reported for gout, myalgia, and dysesthesia because time-to-event data were not collected for these end points. Cumulative incidence ratios are not reported (NR) for neutropenia and myotoxic effects because of the low numbers of events.

† Rhabdomyolysis occurred in one patient in the colchicine group, who had a full recovery.

‡ Data were collected for the Netherlands cohort only. Reporting of these adverse events was requested by the Medicines Evaluation Board in the Netherlands when the trial was expanded to include patients from that country.

Clinical Practice Guideline for Acute Kidney Injury[14]), prior acute coronary syndrome (yes vs. no), prior coronary revascularization (yes vs. no), atrial fibrillation (yes vs. no), statin dose (high dose vs. low or moderate dose), and ezetimibe use (yes vs. no). When examined according to country, the effect of colchicine, as compared with placebo, on the primary end point was directionally consistent but appeared to be quantitatively larger in Australia than in the Netherlands (Fig. S2).

DISCUSSION

Among patients with chronic coronary disease, most of whom were already receiving proven secondary prevention therapies, 0.5 mg of colchicine once daily resulted in a 31% lower relative risk of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization (the primary end point) than placebo, with a hazard ratio of 0.69. The effects of colchicine appeared to be consistent across each component of the primary end point and all secondary composite end points.

The incidence rates of death from any cause and noncardiovascular death were higher with colchicine than with placebo. The observed between-group difference in the incidence of noncardiovascular death was not significant, as shown by the 95% confidence interval, and could have been due to chance, although the hazard ratio of 1.51 is of potential concern. The individual causes of death (Table S7) do not permit a clear interpretation of this finding. In the COLCOT trial, noncardiovascular death occurred in 23 patients who received colchicine and in 20 patients who received placebo.[11]

Among the patients who were enrolled in the run-in phase, 15.4% did not undergo randomization; the most common reason was gastrointestinal upset. Among the patients who had successfully completed the run-in phase and had undergone randomization, 10.5% in each trial group permanently discontinued colchicine or placebo prematurely. Our results provide no evidence for a clinically important interaction between low-dose colchicine and high-dose statins, which were used by 3413 patients (61.8%) in the trial. Myalgia, which was assessed only in the Netherlands cohort, was common in both trial groups, although it was reported more frequently in the colchicine group.

The CANTOS trial provided evidence suggesting that inflammation plays a causal role in the pathogenesis of cardiovascular disease and related complications and that interventions to mitigate inflammation may reduce the risk of cardiovascular events.[6] Our results with colchicine are consistent with those obtained in the first LoDoCo trial and the COLCOT trial and provide further support for the potential benefits of antiinflammatory therapy in patients with coronary disease.[11,12] The magnitude of benefit of low-dose colchicine in the LoDoCo2 trial is consistent with that shown in previous trials of antiinflammatory therapy and in previous trials of other secondary prevention therapies, including lipid-lowering, blood pressure–lowering, and antithrombotic therapies, and a benefit was observed in the patients who were already receiving therapy with these agents.[1,3,16-18] Furthermore, the benefits emerged early and continued to accrue throughout the trial, with no suggestion of attenuation of benefit during up to 5 years of treatment.

The LoDoCo2 trial has several limitations. The percentage of women in the trial was lower than would be expected given the percentage of women with chronic coronary disease in the general population. We did not collect blood-pressure or lipid levels at baseline or during the trial, and we cannot report outcomes according to risk-factor control. We did not routinely measure C-reactive protein levels or other laboratory indicators of inflammation at baseline, and we cannot explore the effects of treatment according to inflammatory state at baseline. However, the effects of treatments were consistent across the majority of clinical subgroups examined.

The results of our trial show that among patients with chronic coronary disease, most of whom were already receiving proven secondary prevention therapies, the occurrence of cardiovascular events was significantly lower with low-dose colchicine than with placebo.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Υπόφυση

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ΟΜΙΛΗΤΗΣ: Αθανάσιος Φούντας

ΝΟΣΟΣ CUSHING

1. **Frete C et al. Non-invasive Diagnostic Strategy in ACTH-dependent Cushing's Syndrome. J Clin Endocrinol Metab. 2020;105(10): 3273-84. dgaa409. doi: 10.1210/clinem/dgaa409.**

CONTEXT: Inferior petrosal sinus sampling (IPSS) is used to diagnose Cushing's disease (CD) when dexamethasone-suppression and CRH tests, and pituitary magnetic resonance imaging (MRI), are negative or give discordant results. However, IPSS is an invasive procedure and its availability is limited.
OBJECTIVE: To test a noninvasive diagnostic strategy associated with 100% positive predictive value (PPV) for CD.
DESIGN: Retrospective study.
SETTING: Two university hospitals.
PATIENTS: A total of 167 patients with CD and 27 patients with ectopic ACTH-syndrome investigated between 2001 and 2016.
MAIN OUTCOME MEASURE(S): Performance of a strategy involving the CRH and desmopressin tests with pituitary MRI followed by thin-slice whole-body computed tomography (CT) scan in patients with inconclusive results.
RESULTS: Using thresholds of a cortisol increase > 17% with an ACTH increase > 37% during the CRH test and a cortisol increase > 18% with an ACTH increase > 33% during the desmopressin test, the combination of both tests gave 73% sensitivity and 98% PPV of CD. The sensitivity and PPV for pituitary MRI were 71% and 99%, respectively. CT scan identified 67% EAS at presentation with no false-positives. The PPV for CD was 100% in patients with positive responses to both tests, with negative pituitary MRI and CT scan. The Negative Predictive Value was 100% in patients with negative responses to both tests, with negative pituitary MRI and positive CT scan. Using this strategy, IPPS could have been avoided in 47% of patients in whom it is currently recommended.
CONCLUSIONS: In conjunction with expert radiologic interpretation, the non-invasive algorithm studied significantly reduces the need for IPSS in the investigation of ACTH-dependent Cushing's syndrome.

2. **Walia R et al. Molecular Imaging Targeting Corticotropin Releasing Hormone Receptor for Corticotropinoma: A Changing Paradigm. J Clin Endocrinol Metab. 2020 Oct 20:dgaa755. doi: 10.1210/clinem/dgaa755. Online ahead of print.**

BACKGROUND: Corticotrophin releasing hormone (CRH) is the major regulator of ACTH secretion from the anterior pituitary and acts via CRH-1 receptors (CRH-1R). Corticotropinoma though autonomous still retain their responsiveness to CRH and hence, we hypothesize that in vivo detection of CRH-1 receptors on pituitary adenoma using Gallium-68 (68Ga) tagged CRH can indicate the functionality of adenoma and combining it with Positron emission tomography-computed tomography (PET-CT) can provide requisite anatomical information.
METHODS: Subjects with ACTH dependent Cushing's syndrome (CS) [n = 27, 24: Cushing's disease (CD), 3: ectopic Cushing's syndrome (ECS)] underwent 68Ga CRH PET-CT. Two nuclear medicine physicians read these images for adenoma delineation and superimposed them on MRI sella. The information so provided was used for intra-operative navigation and compared with operative and histopathological findings.
FINDINGS: 68Ga CRH PET-CT correctly delineated corticotropinoma in all the 24 cases of CD, including the ten cases with size < 6mm (four cases negative on MRI). Corticotropinoma location on 68Ga CRH PET fusion images with MRI were concordant with operative findings and further confirmed on histopathology. There was no tracer uptake in pituitary in two patients with ECS while in another, the diffuse uptake in pituitary suggested ectopic CRH production.
CONCLUSION: 68Ga CRH PET-CT represents a novel non-invasive molecular imaging targeting CRH receptors that not only delineates corticotropinoma and provides surgeon with valuable information for intra-operative tumour navigation but also helps in differentiating pituitary from extra-pituitary source of ACTH dependent Cushing's syndrome.

3. Pivonello R et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8(9):748-761. doi: 10.1016/S2213-8587(20)30240-0.

BACKGROUND: Cushing's disease is a rare endocrine disorder characterised by cortisol overproduction with severe complications. Therapies for cortisol reduction are often necessary. Here we report the outcomes from the pivotal phase III study of osilodrostat (a potent oral inhibitor of cytochrome P450 11B1, mitochondrial [11β-hydroxylase]; Novartis Pharma AG, Basel, Switzerland) in patients with Cushing's disease.
METHODS: LINC 3 was a prospective, multicentre, open-label, phase III study with a double-blind randomised withdrawal period, that comprised four periods. Patients aged 18-75 years, with confirmed persistent or recurrent Cushing's disease (defined as mean 24-h urinary free cortisol [UFC] concentration >1·5 times the upper limit of normal [ULN] and morning plasma adrenocorticotropic hormone above the lower limit of normal) who had previously had pituitary
surgery or irradiation, or were newly diagnosed and who refused surgery or were not surgical candidates, were recruited from 66 hospital sites and private clinical practices in 19 countries. In period 1, open-label osilodrostat was initiated in all participants and adjusted every 2 weeks (1-30 mg twice daily; film-coated tablets for oral administration) on the basis of mean 24-h UFC concentration and safety until week 12. In period 2, weeks 13-24, osilodrostat was continued at the therapeutic dose determined during period 1. In period 3, beginning at week 26, participants who had a mean 24-h UFC concentration of less than or equal to the ULN at week 24, without up-titration after week 12, were randomly assigned (1:1), via an interactive-response technology, stratified by osilodrostat dose at week 24 and history of pituitary irradiation, to continue osilodrostat or switch to placebo for 8 weeks. Participants and investigators were masked to treatment assignment. Ineligible participants continued open-label osilodrostat. In period 4, weeks 35-48, all participants were given open-label osilodrostat until core-study end. The primary objective was to compare the efficacy of osilodrostat versus placebo at the end of period 3. The
primary endpoint was the proportion of participants who had been randomly assigned to treatment or placebo with a complete response (ie, mean 24-h UFC concentration of ≤ULN) at the end of the randomised withdrawal period (week 34), without up-titration during this period. The key secondary endpoint was the proportion of participants with a complete response at the end of the single-arm, open-label period (ie, period 2, week 24) without up-titration during weeks 13-24. Analysis was by intention-to-treat for all patients who received at least one dose of osilodrostat (full analysis set; key secondary

endpoint) or randomised treatment (randomised analysis set; primary endpoint) and safety was assessed in all enrolled patients who received at least one dose of osilodrostat and had at least one post-baseline safety assessment. LINC 3 is registered with ClinicalTrials.gov, NCT02180217, and is now complete.

FINDINGS: Between Nov 12, 2014, and March 22, 2017, 202 patients were screened and 137 were enrolled. The median age was 40·0 years (31·0-49·0) and 106 (77%) participants were female. 72 (53%) participants were eligible for randomisation during the withdrawal phase, of whom 36 were assigned to continue osilodrostat and 35 were assigned to placebo; one patient was not randomly assigned due to investigator decision and continued open-label osilodrostat. More patients maintained a complete response with osilodrostat versus with placebo at week 34 (31 [86%] vs ten [29%]; odds ratio 13·7 [95% CI 3·7-53·4]; p<0·0001). At week 24, 72 (53%; 95% CI 43·9-61·1) of 137 patients maintained a complete response without up-titration after week 12. Most common adverse events (ie, occurred in >25% of participants) were nausea (57 [42%]), headache (46 [34%]), fatigue (39 [28%]), and adrenal insufficiency (38 [28%]). Hypocortisolism occurred in 70 (51%) patients and adverse events related to adrenal hormone precursors occurred in 58 (42%) patients. One patient died, unrelated to study drug, after the core study phase.

INTERPRETATION: Twice-daily osilodrostat rapidly reduced mean 24-h UFC and sustained this reduction alongside improvements in clinical signs of hypercortisolism; it was also generally well tolerated. Osilodrostat is an effective new treatment option that is approved in Europe for the treatment of endogenous Cushing's syndrome and in the USA for Cushing's disease.

FUNDING: Novartis Pharma AG.

ΜΕΓΑΛΑΚΡΙΑ

1. **Fleseriu M et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2020 Oct 20. doi: 10.1007/s11102-020-01091-7. Online ahead of print.**

Guidelines and consensus statements ensure that physicians managing acromegaly patients have access to current information on evidence-based treatments to optimize outcomes. Given significant novel recent advances in understanding acromegaly natural history and individualized therapies, the Pituitary Society invited acromegaly experts to critically review the current literature in the context of Endocrine Society guidelines and Acromegaly Consensus Group statements. This update focuses on how recent key advances affect treatment decision-making and outcomes, and also highlights the likely role of recently FDA-approved therapies as well as novel combination therapies within the treatment armamentarium.

2. **Samson SL et al. Maintenance of Acromegaly Control in Patients Switching From Injectable Somatostatin Receptor Ligands to Oral Octreotide. J Clin Endocrinol Metab. 2020;105(10):e3785-97. doi: 10.1210/clinem/dgaa526.**

PURPOSE: The phase 3 CHIASMA OPTIMAL trial (NCT03252353) evaluated efficacy and safety of oral octreotide capsules (OOCs) in patients with acromegaly who previously demonstrated biochemical control while receiving injectable somatostatin receptor ligands (SRLs).
METHODS: In this double-blind study, patients (N = 56) stratified by prior SRL dose were randomly assigned 1:1 to OOC or placebo for 36 weeks. The primary end point was maintenance of biochemical control at the end of treatment (mean insulin-like growth factor 1 [IGF-1] ≤ 1.0 × upper limit of normal [ULN]; weeks 34 and 36). Time to loss of IGF-1 response and proportion requiring reversion to injectable SRLs were assessed as broader control measures.
RESULTS: Mean IGF-1 measurements were 0.80 and 0.97 × ULN for OOC and 0.84 and 1.69 × ULN for placebo, at baseline and end of treatment, respectively. Mean growth hormone (GH) changed from 0.66 to 0.60 ng/mL for OOCs and 0.90 to 2.57 ng/mL for placebo. Normalization of IGF-1 levels (≤ 1.0 × ULN) was maintained in 58.2% for OOCs vs 19.4% for placebo (P = .008); GH levels were maintained (< 2.5 ng/mL) in 77.7% for OOC vs 30.4% for placebo (P = .0007). Median time to loss of response (IGF-1 > 1.0 or ≥ 1.3 × ULN definitions) for patients receiving placebo was 16 weeks; for patients receiving OOCs, it was not reached for both definitions during the 36-week trial (P < .0001). Of the patients in the OOC group, 75% completed the trial on oral therapy. The OOC safety profile was consistent with previous SRL experience.
CONCLUSIONS: OOCs may be an effective therapy for patients with acromegaly who previously were treated with injectable SRLs.

3. **Coopmans EC et al. Eucaloric Very-Low-Carbohydrate Ketogenic Diet in Acromegaly Treatment. N Engl J Med. 2020;382(22):2161-2162. doi: 10.1056/NEJMc1915808.**

4. **Mazziotti G et al. Treatment of Acromegalic Osteopathy in Real-life Clinical Practice: The BAAC (Bone Active Drugs in Acromegaly) Study. J Clin Endocrinol Metab. 2020 Sep 1;105(9):e3285-92. doi: 10.1210/clinem/dgaa363.**

BACKGROUND: Vertebral fractures (VFs) are a frequent complication of acromegaly, but no studies have been so far published on effectiveness of antiosteoporotic drugs in this clinical setting.
OBJECTIVE: To evaluate whether in real-life clinical practice bone active drugs may reduce the risk of VFs in patients with active or controlled acromegaly.
STUDY DESIGN: Retrospective, longitudinal study including 9 tertiary care endocrine units.
PATIENTS AND METHODS: Two hundred and forty-eight patients with acromegaly (104 males; mean age 56.00 ± 13.60 years) were evaluated for prevalent and incident VFs by quantitative morphometric approach. Bone active agents were used in 52 patients (20.97%) and the median period of follow-up was 48 months (range 12-132).
RESULTS: During the follow-up, 65 patients (26.21%) developed incident VFs in relationship with pre-existing VFs (odds ratio [OR] 3.75; P < .001), duration of active acromegaly (OR 1.01; P = .04), active acromegaly at the study entry (OR 2.48; P = .007), and treated hypoadrenalism (OR 2.50; P = .005). In the entire population, treatment with bone active drugs did not have a significant effect
on incident VFs (P = .82). However, in a sensitive analysis restricted to patients with active acromegaly at study entry (111 cases), treatment with bone active drugs was associated with a lower risk of incident VFs (OR 0.11; P = .004), independently of prevalent VFs (OR 7.65; P < .001) and treated hypoadrenalism (OR 3.86; P = .007).
CONCLUSIONS: Bone active drugs may prevent VFs in patients with active acromegaly.

5. **Giustina A et al. A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update. J Clin Endocrinol Metab. 2020;105(4): e937-46. doi: 10.1210/clinem/dgz096.**

OBJECTIVE: The aim of the Acromegaly Consensus Group was to revise and update the consensus on diagnosis and treatment of acromegaly comorbidities last published in 2013.
PARTICIPANTS: The Consensus Group, convened by 11 Steering Committee members, consisted of 45 experts in the medical and surgical management of acromegaly. The authors received no corporate funding or remuneration.
EVIDENCE: This evidence-based consensus was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence following critical discussion of the current literature on the diagnosis and treatment of acromegaly comorbidities.
CONSENSUS PROCESS: Acromegaly Consensus Group participants conducted comprehensive literature searches for English-language papers on selected topics, reviewed brief presentations on each topic, and discussed current practice and recommendations in breakout groups. Consensus recommendations were developed based on all presentations and discussions. Members of the Scientific Committee graded the quality of the supporting evidence and the consensus recommendations using the GRADE system.
CONCLUSIONS: Evidence-based approach consensus recommendations address important clinical issues regarding multidisciplinary management of acromegaly-related cardiovascular, endocrine, metabolic, and oncologic comorbidities, sleep apnea, and bone and joint disorders and their sequelae, as well as their effects on quality of life and mortality.

6. Geer EB et al. Observed discordance between outcomes reported by acromegaly patients and their treating endocrinology medical provider. Pituitary. 2020;23(2):140-148. doi: 10.1007/s11102-019-01013-2.

BACKGROUND: Acromegaly patients, even those with IGF-1 values within the normal range receiving somatostatin receptor ligands (SRLs), often suffer from significant symptoms. It is not known to what extent patients' medical providers are aware of the frequency and severity of acromegaly symptoms or level of treatment satisfaction with SRLs. This study sought to examine the concordance between outcomes reported by acromegaly patients treated with long-acting SRLs and those perceived by their medical provider.
METHODS: US acromegaly patients on a stable dose of SRL and seen by their medical provider in the past year completed an online survey which included the Acro-TSQ. Their medical providers were interviewed about the perception of their patient's symptoms, level of control, and general health, and completed relevant portions of the Acro-TSQ. Concordance between patient and medical provider reported data was examined.
RESULTS: Medical providers reported that their patients experienced acromegaly symptoms on a regular basis, however, there was poor agreement between patients and medical providers on the frequency, severity, and pattern of symptoms, as well as on the severity of injection site reactions and multiple domains of the Acro-TSQ, with patients generally reporting symptoms and injection site reactions more often and with higher severity than medical providers.
CONCLUSIONS: Medical providers were aware that their patients who were receiving a stable dose of SRL regularly experienced acromegaly symptoms. Addressing discordance in patient- and medical provider-reported frequency and severity of acromegaly symptoms and injection site reactions by facilitating better communication may improve care of acromegaly patients.

ΠΡΟΛΑΚΤΙΝΩΜΑΤΑ

1. **Kim D et al. Prolactin ≤1 ng/mL predicts macroprolactinoma reduction after cabergoline therapy. Eur J Endocrinol. 2020;182(2):177-183. doi: 10.1530/EJE-19-0753.**

OBJECTIVE: The association between prolactin level variation and prolactinoma size reduction remains unclear. This study aimed to determine the prolactin level cut-off predictive of a tumor size reduction.
DESIGN: Retrospective cohort study.
METHODS: We reviewed medical records of patients with prolactinoma who received primary cabergoline therapy and for whom complete data on pituitary hormone assays and sellar MRI at baseline and 3 months post treatment were available. We tested whether the certain prolactin level after 3 months post treatment predicted better response.
RESULTS: Prolactin levels normalized in 109 (88.6%) of 123 included macroprolactinoma patients. The mean tumor size reduction was 22.9%, and patients in the lowest prolactin tertile (≤0.7) had the highest frequency of tumor size reductions of ≥20% (73.7 vs 52.9% and 45.9% in tertiles 2 (>0.7 to 2.6) and 3 (>2.6 to 20), P = 0.015). Patients with prolactin levels ≤1 ng/mL exhibited larger tumor size reductions vs those with prolactin levels of 1-20 (27.2 ± 18.3% vs 19.5 ± 13.9%, P = 0.014), 1-10 (19.3 ± 13.7%, P = 0.017) and 1-5 ng/mL (19.2 ± 14.3%, P = 0.039). A multivariable logistic regression analysis revealed that a prolactin level ≤1 ng/mL at 3 months and high-dose
cabergoline therapy were significantly associated with tumor size reductions of ≥20% (odds ratio (OR): 2.8, 95% confidence interval (CI): 1.2-6.7, P = 0.017; OR: 2.0, 95% CI: 1.0-3.9, P = 0.043).
CONCLUSIONS: A prolactin level ≤1 ng/mL at 3 months after cabergoline treatment was correlated with a significant tumor size reduction in patients with macroprolactinoma. This finding may help clinical decision making when treating macroprolactinoma patients.

2. **Zamanipoor Najafabadi AH et al. Surgery as a Viable Alternative First-Line Treatment for Prolactinoma Patients. A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2020;105(3):e32-41. doi: 10.1210/clinem/dgz144.**

CONTEXT: The improved remission and complication rates of current transsphenoidal surgery warrant reappraisal of the position of surgery as a viable alternative to dopamine agonists in the treatment algorithm of prolactinomas.
OBJECTIVE: To compare clinical outcomes after dopamine agonist withdrawal and transsphenoidal surgery in prolactinoma patients.
METHODS: Eight databases were searched up to July 13, 2018. Primary outcome was disease remission after drug withdrawal or surgery. Secondary outcomes were biochemical control and side effects during dopamine agonist treatment and postoperative complications. Fixed- or random-effects meta-analysis was performed to estimate pooled proportions. Robustness of results was assessed by sensitivity analyses.
RESULTS: A total of 1469 articles were screened: 55 (10 low risk of bias) on medical treatment (n = 3564 patients) and 25 (12 low risk of bias) on transsphenoidal surgery (n = 1836 patients). Long-term disease remission after dopamine agonist withdrawal was 34% (95% confidence interval [CI], 26-46) and 67% (95% CI, 60-74) after surgery. Subgroup analysis of microprolactinomas showed 36% (95% CI, 21-52) disease remission after dopamine agonist withdrawal, and 83% (95% CI, 76-90) after surgery. Biochemical control was achieved in 81% (95% CI, 75-87) of patients during dopamine agonists with side effects in 26% (95% CI, 13-41). Transsphenoidal surgery resulted in 0% mortality, 2% (95% CI, 0-5) permanent diabetes insipidus, and 3% (95% CI, 2-5) cerebrospinal fluid leakage. Multiple sensitivity analyses yielded similar results.
CONCLUSIONS: In the majority of prolactinoma patients, disease remission can be achieved through surgery, with low risks of long-term surgical complications, and disease remission is less often achieved with dopamine agonists.

3. **De Sousa SMC et al. Impulse Control Disorders in Dopamine Agonist-Treated Hyperprolactinemia: Prevalence and Risk Factors. J Clin Endocrinol Metab. 2020;105(3): e108-18. doi: 10.1210/clinem/dgz076.**

CONTEXT: There are growing reports of dopamine agonist (DA)-induced impulse control disorders (ICDs) in hyperprolactinemic patients. However, the magnitude of this risk and predictive factors remain uncertain.
OBJECTIVE: To determine ICD prevalence and risk factors in DA-treated hyperprolactinemic patients compared to community controls.
DESIGN, SETTING AND PARTICIPANTS: Multicenter cross-sectional analysis of 113 patients and 99 healthy controls.
MAIN OUTCOME MEASURES: Participants completed a neuropsychological questionnaire consisting of the Depression Anxiety Stress Scale (DASS21), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-S), Hypersexual Behavior Inventory (HBI), Hypersexual Behavior Consequences Scale and Social Desirability Response Set Scale. Demographic and clinical data were collated to determine ICD risk factors. Patients testing positive for an ICD were offered a semistructured psychological interview.
RESULTS: Patients were more likely than controls to test positive by QUIP-S for any ICD (61.1 vs 42.4%, P = .01), hypersexuality (22.1 vs 8.1%, P = .009), compulsive buying (15.9 vs 6.1%, P = .041) and punding (18.6 vs 6.1%, P = 0.012), and by HBI for hypersexuality (8.0 vs 0.0%, P = 0.004). Independent risk factors were male sex (odds ratio [OR] 13.85), eugonadism (OR 7.85), Hardy's tumor score and psychiatric comorbidity (OR 6.86) for hypersexuality, and age (OR 0.95) for compulsive buying. DASS21 subset scores were higher in patients vs controls and in patients with vs without different ICDs. Only 19/51 (37.3%) interviewed patients were aware of the relationship between DAs and ICDs before the study.
CONCLUSIONS: DA therapy poses a high, previously underestimated risk of ICDs, especially in the form of hypersexuality in eugonadal men.

TSH ΕΚΚΡΙΤΙΚΑ ΑΔΕΝΩΜΑΤΑ ΥΠΟΦΥΣΗΣ

3. **Han R et al. Diagnosing Thyrotropin-Secreting Pituitary Adenomas by Short-Term Somatostatin Analogue Test. Thyroid. 2020;30(9):1236-1244. doi: 10.1089/thy.2019.0470.**

Background: Diagnosis of thyrotropin (TSH)-secreting pituitary adenomas (TSHoma) before surgery remains a challenge, especially for microadenomas. We aimed to establish a short-term somatostatin analogue (SSA) test to differentiate TSHomas from other causes of syndromes of inappropriate secretion of TSH (IST), mainly resistance to thyroid hormone β (RTHβ).

Materials and Methods: We first evaluated the sensitivity and specificity of SSA test in a training cohort (TSHoma, n = 32; RTHβ, n = 20). The test was then validated in an independent cohort (TSHoma, n = 9; RTHβ, n = 2). We finally applied the SSA test in 12 perceptively enrolled IST cases with negative imaging findings and absent thyroid hormone receptor beta (THRB) mutations or mixed hormone imbalances.

Results: Both TSHoma and RTHβ patients showed a decrease of TSH at the start of the SSA test, but the velocity of the TSH suppression slowly decreased in RTHβ patients after 2 hours. The suppression ratio of TSH at 24 hours versus 2 and 0 hours was significantly greater in TSHoma patients compared with RTHβ patients (70.58% ± 18.6% vs. 6.01% ± 25.41%, $p < 0.0001$, 79.83% ± 12.79% vs. 51.16% ± 13.62%, $p < 0.0001$, respectively). The 24- versus 2-hour suppression ratio showed the best diagnostic accuracy at a cut point of 44.46% in the training cohort, with a sensitivity of 95.00%, a specificity of 93.75%, and a positive predictive value (PPV) of 88.89%. The accuracy was confirmed in the validation cohort. Three out of 12 patients in the prospective cohort showed a TSH suppression ratio greater than 44.46% and all developed microadenomas during follow-up.

Conclusions: A short-term SSA test provides an alternative diagnostic approach for TSHomas. A positive SSA test result is suggestive for a TSHoma even before positive findings become apparent on pituitary imaging. However, studies including larger number of patients, especially those with RTHβ, are needed to confirm our findings.

ΜΗ ΛΕΙΤΟΥΡΓΙΚΑ ΑΔΕΝΩΜΑΤΑ ΥΠΟΦΥΣΗΣ

1. **Freda PU et al. Presenting Features in 269 Patients With Clinically Nonfunctioning Pituitary Adenomas Enrolled in a Prospective Study. J Endocr Soc. 2020 Feb 18;4(4):bvaa021. doi: 10.1210/jendso/bvaa021. eCollection 2020 Apr 1.**

CONTEXT: Clinically nonfunctioning pituitary adenomas (CNFPAs) typically remain undetected until mass effect symptoms develop. However, currently, head imaging is performed commonly for many other indications, which may increase incidental discovery of CNFPAs. Since current presentation and outcome data are based on older, retrospective series, a prospective characterization of a contemporary CNFPA cohort was needed.
OBJECTIVE: To determine the prevalence of incidental presentation and hypopituitarism and its predictors in a CNFPA cohort that spanned 6 to 9 mm micro- to macroadenoma included observational and surgical therapy.
METHODS: At enrollment in a prospective, observational study, 269 patients with CNFPAs were studied by history, examination, blood sampling, and pituitary imaging analysis and categorized into incidental or symptoms presentation groups that were compared.
RESULTS: Presentation was incidental in 48.7% of patients and due to tumor symptoms in 51.3%. In the symptoms and incidental groups, 58.7% and 27.4% of patients had hypopituitarism, respectively, and 25% of patients with microadenomas had hypopituitarism. Many had unappreciated signs and symptoms of pituitary disease. Most tumors were macroadenomas (87%) and were larger in the symptoms than incidental and hypopituitary groups than in the eupituitary groups. The patients in the incidental group were older, and males were older and had larger tumors in both the incidental and symptoms groups.
CONCLUSIONS: Patients with CNFPAs commonly present incidentally and with previously unrecognized hypopituitarism and symptoms that could have prompted earlier diagnosis. Our data support screening all large micro and macro-CNFPAs for hypopituitarism. Most patients with CNFPAs still have mass effect signs at presentation, suggesting the need for more awareness of pituitary disease. Our ongoing, prospective observation of this cohort will assess outcomes of these CNFPA groups.

2. **Marques P et al. Significant Benefits of AIP Testing and Clinical Screening in Familial Isolated and Young-onset Pituitary Tumors. J Clin Endocrinol Metab. 2020;105(6):e2247-60. doi: 10.1210/clinem/dgaa040.**

CONTEXT: Germline mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene are responsible for a subset of familial isolated pituitary adenoma (FIPA) cases and sporadic pituitary neuroendocrine tumors (PitNETs).
OBJECTIVE: To compare prospectively diagnosed AIP mutation-positive (AIPmut) PitNET patients with clinically presenting patients and to compare the clinical characteristics of AIPmut and AIPneg PitNET patients.
DESIGN: 12-year prospective, observational study.
PARTICIPANTS & SETTING: We studied probands and family members of FIPA kindreds and sporadic patients with disease onset ≤18 years or macroadenomas with onset ≤30 years (n = 1477). This was a collaborative study conducted at referral centers for pituitary diseases.
INTERVENTIONS & OUTCOME: AIP testing and clinical screening for pituitary disease. Comparison of characteristics of prospectively diagnosed (n = 22) vs clinically presenting AIPmut PitNET patients (n = 145), and AIPmut (n = 167) vs AIPneg PitNET patients (n = 1310).
RESULTS: Prospectively diagnosed AIPmut PitNET patients had smaller lesions with less suprasellar extension or cavernous sinus invasion and required fewer treatments with fewer operations and no radiotherapy compared with clinically presenting cases; there were fewer cases with active disease and hypopituitarism at last follow-up. When comparing AIPmut and AIPneg cases, AIPmut patients were more often males, younger, more often had GH excess, pituitary apoplexy, suprasellar extension, and more patients required multimodal therapy, including radiotherapy. AIPmut patients (n = 136) with GH excess were taller than AIPneg counterparts (n = 650).
CONCLUSIONS: Prospectively diagnosed AIPmut patients show better outcomes than clinically presenting cases, demonstrating the benefits of genetic and clinical screening. AIP-related pituitary disease has a wide spectrum ranging from aggressively growing lesions to stable or indolent disease course.

ΕΠΙΘΕΤΙΚΑ ΑΔΕΝΩΜΑΤΑ ΥΠΟΦΥΣΗΣ – ΥΠΟΦΥΣΙΑΚΑ ΚΑΡΚΙΝΩΜΑΤΑ

1. **Elbelt U et al. Efficacy of Temozolomide Therapy in Patients With Aggressive Pituitary Adenomas and Carcinomas-A German Survey. J Clin Endocrinol Metab. 2020;105(3):e660-75. doi: 10.1210/clinem/dgz211.**

CONTEXT: Despite growing evidence that temozolomide (TMZ) therapy is effective for the treatment of aggressive pituitary tumors (APTs) or carcinomas (PCs), individual therapy decisions remain challenging.
OBJECTIVE: We therefore aimed to report on clinical characteristics leading to initiation of TMZ therapy and to add evidence on TMZ long-term effectiveness.
DESIGN AND SUBJECTS: Retrospective survey on TMZ treatment in patients with APTs or PCs. TMZ therapy was initiated in 47 patients (22 females) with APTs (n = 34) or PCs (n = 13). Mean age at diagnosis was 45 ± 15 years. The immunohistochemical subtypes were corticotroph (n = 20), lactotroph (n = 18), and nonfunctioning (n = 9) tumors. TMZ therapy started 8 years after initial diagnosis using a standard regimen (median 6 cycles) for the majority of patients.
RESULTS: Long-term radiological response to TMZ after a median follow-up of 32 months with 4 patients still on TMZ therapy was tumor regression for 9 (20%), stable disease for 8 (17%), and tumor progression for 29 patients (63%) (outcome data available for 46 patients). Progression occurred 16 months after initiation of TMZ. Median estimated progression-free survival was 23 months. Disease stabilization and median progression-free survival did not differ between patients with APTs or PCs. Predictors of tumor response were not identified. Overall, TMZ was well tolerated.
CONCLUSION: We performed a nationwide survey on TMZ therapy in patients with APTs and PCs. While early response rates to TMZ are promising, long-term outcome is less favorable. Prolonged TMZ administration should be considered. We were not able to confirm previously reported predictors of tumor response to TMZ.

ΚΡΑΝΙΟΦΑΡΥΓΓΙΩΜΑΤΑ

1. **Cossu G et al. Surgical management of craniopharyngiomas in adult patients: a systematic review and consensus statement on behalf of the EANS skull base section. Acta Neurochir (Wien). 2020;162(5):1159-77. doi: 10.1007/s00701-020-04265-1.**

BACKGROUND AND OBJECTIVE: Craniopharyngiomas are locally aggressive neuroepithelial tumors infiltrating nearby critical neurovascular structures. The majority of published surgical series deal with childhood-onset craniopharyngiomas, while the optimal surgical management for adult-onset tumors remains unclear. The aim of this paper is to summarize the main principles
defining the surgical strategy for the management of craniopharyngiomas in adult patients through an extensive systematic literature review in order to formulate a series of recommendations.
MATERIAL AND METHODS: The MEDLINE database was systematically reviewed (January 1970-February 2019) to identify pertinent articles dealing with the surgical management of adult-onset craniopharyngiomas. A summary of literature evidence was proposed after discussion within the EANS skull base section.
RESULTS: The EANS task force formulated 13 recommendations and 4 suggestions. Treatment of these patients should be performed in tertiary referral centers. The endonasal approach is presently recommended for midline craniopharyngiomas because of the improved GTR and superior endocrinological and visual outcomes. The rate of CSF leak has strongly diminished with the use of the multilayer reconstruction technique. Transcranial approaches are recommended for tumors presenting lateral extensions or purely intraventricular. Independent of the technique, a maximal but hypothalamic-sparing resection should be performed to limit the occurrence of postoperative hypothalamic syndromes and metabolic complications. Similar principles should also be applied for tumor recurrences. Radiotherapy or intracystic agents are alternative treatments when no further surgery is possible. A multidisciplinary long-term follow-up is necessary.

2. **van Santen SS et al. Body Composition and Bone Mineral Density in Craniopharyngioma Patients: A Longitudinal Study Over 10 Years. J Clin Endocrinol Metab. 2020 Dec 1;105(12):dgaa607. doi: 10.1210/clinem/dgaa607.**

CONTEXT: Patients with craniopharyngioma suffer from obesity and impaired bone health. Little is known about longitudinal changes in body composition and bone mineral density (BMD).
OBJECTIVE: To describe body composition and BMD (change).
DESIGN: Retrospective longitudinal study.
SETTING: Two Dutch/Swedish referral centers.
PATIENTS: Patients with craniopharyngioma (n = 112) with a dual X-ray absorptiometry (DXA) scan available (2 DXA scans, n = 86; median Δtime 10.0 years; range 0.4-23.3) at age ≥ 18 years (58 [52%] male, 50 [45%] childhood onset).
MAIN OUTCOME MEASURES: Longitudinal changes of body composition and BMD, and associated factors of ΔZ-score (sex and age standardized).
RESULTS: BMI (from 28.8 ± 4.9 to 31.2 ± 5.1 kg/m2, P < .001), fat mass index (FMI) (from 10.5 ± 3.6 to 11.9 ± 3.8 kg/m2, P = .001), and fat free mass index (FFMI) (from 18.3 ± 3.2 to 19.1 ± 3.2 kg/m2, P < .001) were high at baseline and increased. Fat percentage and Z-scores of body composition did not increase, except for FFMI Z-scores (from 0.26 ± 1.62 to 1.06 ± 2.22, P < .001). Z-scores of total body, L2-L4, femur neck increased (mean difference 0.61 ± 1.12, P < .001; 0.74 ± 1.73, P < .001; 0.51 ± 1.85, P = .02). Linear regression models for ΔZ-score were positively associated with growth hormone replacement therapy (GHRT) (femur neck: beta 1.45 [95% CI 0.51-2.39]); and negatively with radiotherapy (femur neck: beta -0.79 [-1.49 to -0.09]), glucocorticoid dose (total body: beta -0.06 [-0.09 to -0.02]), and medication to improve BMD (L2-L4: beta -1.06 [-1.84 to -0.28]).
CONCLUSIONS: Z-scores of BMI, fat percentage, and FMI remained stable in patients with craniopharyngioma over time, while Z-scores of FFMI and BMD increased. Higher glucocorticoid dose and radiotherapy were associated with BMD loss and GHRT with increase.

ΚΥΣΤΕΙΣ RATHKE

1. **Lu VM et al. Recurrence of Rathke's cleft cysts based on gross total resection of cyst wall: a meta-analysis. Neurosurg Rev. 2020;43(3):957-66. doi: 10.1007/s10143-019-01107-2.**

Rathke's cleft cysts (RCCs) are benign growths of the embryological Rathke's pouch. Surgical decompression provides effective symptomatic relief in most cases; however, the effect of gross total resection (GTR) of the cyst wall on recurrence, as well as pituitary function, is unclear.

The aim of this meta-analysis was to pool the current literature and ascertain the recurrence control afforded by GTR of the cyst wall compared with subtotal resection (STR).

Searches of seven electronic databases from inception to January 2019 were conducted following PRISMA guidelines, resulting in 476 articles to be screened. Outcomes were analyzed using meta-analysis of proportions.

A total of 10 retrospective cohort studies satisfied selection criteria, describing 655 surgically managed RCC cases, with 254 (39%) and 401 (61%) achieving GTR and STR of the cyst wall, respectively. GTR was associated with significantly reduced overall RCC recurrence by fixed-effects (FE) modeling (RR, 0.66; 95% CI, 0.45-0.96), but not by random effects (RE) modeling (RR, 0.75; 95% CI, 0.51-1.12). Based on both models, GTR was associated with significantly reduced

symptomatic recurrence (RE model, RR, 0.37, 95% CI, 0.14-0.95) and significantly increased postoperative diabetes insipidus (RE model, RR, 2.60; 95% CI, 1.34-5.03). There was insufficient data to evaluate other pituitary axes in this context.

The current evidence indicates that GTR of the RCC cyst wall has the potential to affect the incidence of overall and symptomatic RCC recurrences, as well as drive postoperative DI incidence. However, expectations of clinical and pragmatic benefit following cyst wall resection should be titrated carefully against the potential for postoperative and pituitary morbidities which

currently remain poorly defined. Greater granularity is required to understand all factors that can influence recurrence and quality of life when evaluating resection of RCC.

ΥΠΟΦΥΣΙΤΙΔΑ

1. **Türe U et al. Hypothalamitis: A Novel Autoimmune Endocrine Disease. A Literature Review and Case Report. J Clin Endocrinol Metab. 2020 Oct 26:dgaa771. doi: 10.1210/clinem/dgaa771.**

The relationship between the endocrine system and autoimmunity has been recognized for a long time and one of the best examples of autoimmune endocrine disease is autoimmune hypophysitis. A better understanding of autoimmune mechanisms and radiological, biochemical, and immunological developments have given rise to the definition of new autoimmune disorders including autoimmunity-related hypothalamic-pituitary disorders. However, whether hypothalamitis may occur as a distinct entity, is still matter of debate. Here we describe a 35-year-old woman with growing suprasellar mass, partial empty sella, central diabetes insipidus, hypopituitarism, and hyperprolactinemia. Histopathologic examination of surgically removed suprasellar mass revealed lymphocytic infiltrate suggestive of an autoimmune disease with hypothalamic involvement. The presence of anti-hypothalamus antibodies to AVP-secreting cells (AVPcAb) at high titers and the absence of anti-pituitary antibodies suggested the diagnosis of isolated hypothalamitis. Some similar conditions have sometimes been reported in the literature but the simultaneous double finding of lymphocytic infiltrate and the presence of AVPcAb so far has never been reported. We think that the hypothalamitis can be considered a new isolated autoimmune disease affecting the hypothalamus while the lymphocytic infundibulo-neurohypophysitis can be a consequence of hypothalamitis with subsequent autoimmune involvement of the pituitary. To our knowledge this is the first observation of autoimmune hypothalamic involvement with central diabetes insipidus, partial empty sella, anti-hypothalamic antibodies and hypopituitarism.

ΥΠΟΦΥΣΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

1. **Sävendahl L et al. Long-term mortality after childhood growth hormone treatment: the SAGhE cohort study. Lancet Diabetes Endocrinol. 2020;8(8):683-92. doi: 10.1016/S2213-8587(20)30163-7.**

BACKGROUND: Recombinant human growth hormone has been used for more than 30 years and its indications have increased worldwide. There is concern that this treatment might increase mortality, but published data are scarce. We present data from the entire dataset of all eight countries of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) consortium, with the aim of studying long-term overall and cause-specific mortality in young adult patients treated with recombinant human growth hormone during childhood and relating this to the underlying diagnosis.
METHODS: This cohort study was done in eight European countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK). Patients were classified a priori based on pre-treatment perceived mortality risk from their underlying disease and followed up for cause-specific mortality. Person-years at risk of mortality and expected rates from general population data were used to calculate standardised mortality ratios (SMRs).
FINDINGS: The cohort comprised 24 232 patients treated with recombinant human growth hormone during childhood, with more than 400 000 patient-years of follow-up. In low-risk patients with isolated growth hormone deficiency or idiopathic short stature, all-cause mortality was not significantly increased (SMR 1·1, 95% CI 0·9-1·3). In children born small for gestational age, all-cause mortality was significantly increased when analysed for all countries (SMR 1·5, CI 1·1-1·9), but this result was driven by the French subcohort. In patients at moderate or high risk, mortality was increased (SMR 3·8, 3·3-4·4; and 17·1, 15·6-18·7, respectively). Mortality was not associated with mean daily or cumulative doses of recombinant human growth hormone for any of the risk groups. Cause-specific mortality from diseases of the circulatory and haematological systems was increased in all risk groups.
INTERPRETATION: In this cohort, the largest, to our knowledge, with long-term follow-up of patients treated with recombinant human growth hormone during childhood, all-cause mortality was associated with underlying diagnosis. In patients with isolated growth hormone deficiency or idiopathic short stature, recombinant human growth hormone treatment was not associated with increased all-cause mortality. However, mortality from certain causes was increased, emphasising the need for further long-term surveillance.

2. **Johannsson G et al. Once-weekly Somapacitan is Effective and Well Tolerated in Adults with GH Deficiency: A Randomized Phase 3 Trial. J Clin Endocrinol Metab. 2020;105(4):e1358-76. doi: 10.1210/clinem/dgaa049.**

CONTEXT: Growth hormone (GH) replacement requires daily GH injections, which is burdensome for some adult patients with GH deficiency (AGHD).
OBJECTIVE: To demonstrate efficacy and safety of somapacitan, a once-weekly reversible albumin-binding GH derivative, versus placebo in AGHD.
DESIGN: Randomized, parallel-group, placebo-controlled (double-blind) and active-controlled (open-label) phase 3 trial, REAL 1 (NCT02229851).
SETTING: Clinics in 17 countries.
PATIENTS: Treatment-naïve patients with AGHD (n = 301 main study period, 272 extension period); 257 patients completed the trial.
INTERVENTIONS: Patients were randomized 2:2:1 to once-weekly somapacitan, daily GH, or once-weekly placebo for 34 weeks (main period). During the 52-week extension period, patients continued treatment with somapacitan or daily GH.
MAIN OUTCOME MEASURES: Body composition measured using dual-energy x-ray absorptiometry (DXA). The primary endpoint was change in truncal fat percentage to week 34. Insulin-like growth factor 1 (IGF-I) standard deviation score (SDS) values were used to dose titrate.
RESULTS: At 34 weeks, somapacitan significantly reduced truncal fat percentage (estimated difference: -1.53% [-2.68; -0.38]; P = 0.0090), demonstrating superiority compared with placebo, and it improved other body composition parameters (including visceral fat and lean body mass) and IGF-I SDS. At 86 weeks, improvements were maintained with both somapacitan and daily GH.
Somapacitan was well tolerated, with similar adverse events (including injection-site reactions) compared with daily GH.
CONCLUSIONS: In AGHD patients, somapacitan administered once weekly demonstrated superiority over placebo, and the overall treatment effects and safety of somapacitan were in accordance with known effects and safety of GH replacement for up to 86 weeks of treatment. Somapacitan may provide an effective alternative to daily GH in AGHD.

3. **Ebrahimi F et al. Excess Mortality Among Hospitalized Patients With Hypopituitarism-A Population-Based, Matched-Cohort Study. J Clin Endocrinol Metab. 2020;105(11): e3910-8. doi: 10.1210/clinem/dgaa517.**

CONTEXT: Patients with hypopituitarism face excess mortality in the long-term outpatient setting. However, associations of pituitary dysfunction with outcomes in acutely hospitalized patients are lacking.
OBJECTIVE: The objective of this work is to assess clinical outcomes of hospitalized patients with hypopituitarism with or without diabetes insipidus (DI).
DESIGN, SETTING, AND PATIENTS: In this population-based, matched-cohort study from 2012 to 2017, hospitalized adult patients with a history of hypopituitarism were 1:1 propensity score-matched with a general medical inpatient cohort.
MAIN OUTCOME MEASURES: The primary outcome was in-hospital mortality. Secondary outcomes included all-cause readmission rates within 30 days and 1 year, intensive care unit (ICU) admission rates, and length of hospital stay.
RESULTS: After matching, 6764 cases were included in the study. In total, 3382 patients had hypopituitarism and of those 807 (24%) suffered from DI. All-cause in-hospital mortality occurred in 198 (5.9%) of patients with hypopituitarism and in 164 (4.9%) of matched controls (odds ratio [OR] 1.32, [95% CI, 1.06-1.65], P = .013). Increased mortality was primarily observed in patients with DI (OR 3.69 [95% CI, 2.44-5.58], P < .001). Patients with hypopituitarism had higher ICU admissions (OR 1.50 [95% CI, 1.30-1.74], P < .001), and faced a 2.4-day prolonged length of hospitalization (95% CI, 1.94-2.95, P < .001) compared to matched controls. Risk of 30-day (OR 1.31 [95% CI, 1.13-1.51], P < .001) and 1-year readmission (OR 1.29 [95% CI, 1.17-1.42], P < .001) was higher among patients with hypopituitarism as compared with medical controls.
CONCLUSIONS: Patients with hypopituitarism are highly vulnerable once hospitalized for acute medical conditions with increased risk of mortality and adverse clinical outcomes. This was most pronounced among those with DI.

4. **Jullien N et al. Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort. Clin Endocrinol (Oxf). 2020 Oct 24. doi: 10.1111/cen.14355.**

CONTEXT: The international GENHYPOPIT network collects phenotypical data and screens genetic causes of non-acquired hypopituitarism.
AIMS: To describe main phenotype patterns and their evolution through life.
DESIGN: Patients were screened according to their phenotype for coding sequence variations in 8 genes: HESX1, LHX3, LHX4, PROP1, POU1F1, TBX19, OTX2 and PROKR2.
RESULTS: Among 1213 patients (1143 index cases), the age of diagnosis of hypopituitarism was congenital (24%), in childhood (28%), at puberty (32%), in adulthood (7.2%) or not available (8.8%). Noteworthy, pituitary hormonal deficiencies kept on evolving during adulthood in 49 of patients. Growth Hormone deficiency (GHD) affected 85.8% of patients and was often the first diagnosed deficiency. AdrenoCorticoTropic Hormone deficiency rarely preceded GHD, but usually followed it by over 10 years. Pituitary Magnetic Resonance Imaging (MRI) abnormalities were common (79.7%), with 39.4% pituitary stalk interruption syndrome (PSIS). The most frequently associated extrapituitary malformations were ophthalmological abnormalities (16.1%). Prevalence of identified mutations was 7.3% of index cases (84/1143) and 29.5% in familial cases (n = 146). Genetic analysis in 449 patients without extrapituitary phenotype revealed 36 PROP1, 2 POU1F1 and 17 TBX19 mutations.
CONCLUSION: This large international cohort highlights atypical phenotypic presentation of constitutional hypopituitarism, such as post pubertal presentation or adult progression of hormonal deficiencies. These results justify long-term follow-up, and the need for systematic evaluation of associated abnormalities. Genetic defects were rarely identified, mainly PROP1 mutations in pure endocrine phenotypes.

ΑΠΟΙΟΣ ΔΙΑΒΗΤΗΣ

1. **Devuyst F et al. Central diabetes insipidus and pituitary stalk thickening in adults: distinction of neoplastic from non-neoplastic lesions. Eur J Endocrinol. 2020;181(3):95-105. doi: 10.1530/EJE-20-0058.**

CONTEXT: Association of central diabetes insipidus (CDI) and pituitary stalk thickening (PST) may have several etiologies (including malignancies) and differential diagnosis remains often difficult.
OBJECTIVE: The purpose of this study was to identify which clinical, biochemical or radiological features could help clinicians to make an etiological diagnosis, especially distinguishing neoplastic from non-neoplastic pituitary stalk lesions.
DESIGNS AND METHODS: We retrospectively analyzed clinical, biochemical, radiological and histological data of 38 adult patients diagnosed with CDI and PST of proven etiology.
RESULTS: Of the 38 pituitary stalk lesions included, 11 (29%) were neoplastic. A histopathological diagnosis was obtained in 22/38 (58%) patients. The three most frequently observed etiologies of PST were neuroinfundibulitis (34%), germinoma (21%) and histiocytosis (18%). Pituitary stalk thickness was larger for neoplastic lesions, particularly germinomas. Male gender and a very young age were statistically associated with a risk of germinoma. At least one anterior pituitary deficit was observed in nearly 60% of patients. Patients with neoplastic PST were more affected by multiple anterior pituitary dysfunction than patients with benign PST. A high serum prolactin level was individually the best predictor of a neoplastic origin (90% sensitivity and 60% specificity for a serum prolactin level 1.27-fold above the normal upper limit (ULN)).
CONCLUSION: We confirm a relatively high risk of malignancy in adult patients presenting with the association of CDI and PST. Young age, male gender, a very large thickening of the stalk, multiple anterior pituitary deficits and prolactin above 1.3× ULN increase the likelihood of a neoplastic origin.

2. **Bologna K et al. Effect of Arginine on the Hypothalamic-Pituitary-Adrenal Axis in Individuals With and Without Vasopressin Deficiency. J Clin Endocrinol Metab. 2020;105(7): e2327-36. doi: 10.1210/clinem/dgaa157.**

CONTEXT: Arginine stimulates pituitary hormones, like growth hormone and vasopressin, but its effect on the hypothalamic-pituitary-adrenal (HPA) axis is unknown. Arginine may also stimulate the HPA axis, possibly through a mechanism involving vasopressin.
OBJECTIVE: To investigate the effect of arginine on adrenocorticotropic hormone (ACTH) and cortisol in subjects with and without vasopressin deficiency.
DESIGN: Prospective study, University Hospital Basel.
PARTICIPANTS: 38 patients with central diabetes insipidus, 58 patients with primary polydipsia, and 50 healthy controls.
INTERVENTION: Arginine infusion with measurement of ACTH, cortisol and copeptin at baseline and 30, 45, 60, 90, and 120 minutes.
RESULTS: We found different response patterns to arginine: in patients with diabetes insipidus (and low stimulated copeptin levels) median (interquartile range [IQR]) ACTH and cortisol increased from 22.9 (16.8, 38.7) to 36.6 (26.2, 52.1) ng/L and from 385 (266, 463) to 467 (349, 533) nmol/L, respectively. In contrast, median (IQR) ACTH and cortisol levels decreased in patients with primary polydipsia (despite high stimulated copeptin levels): ACTH from 17.3 (12.3, 23) to 14.8 (10.9, 19.8) ng/L and cortisol from 343 (262, 429) to 272 (220.8, 360.3) nmol/L; likewise, in healthy controls: ACTH from 26.5 (17.6, 35.7) to 14.8 (12.1, 22.7) ng/L and cortisol from 471 (393.3, 581.8) to 301.5 (206.5, 377.8) nmol/L.
CONCLUSION: Diabetes insipidus is associated with increased responsiveness of ACTH/cortisol to arginine. In contrast, arginine does not stimulate the HPA axis in healthy controls or in primary polydipsia.

COVID-19 ΚΑΙ ΥΠΟΦΥΣΙΑΚΗ ΝΟΣΟΣ

1. **Fleseriu M et al. Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic-an international perspective. Pituitary. 2020;23(4):327-37. doi: 10.1007/s11102-020-01059-7.**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral strain that has caused the coronavirus disease 2019 (COVID-19) pandemic, has presented healthcare systems around the world with an unprecedented challenge. In locations with significant rates of viral transmission, social distancing measures and enforced 'lockdowns' are the new 'norm' as governments try to prevent healthcare services from being overwhelmed. However, with these measures have come important challenges for the delivery of existing services for other diseases and conditions. The clinical care of patients with pituitary disorders typically involves a multidisciplinary team, working in concert to deliver timely, often complex, disease investigation and management, including pituitary surgery. COVID-19 has brought about major disruption to such services, limiting access to care and opportunities for testing (both laboratory and radiological), and dramatically reducing the ability to safely undertake transsphenoidal surgery. In the absence of clinical trials to guide management of patients with pituitary disease during the COVID-19 pandemic, herein the Professional Education Committee of the Pituitary Society proposes guidance for continued safe management and care of this population.

2. **Newell-Price J et al. ENDOCRINOLOGY IN THE TIME OF COVID-19: Management of Cushing's syndrome. Eur J Endocrinol. 2020;183(1):G1-7. doi: 10.1530/EJE-20-0352.**

Clinical evaluation should guide those needing immediate investigation. Strict adherence to COVID-19 protection measures is necessary. Alternative ways of consultations (telephone, video) should be used. Early discussion with regional/national experts about investigation and management of potential and existing patients is strongly encouraged. Patients with moderate or severe clinical features need urgent investigation and management. Patients with active Cushing's syndrome, especially when severe, are immunocompromised and vigorous adherence to the principles of social isolation is recommended. In patients with mild features or in whom a diagnosis is less likely, clinical re-evaluation should be repeated at 3 and 6 months or deferred until the prevalence of SARS-CoV-2 has significantly decreased; however, those individuals should be encouraged to maintain social distancing. Diagnostic pathways may need to be very different from usual recommendations in order to reduce possible exposure to SARS-CoV-2. When extensive differential diagnostic testing and/or surgery is not feasible, it should be deferred and medical treatment should be initiated. Transsphenoidal pituitary surgery should be delayed during high SARS-CoV-2 viral prevalence. Medical management rather than surgery will be the used for most patients, since the short- to mid-term prognosis depends in most cases on hypercortisolism rather than its cause; it should be initiated promptly to minimize the risk of infection in these immunosuppressed patients. The risk/benefit ratio of these recommendations will need re-evaluation every 2-3 months from April 2020 in each country (and possibly local areas) and will depend on the local health care structure and phase of pandemic.

3. **Christ-Crain M et al. ENDOCRINOLOGY IN THE TIME OF COVID-19: Management of diabetes insipidus and hyponatraemia. Eur J Endocrinol. 2020;183(1):G9-15. doi: 10.1530/EJE-20-0338.**

COVID-19 has changed the nature of medical consultations, emphasizing virtual patient counseling, with relevance for patients with diabetes insipidus (DI) or hyponatraemia. The main complication of desmopressin treatment in DI is dilutional hyponatraemia. Since plasma sodium monitoring is not always possible in times of COVID-19, we recommend to delay the desmopressin dose once a week until aquaresis occurs allowing excess retained water to be excreted. Patients
should measure their body weight daily. Patients with DI admitted to the hospital with COVID-19 have a high risk for mortality due to volume depletion. Specialists must supervise fluid replacement and dosing of desmopressin. Patients after pituitary surgery should drink to thirst and measure their body weight daily to early recognize the development of the postoperative syndrome of inappropriate antidiuresis (SIAD). They should know hyponatraemia symptoms. The
prevalence of hyponatraemia in patients with pneumonia due to COVID-19 is not yet known, but seems to be low. In contrast, hypernatraemia may develop in COVID-19 patients in ICU, from different multifactorial reasons, for example, due to insensible water losses from pyrexia, increased respiration rate and use of diuretics. Hypernatraemic dehydration may contribute to the high risk of acute kidney injury in COVID-19. IV fluid replacement should be administered with caution in severe cases of COVID-19 because of the risk of pulmonary oedema.

Ινσουλινο-εξαρτώμενος Σακχαρώδης διαβήτης

ΠΡΟΕΔΡΟΣ: Βαρβάρα Βλασσοπούλου
ΟΜΙΛΗΤΗΣ: Βασιλική Μπράβη

1. NON-INSULIN ADJUNCTS IN T1D

Trends in Endocrinology & Metabolism

CellPress
REVIEWS

Review

Reducing Type 1 Diabetes Mortality: Role for Adjunctive Therapies?

Jennifer R. Snaith,[1,2,3,4,5] Deborah J. Holmes-Walker,[2,5] and Jerry R. Greenfield[1,3,4,*]

Individuals with type 1 diabetes (T1D) frequently fail to achieve glycemic goals and have excess cardiovascular risk and premature death. Adjunctive agents may play a role in reducing morbidity, mortality, and the adverse sequelae of insulin treatment. A surge in type 2 diabetes drug development has revealed agents with benefits beyond glucose lowering, including cardiovascular risk reduction. Could these benefits translate to T1D? Specific trials for T1D demonstrate substantial hemoglobin (Hb)A1c reductions with sodium glucose cotransporter inhibitors (SGLTis) and glucagon-like peptide (GLP)1 agonists, and modest improvements with metformin, dipeptidyl peptidase-4 inhibitor (DPP4i), and pramlintide. Studies exploring cardiovascular risk reduction are warranted. This review synthesizes the emerging literature for researchers and clinicians treating people with T1D. Challenges in T1D research are discussed.

Type 1 Diabetes in Context

Type 1 diabetes (T1D; see Glossary) is characterized by insulin deficiency due to autoimmune destruction of pancreatic beta cells and globally constitutes 5–10% of the overall diabetes burden and the incidence is rising [1]. T1D is complicated by microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery, cerebrovascular, and peripheral vascular) complications. Of all complications, cardiovascular (CV) disease is the chief contributor to the threefold higher mortality risk relative to the general population [2,3].

Highlights

Therapies developed for use in T2D have cardiovascular and renal protective properties.

Clinical trials testing these agents in T1D assess their ability to mitigate side effects of insulin (weight gain and hypoglycemia) and improve achievement of glycemic goals. There is little focus on cardiovascular endpoints in current clinical trials.

Conducting clinical trials in T1D has unique challenges.

Adjunctive agents in T1D have potential to close morbidity and mortality gaps, but this is yet to be verified by the current evidence base.

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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REVIEW

Empagliflozin in type 1 diabetes

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Abstract: There is a clear unmet need in people living with type 1 diabetes (T1D). Although the quality of life of people with T1D has improved, issues like hypoglycemia, weight gain and variability in glucose profiles remain. In this review, the clinical efficacy and safety of empagliflozin, a sodium-glucose cotransporter type 2 (SGLT2) inhibitor in T1D, is described based on a review of phase 2 and 3 studies to date. Empagliflozin and SGLT2 inhibitors, in general, are effective glucose-lowering drugs, which also work in people with T1D. Recent phase II and III studies, including the EASE trials for empagliflozin, showed a clear beneficial effect on HbA1c, body weight, glucose variability and total daily insulin use in people with T1D. No increase in hypoglycemia risk, in particular severe hypoglycemia, was observed, but genital infections were more prevalent. The use of SGLT2 inhibitors comes with a decrease in insulin doses, making individuals more prone to diabetic ketoacidosis (DKA). The uniqueness of the EASE program is that here, a very low dose of empagliflozin was used, with less, but still present, effects on metabolic outcomes, but interestingly a lower risk of DKA. Importantly, even in the higher doses of empagliflozin, it is clear that the overall risk for DKA remains low, most likely by educating patients and caretakers intensively on this subject. In conclusion, evidence is building on the potential of using empagliflozin, like other SGLT2 inhibitors, in T1D. However, to date, the use of empagliflozin is not approved in people with T1D. Clinicians will have to weigh the potential short- and long-term benefits of these adjunct therapies versus the potential acute side effects, in particular, the small but real risk of DKA in the individual T1D patient.

Keywords: type 1 diabetes, SGLT2 inhibitor, empagliflozin, EASE trials

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Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials

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OBJECTIVE

To evaluate the safety and efficacy of empagliflozin 10- and 25-mg doses plus a unique lower dose (2.5 mg) as adjunct to intensified insulin in patients with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

The EASE (Empagliflozin as Adjunctive to inSulin thErapy) program (N = 1,707) included two double-blind, placebo-controlled phase 3 trials: EASE-2 with empagliflozin 10 mg (n = 243), 25 mg (n = 244), and placebo (n = 243), 52-week treatment; and EASE-3 with empagliflozin 2.5 mg (n = 241), 10 mg (n = 248), 25 mg (n = 245), and placebo (n = 241), 26-week treatment. Together they evaluated empagliflozin 10 mg and 25 mg, doses currently approved in treatment of type 2 diabetes, and additionally 2.5 mg on 26-week change in glycated hemoglobin (primary end point) and weight, glucose time-in-range (>70 to ≤180 mg/dL), insulin dose, blood pressure, and hypoglycemia.

RESULTS

The observed largest mean placebo-subtracted glycated hemoglobin reductions were −0.28% (95% CI −0.42, −0.15) for 2.5 mg, −0.54% (−0.65, −0.42) for 10 mg, and −0.53% (−0.65, −0.42) for 25 mg (all P < 0.0001). Empagliflozin 2.5/10/25 mg doses, respectively, reduced mean weight by −1.8/−3.0/−3.4 kg (all P < 0.0001); increased glucose time-in-range by +1.0/+2.9/+3.1 h/day (P < 0.0001 for 10 and 25 mg); lowered total daily insulin dose by −6.4/−13.3/−12.7% (all P < 0.0001); and decreased systolic blood pressure by −2.1/−3.9/−3.7 mmHg (all P < 0.05). Genital infections occurred more frequently on empagliflozin. Adjudicated diabetic ketoacidosis occurred more with empagliflozin 10 mg (4.3%) and 25 mg (3.3%) but was comparable between empagliflozin 2.5 mg (0.8%) and placebo (1.2%). Severe hypoglycemia was rare and frequency was similar between empagliflozin and placebo.

CONCLUSIONS

Empagliflozin improved glycemic control and weight in T1D without increasing hypoglycemia. Ketoacidosis rate was comparable between empagliflozin 2.5 mg and placebo but increased with 10 mg and 25 mg. Ketone monitoring for early ketoacidosis detection and intervention and lower empagliflozin doses may help to reduce this risk.

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See accompanying articles, pp. 2444 and 2552.

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ADIS DRUG EVALUATION

Sotagliflozin: A Review in Type 1 Diabetes

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Published online: 25 November 2019

Abstract

Sotagliflozin (Zynquista™) is the first dual inhibitor of sodium-glucose co-transporter-1 and -2 (SGLT1 and 2). In the phase 3, inTANDEM 1–3 trials, adjunctive use of oral sotagliflozin (200 mg or 400 mg once daily) improved glycaemic control and reduced bodyweight and insulin requirements relative to placebo over 24 weeks of treatment in adults whose type 1 diabetes (T1D) was inadequately controlled by insulin therapy. Similar benefits were seen with the drug in patients who were overweight/obese [i.e. body mass index (BMI) $\geq$ 27 kg/m^2] in inTANDEM 1 and 2 (pooled). The benefits of sotagliflozin were largely maintained over 52 weeks of treatment. Overall, use of sotagliflozin in this setting is generally well tolerated and reduces, or at least does not increase, the likelihood of hypoglycaemia; however, as with other SGLT inhibitors, sotagliflozin carries a risk of diabetic ketoacidosis (DKA). On the basis of its risk/benefit profile, sotagliflozin is indicated in the EU as an adjunct to insulin in adults with T1D with a BMI $\geq$ 27 kg/m^2 who have failed to achieve adequate glycaemic control despite optimal insulin therapy, thus expanding the currently limited adjunctive oral treatment options available for use in this population.

Effect of dapagliflozin as an adjunct to insulin over 52 weeks in individuals with type 1 diabetes: post-hoc renal analysis of the DEPICT randomised controlled trials

Per-Henrik Groop, Paresh Dandona, Moshe Phillip, Pieter Gillard, Steven Edelman, Johan Jendle, John Xu, Markus F Scheerer, Fredrik Thoren, Nayyar Iqbal, Enrico Repetto, Chantal Mathieu

Summary

Background The DEPICT-1 and DEPICT-2 studies showed that dapagliflozin as an adjunct to insulin in individuals with inadequately controlled type 1 diabetes improved glycaemic control and bodyweight, without increase in risk of hypoglycaemia. We aimed to determine the effect of dapagliflozin on urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) using pooled data from the DEPICT studies.

Methods In this post-hoc analysis, we used data pooled from both DEPICT studies (DEPICT-1 ran from Nov 11, 2014, to Aug 25, 2017; DEPICT-2 ran from July 8, 2015, to April 18, 2018), in which participants were aged 18–75 years, with inadequately controlled type 1 diabetes and with a baseline UACR of at least 30 mg/g. In the DEPICT studies, participants were randomly assigned (1:1:1) to receive dapagliflozin (5 mg or 10 mg) or placebo all plus insulin, for 24 weeks, with a 28-week long-term extension (ie, 52 weeks in total). In this post-hoc analysis, we assessed the percentage change from baseline in UACR and in eGFR, up to 52 weeks. UACR, eGFR, and safety were assessed in all eligible participants who had received at least one dose of study drug. HbA_{1c}, bodyweight, and systolic blood pressure were assessed in all participants who received at least one dose of study drug during the first 24-week period, and who had a baseline and any post-baseline assessment for that parameter. The DEPICT trials were registered with ClinicalTrials.gov, NCT02268214 (DEPICT-1), NCT02460978 (DEPICT-2), and are now complete.

Results 251 participants with albuminuria at baseline were included in this post-hoc analysis; of whom 80 (32%) had been randomly assigned to dapagliflozin 5 mg, 84 (33%) to dapagliflozin 10 mg, and 87 (35%) to placebo. Compared with placebo, treatment with both dapagliflozin doses improved UACR over 52 weeks. At week 52, mean difference in change from baseline versus placebo in UACR was –13·3% (95% CI –37·2 to 19·8) for dapagliflozin 5 mg and –31·1% (–49·9 to –5·2) for dapagliflozin 10 mg. No notable change from baseline was seen in eGFR, with a mean difference in change from baseline versus placebo of 3·27 mL/min per 1·73 m² (95% CI –0·92 to 7·45) for dapagliflozin 5 mg and 2·12 mL/min per 1·73 m² (–2·03 to 6·27) for dapagliflozin 10 mg. Similar proportions of participants in each treatment group had adverse events and serious adverse events, including hypoglycaemia and diabetic ketoacidosis; no new safety signals were identified in this population.

Interpretation Treatment with dapagliflozin resulted in UACR reduction, which might provide renoprotective benefits in individuals with type 1 diabetes and albuminuria. Dedicated prospective studies are needed to confirm these findings as prespecified endpoints.

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See Comment page 803

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ADIS DRUG EVALUATION

Dapagliflozin: A Review in Type 1 Diabetes

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Abstract

Oral dapagliflozin (Edistride®, Forxiga®) is approved in the EU at a dosage of 5 mg/day as an adjunct to insulin in adults with type 1 diabetes (T1D) and a body mass index (BMI) of ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. As a highly selective SGLT2 inhibitor, dapagliflozin decreases plasma glucose levels independently of insulin action and enables glycaemic control improvement without increasing the risks associated with intensive insulin therapy. In the phase III DEPICT-1 and -2 trials, dapagliflozin 5 mg/day as an adjunct to insulin improved glycaemic control and reduced total daily insulin dose and bodyweight relative to placebo in adults with inadequately controlled T1D, including in patients with a BMI of ≥ 27 kg/m^2, over 24 weeks of treatment. In extensions of these trials, these improvements were maintained up to 52 weeks. Dapagliflozin was generally well tolerated with a manageable safety profile and a hypoglycaemia profile generally similar to placebo. The incidence of diabetic ketoacidosis with dapagliflozin in patients with a BMI ≥ 27 kg/m^2 was less than half that of the overall population who received dapagliflozin. Dapagliflozin is the first SGLT2 inhibitor to be approved for use in T1D and, while further clinical experience in T1D is required to more definitively establish its efficacy and safety profile, it provides a promising adjunctive treatment option for adults with T1D and a BMI of ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Diabetes Care Volume 42, June 2019

International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium–Glucose Cotransporter (SGLT) Inhibitors

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Sodium–glucose cotransporter (SGLT) inhibitors are new oral antidiabetes medications shown to effectively reduce glycated hemoglobin (A1C) and glycemic variability, blood pressure, and body weight without intrinsic properties to cause hypoglycemia in people with type 1 diabetes. However, recent studies, particularly in individuals with type 1 diabetes, have demonstrated increases in the absolute risk of diabetic ketoacidosis (DKA). Some cases presented with near-normal blood glucose levels or mild hyperglycemia, complicating the recognition/diagnosis of DKA and potentially delaying treatment. Several SGLT inhibitors are currently under review by the U.S. Food and Drug Administration and European regulatory agencies as adjuncts to insulin therapy in people with type 1 diabetes. Strategies must be developed and disseminated to the medical community to mitigate the associated DKA risk. This Consensus Report reviews current data regarding SGLT inhibitor use and provides recommendations to enhance the safety of SGLT inhibitors in people with type 1 diabetes.

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Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial

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Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial

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Summary

Background The combination of insulin and glucagon-like peptide-1 (GLP-1) receptor agonist therapy improves glycaemic control, induces weight loss, and reduces insulin dose needed in type 2 diabetes. We assessed the efficacy and safety of the GLP-1 receptor agonist liraglutide as an add-on therapy to insulin for overweight adult patients with type 1 diabetes.

Methods We did a randomised, double-blind, placebo-controlled trial at Steno Diabetes Center (Gentofte, Denmark). Patients aged 18 years or older with type 1 diabetes, insufficient glycaemic control (HbA_{1c} >8% [64 mmol/mol]), and overweight (BMI >25 kg/m²) were randomly assigned (1:1) to receive insulin treatment plus either liraglutide or placebo (saline solution) by subcutaneous injection once per day. Randomisation was done in blocks of four. Treatment assignment was masked to investigators and patients. Treatment lasted 24 weeks and liraglutide was started at a dose of 0·6 mg per day, escalated to 1·2 mg per day after 1 week, and then again to 1·8 mg per day after another week. Intervals between dose increments could be extended at the discretion of the investigator. The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were changes in hypoglycaemic events, glycaemic variability, glycaemic excursions, insulin dose, bodyweight, postprandial plasma concentrations of glucagon and GLP-1, gastric emptying, blood pressure, heart rate, patient-reported outcome measures, time spent in hypoglycaemia, near-normoglycaemia, and hyperglycaemia, plasma fasting glucose, mean glucose, and cholesterol. Efficacy analyses were calculated by use of a mixed model, whereby a patient's data are used as long as the patient is in the study. The safety analyses were done in the intention-to-treat population, which consisted of all patients who received at least one dose of their randomly assigned study drug. This study is registered with ClinicalTrials.gov, number NCT01612468.

Findings Between July 10, 2012, and May 30, 2014, we enrolled 100 patients with type 1 diabetes, with 50 patients allocated liraglutide and 50 to placebo. Four patients from the liraglutide group and six patients from the placebo group discontinued treatment before 24 weeks. At the end of treatment, change in HbA_{1c} from baseline did not differ between groups (–0·5%, 95% CI –0·8 to –0·4 [–6·0 mmol/mol, 95% CI –8·7 to –4·4] with liraglutide *vs* –0·3%, –0·6 to –0·2 [–4·0 mmol/mol, –6·6 to –2·3] with placebo; between-group difference –0·2% [–0·5 to 0·1; 2·2 mmol/mol, –5·5 to 1·1], p=0·1833). The number of hypoglycaemic events was reduced with liraglutide, with an incident rate ratio of 0·82 (95% CI 0·74 to 0·90). However, we detected no changes in glycaemic variability (continuous overall net glycaemic action per 60 min from 10·3 [95% CI 9·8 to 10·8] to 9·9 [9·2 to 10·6] in the liraglutide treated patients *vs* 10·2 [9·7 to 10·7] to 9·7 [9·1 to 10·3] in the placebo treated patients). Both bolus insulin (difference –5·8 IU, 95% CI –10·7 to –0·8, p=0·0227) and bodyweight (difference –6·8 kg, 95% CI –12·2 to –1·4, p=0·0145) decreased with liraglutide treatment compared with placebo. Heart rate increased with liraglutide, with a difference between groups of 7·5 bpm (95% CI 2·8–12·2, p=0·0019). Postprandial plasma glucagon and GLP-1 concentrations did not differ between groups (difference between groups at end of treatment: –408 mmol/L per 240 min [95% CI –941 to 125, p=0·1309] for glucagon and –266 mmol/L per 240 min [–1034 to 501, p=0·4899] for GLP-1). Gastric emptying was delayed after 3 weeks of treatment with liraglutide (19·9 min, 95% CI 0·8 to 39·0, p=0·0412), but we detected no difference after 24 weeks of treatment (–1·5 min, –20·5 to 17·6, p=0·8793). Patient-reported outcome measures differed between groups only with respect to perceived frequency of hypoglycaemia, which was higher with placebo, with a difference between groups of –0·6 (95% CI –1·1 to –0·07, p=0·0257). Liraglutide was associated with more frequent nausea (29 [58%] patients with liraglutide *vs* five [10%] with placebo), dyspepsia (11 [22%] patients with liraglutide *vs* one [2%] with placebo), diarrhoea (ten [20%] patients with liraglutide *vs* one [2%] with placebo), decreased appetite (seven patients [14%] with liraglutide *vs* none with placebo), and vomiting (seven [14%] patients with liraglutide *vs* one [2%] with placebo).

Interpretation In patients with type 1 diabetes, overweight, and insufficient glycaemic control, the reduction in HbA_{1c} did not differ between insulin plus placebo and insulin plus liraglutide treatment. Liraglutide was associated with reductions in hypoglycaemic events, bolus and total insulin dose, and bodyweight, and increased heart rate.

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Diabetes Care Volume 39, October 2016

Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial

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OBJECTIVE

To investigate whether liraglutide added to treat-to-target insulin improves glycemic control and reduces insulin requirements and body weight in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

A 52-week, double-blind, treat-to-target trial involving 1,398 adults randomized 3:1 to receive once-daily subcutaneous injections of liraglutide (1.8, 1.2, or 0.6 mg) or placebo added to insulin.

RESULTS

HbA_{1c} level was reduced 0.34–0.54% (3.7–5.9 mmol/mol) from a mean baseline of 8.2% (66 mmol/mol), and significantly more for liraglutide 1.8 and 1.2 mg compared with placebo (estimated treatment differences [ETDs]: 1.8 mg liraglutide −0.20% [95% CI −0.32; −0.07]; 1.2 mg liraglutide −0.15% [95% CI −0.27; −0.03]; 0.6 mg liraglutide −0.09% [95% CI −0.21; 0.03]). Insulin doses were reduced by the addition of liraglutide 1.8 and 1.2 mg versus placebo (estimated treatment ratios: 1.8 mg liraglutide 0.92 [95% CI 0.88; 0.96]; 1.2 mg liraglutide 0.95 [95% CI 0.91; 0.99]; 0.6 mg liraglutide 1.00 [95% CI 0.96; 1.04]). Mean body weight was significantly reduced in all liraglutide groups compared with placebo ETDs (1.8 mg liraglutide −4.9 kg [95% CI −5.7; −4.2]; 1.2 mg liraglutide −3.6 kg [95% CI −4.3; −2.8]; 0.6 mg liraglutide −2.2 kg [95% CI −2.9; −1.5]). The rate of symptomatic hypoglycemia increased in all liraglutide groups (estimated rate ratios: 1.8 mg liraglutide 1.31 [95% CI 1.07; 1.59]; 1.2 mg liraglutide 1.27 [95% CI 1.03; 1.55]; 0.6 mg liraglutide 1.17 [95% CI 0.97; 1.43]), and hyperglycemia with ketosis increased significantly for liraglutide 1.8 mg only (event rate ratio 2.22 [95% CI 1.13; 4.34]).

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**A complete list of the ADJUNCT ONE Investigators can be found in the Supplementary Data online.*

Efficacy and safety of meal-time administration of short-acting exenatide for glycaemic control in type 1 diabetes (MAG1C): a randomised, double-blind, placebo-controlled trial

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Summary

Background In type 2 diabetes, long-acting GLP-1 receptor agonists lower fasting plasma glucose and improve glycaemic control via their insulinotropic and glucagonostatic effects. In type 1 diabetes, their efficacy as an add-on treatment to insulin therapy is modest. Short-acting GLP-1 receptor agonists also lower postprandial glucose excursions in type 2 diabetes by decelerating gastric emptying rate. We aimed to test the efficacy of a short-acting GLP-1 receptor agonist in type 1 diabetes.

Methods In the single-centre, parallel-group, randomised, double-blind, placebo-controlled MAG1C trial, patients with type 1 diabetes on multiple daily injection therapy aged 18 years and older with HbA_{1c} 59–88 mmol/mol (7·5–10·0%) and a BMI of more than 22·0 kg/m² were randomly assigned (1:1) through a computer-generated randomisation list to preprandial subcutaneous injection of 10 µg exenatide (Byetta) or placebo three times daily for 26 weeks as an add-on treatment to usual insulin therapy. Clinically assessed insulin titration was done by study staff. Participants and investigators were masked to treatment allocation. The primary endpoint was between-group difference in HbA_{1c} after 26 weeks. Data were analysed with a baseline-adjusted linear mixed model in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT03017352, and is completed.

Findings Between Jan 4, 2017, and Jan 16, 2019, 108 participants were randomly assigned, 54 to exenatide and 54 to placebo; 23 participants discontinued treatment (17 in the exenatide group and six in the placebo group). From a baseline-adjusted mean of 66·4 mmol/mol (95% CI 64·9–67·8 [8·2%, 8·1–8·4]), HbA_{1c} changed by –3·2 mmol/mol (–5·0 to –1·4 [–0·3%, –0·5 to –0·1]) with exenatide and –2·1 mmol/mol (–3·7 to –0·6 [–0·2%, –0·3 to –0·1]) with placebo after 26 weeks (estimated treatment difference of –1·1 mmol/mol (–3·4 to 1·2 [–0·1%, –0·3 to 0·1]; p=0·36). Exenatide increased the number of self-reported gastrointestinal adverse events (primarily nausea [48 events among 37 patients with exenatide, nine with placebo among 9 patients]). Two serious adverse events occurred in the exenatide group, and six occurred in the placebo group (none were considered to be related to the study drug).

Interpretation Short-acting exenatide does not seem to have a future as a standard add-on treatment to insulin therapy in type 1 diabetes.

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2. T1D AND TECHNOLOGY

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Diabetology & Metabolic Syndrome

REVIEW Open Access

Time in range: a new parameter to evaluate blood glucose control in patients with diabetes

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Abstract

The International Consensus in Time in Range (TIR) was recently released and defined the concept of the time spent in the target range between 70 and 180 mg/dL while reducing time in hypoglycemia, for patients using Continuous Glucose Monitoring (CGM). TIR was validated as an outcome measures for clinical Trials complementing other components of glycemic control like Blood glucose and HbA1c. The challenge is to implement this practice more widely in countries with a limited health public and private budget as it occurs in Brazil. Could CGM be used intermittently? Could self-monitoring blood glucose obtained at different times of the day, with the amount of data high enough be used? More studies should be done, especially cost-effective studies to help understand the possibility of having sensors and include TIR evaluation in clinical practice nationwide.

Keywords: Time in range, Glycated hemoglobin, Continuous glucose monitoring, Hypoglycemia

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Time in Range from Continuous Glucose Monitoring: A Novel Metric for Glycemic Control

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Glycosylated hemoglobin (HbA1c) has been the sole surrogate marker for assessing diabetic complications. However, consistently reported limitations of HbA1c are that it lacks detailed information on short-term glycemic control and can be easily interfered with by various clinical conditions such as anemia, pregnancy, or liver disease. Thus, HbA1c alone may not represent the real glycemic status of a patient. The advancement of continuous glucose monitoring (CGM) has enabled both patients and healthcare providers to monitor glucose trends for a whole single day, which is not possible with HbA1c. This has allowed for the development of core metrics such as time spent in time in range (TIR), hyperglycemia, or hypoglycemia, and glycemic variability. Among the 10 core metrics, TIR is reported to represent overall glycemic control better than HbA1c alone. Moreover, various evidence supports TIR as a predictive marker of diabetes complications as well as HbA1c, as the inverse relationship between HbA1c and TIR reveals. However, there are more complex relationships between HbA1c, TIR, and other CGM metrics. This article provides information about 10 core metrics with particular focus on TIR and the relationships between the CGM metrics for comprehensive understanding of glycemic status using CGM.

Keywords: Blood glucose; Blood glucose self-monitoring; Diabetes complications; Glycated hemoglobin A

Evolution of Diabetes Technology

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KEYWORDS

• Artificial pancreas • Type 1 diabetes • Continuous glucose monitoring
• Insulin pump • Technology • Closed loop • Self-monitoring of blood glucose
• Multiple daily injections

KEY POINTS

- Diabetes technology is rapidly changing traditional care; safety, efficacy, and cost-effectiveness are driving reimbursement and adoption.
- Insulin pump use is associated with improved metabolic control, less glucose variability, less hypoglycemia, and improved quality of life.
- Continuous glucose monitoring is strongly associated with improved metabolic control, more time in range, less time in hypoglycemia, reduced anxiety, and improved quality of life; insulin-dosing advisors improve decision making.
- Glucose-responsive automated insulin delivery, currently at the hybrid closed-loop stage, achieves the highest time in range, lowest hypoglycemia, and favorable quality of life.
- Achievable targets for time in range and standard visualization of the continuous glucose monitoring data will help professionals and individuals with diabetes improve long-term outcomes with less disease burden; integrated decision support systems will further improve routine diabetes care.

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Automated Insulin Delivery in Children with Type 1 Diabetes

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KEYWORDS

• Diabetes • Insulin • Children • Insulin pump

KEY POINTS

- The advent of insulin pump therapy marked an important milestone in diabetes treatment and has become the tipping point for automated insulin delivery (AID).
- Continuous glucose monitor (CGM)-integrated insulin pump treatment made the real-time optimization of diabetes mellitus control possible and introduced us to the smart insulin pump systems with a dynamic treatment response.
- The aim of this review is to summarize evidence from AID studies conducted in children with type 1 diabetes and discuss the outlook for future generation AID systems from a pediatric treatment perspective.

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COMMENTARY

A Clinical Guide to Advanced Diabetes Devices and Closed-Loop Systems Using the CARES Paradigm

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Keywords: Type 1 diabetes, CSII pump, CGM, Artificial pancreas, Hybrid closed-loop, PLGS.

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Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

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Improvements in sensor accuracy, greater convenience and ease of use, and expanding reimbursement have led to growing adoption of continuous glucose monitoring (CGM). However, successful utilization of CGM technology in routine clinical practice remains relatively low. This may be due in part to the lack of clear and agreed-upon glycemic targets that both diabetes teams and people with diabetes can work toward. Although unified recommendations for use of key CGM metrics have been established in three separate peer-reviewed articles, formal adoption by diabetes professional organizations and guidance in the practical application of these metrics in clinical practice have been lacking. In February 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel of physicians, researchers, and individuals with diabetes who are expert in CGM technologies to address this issue. This article summarizes the ATTD consensus recommendations for relevant aspects of CGM data utilization and reporting among the various diabetes populations.

This international consensus report has been endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society.

3. T1DM and CARDIOVASCULAR DISEASE/MORTALITY

Risk Factors for Cardiovascular Disease (CVD) in Adults with Type 1 Diabetes: Findings from Prospective Real-life T1D Exchange Registry

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Context: Cardiovascular disease (CVD) is a major cause of mortality in adults with type 1 diabetes.

Objective: We prospectively evaluated CVD risk factors in a large, contemporary cohort of adults with type 1 diabetes living in the United States.

Design: Observational study of CVD and CVD risk factors over a median of 5.3 years.

Setting: The T1D Exchange clinic network.

Patients: Adults (age ≥ 18 years) with type 1 diabetes and without known CVD diagnosed before or at enrollment.

Main Outcome Measure: Associations between CVD risk factors and incident CVD were assessed by multivariable logistic regression.

Results: The study included 8,727 participants (53% female, 88% non-Hispanic white, median age 33 years [interquartile ratio {IQR} = 21, 48], type 1 diabetes duration 16 years [IQR = 9, 26]). At enrollment, median HbA1c was 7.6% (66 mmol/mol) (IQR = 6.9 [52], 8.6 [70]), 33% used a statin, and 37% used blood pressure medication. Over a mean follow-up of 4.6 years, 325 (3.7%) participants developed incident CVD. Ischemic heart disease was the most common CVD event. Increasing age, body mass index, HbA1c, presence of hypertension and dyslipidemia, increasing

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Abbreviations: CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDC, Pittsburgh Epidemiology of Diabetes Complications; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; T1D, type 1 diabetes; TG, triglyceride

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REVIEW

Cardiovascular Risk in Type 1 Diabetes Mellitus

Jonathan Schofield · Jan Ho · Handrean Soran

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is associated with premature cardiovascular disease (CVD), but the underlying mechanisms remain poorly understood. The American Diabetes Association and the European Association for the Study of Diabetes recently updated their position statement on the management of type 2 diabetes mellitus (T2DM) to include additional focus on cardiovascular risk; improved management of risk factors in T1DM is also needed. There are important differences in the pathophysiology of CVD in T1DM and T2DM. Hyperglycaemia appears to have a more profound effect on cardiovascular risk in T1DM than T2DM, and other risk factors appear to cause a synergistic rather than additive effect, so achievement of treatment targets for all recognized risk factors is crucial to reducing cardiovascular risk. Here we discuss the evidence for addressing established cardiovascular risk factors, candidate biomarkers and surrogate measurements, and possible interventions.

Keywords: Cardiovascular disease; Cardiovascular risk; Type 1 diabetes mellitus

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Lipid management for cardiovascular risk reduction in type 1 diabetes

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Abstract

Purpose of review—To review the recent evidence for lipid management in type 1 diabetes (T1D) for cardiovascular risk reduction.

Recent findings—Individuals with T1D are at increased risk for cardiovascular morbidity and mortality, with atherosclerosis beginning as early as adolescence. Elevated low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein (a) are associated with increased cardiovascular risk in T1D. Although high-density lipoprotein cholesterol (HDL-C) in T1D is often normal or higher than in nondiabetic controls, HDL in T1D has structural alterations, which make it proatherogenic rather than cardioprotective. Similarly, although LDL-C is not particularly elevated in T1D, LDL still contributes to cardiovascular risk. Studies in individuals with diabetes have primarily included T2D participants, with a much smaller number of T1D participants; such studies have shown that lipid-lowering therapies, such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce LDL-C levels and cardiovascular events in both those with and without diabetes. Individuals with T1D have increased cholesterol absorption, suggesting that ezetimibe may be particularly effective in T1D. Results of the REDUCE-IT trial show cardiovascular risk reduction from high-dose omega-3 fatty acid (Icosapent Ethyl) therapy in patients with diabetes (primarily type 2 diabetes), independent of triglyceride lowering, but similar data in T1D are currently lacking.

Summary—Individuals with T1D are at high risk of cardiovascular disease, necessitating close lipid monitoring and management from adolescence through adulthood.

Keywords

cardiovascular disease; lipid; low-density lipoprotein cholesterol; type 1 diabetes

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RESEARCH ARTICLE

WILEY

Young adult patients with type 1 diabetes have a higher risk of mortality than those of similar age with type 2 diabetes: A nationwide analysis in Hungary

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Abstract

BACKGROUND: There are few papers comparing complications of type 1 diabetes with those of a similarly young age with type 2 diabetes. The aim of our nationwide study was to compare the risks of mortality and morbidities between the two types of diabetes (age ≤ 40).

METHODS: We identified all young adult patients with type 1 diabetes who were recorded in the database of the Hungarian National Health Insurance Fund between 2001 and 2014 (n = 11 863) and compared them with a population of similar age with young adult type 2 diabetes (n = 47 931). The incidence of all-cause mortality, myocardial infarction, stroke, any type of cancer, diabetic ketoacidosis, and hypoglycemia was followed from the onset of diabetes to the date of death or end of study period.

RESULTS: The risks of all-cause mortality were significantly higher in patients with type 1 compared with patients with type 2 diabetes (hazard ratio, 95%CI; 2.17, 1.95-2.41; $P < .0001$). The risks of myocardial infarction (0.90, 0.71-1.13; $P = 0.36$) and stroke (1.06, 0.87-1.29; $P = .582$) were not significantly different in type 1 compared with type 2. In contrast, the risk of cancer (1.35, 1.15-1.59; $P = .0003$), dialysis (2.20, 1.76-2.75; $P < .0001$), hypoglycemia (7.70, 6.45-9.18; $P < .0001$), and ketoacidosis (22.12, 19.60-25.00; $P < .0001$) was higher among patients with type 1 compared with those with type 2 diabetes.

CONCLUSIONS: A comparatively higher incidence of diabetic ketoacidosis and hypoglycemia and higher risk of cancer and dialysis in patients with type 1 diabetes than in those with type 2 may play a role in the higher risk of mortality.

KEYWORDS

all-cause mortality, cardiovascular morbidity, diabetic ketoacidosis, hypoglycemia, type 1 diabetes, type 2 diabetes

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International Diabetes Federation

Standard mortality rates and years of life lost for serologically defined adult-onset type 1 and type 2 diabetes – A fifteen year follow-up

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ABSTRACT

Aims: The Diabetes Incidence in Kronoberg (DIK) study of adult-onset diabetes used serological classification. Standard Mortality Rates (SMR) and Years of Life Lost (YLL) 15 years after adult-onset (18–100 years) of diabetes were compared to the population of Kronoberg.
Methods: Of 1609/1660 (97%) patients, 112 (7%) had type 1 (T1D) (GADA$^+$ and/or ICA$^+$, and/or C-peptide < 0.25 nmol/l), and 1497 (93%) had type 2 diabetes (T2D) (antibody$^-$ and C-peptide ≥ 0.25 nmol/l). The National Swedish Mortality Register provided time of death.
Results: For T1D SMR did not differ from the Kronoberg population in any age group. In T2D SMR was 1.20 (1.12–1.29). After 15 years 26% (29/112) T1D and 52% (785/1497) T2D patients had died, $p < 0.0001$. In T2D SMR was 5.6 (30–39 years), 2 (40–59 years), 1.4 (60–69 years), and thereafter no difference. There were no significant sex differences in mortality, and no YLL to adult-onset T1D, but five YLL to T2D for onset at ages 20–60 years.
Conclusions: For adult-onset T1D SMR did not differ from the general population, in contrast to previous findings in childhood-onset (< 30 years of age) T1D. The difference in mortality between persons with diabetes and the general population was due to higher mortality in T2D.

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ISCHEMIC HEART DISEASE (D MUKHERJEE, SECTION EDITOR)

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

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Published online: 22 April 2019

Abstract

Purpose of Review The aims of this review are to summarize recent data on mortality and cardiovascular disease (CVD) in type 1 and type 2 diabetes and to determine the interventions that could have contributed to a reduction in mortality.

Recent Findings Recent studies found a downward trend in mortality and CVD among both diabetics and non-diabetics worldwide over the last few decades. The decline among diabetics is steeper than that among non-diabetics. Despite a parallel trend of decline, an approximately twofold difference in mortality and CVD between the two populations remains.

Summary A greater emphasis on glycemic control, management of cardiovascular risk factors, quality improvement programs, and advances in treatment of conditions associated diabetes are the factors that potentially contributed to the improvement. Although the trend is encouraging, a rising prevalence of diabetes will continue the absolute disease burden to the society. Future interventions should focus on prevention of diabetes.

Keywords Diabetes mellitus, type 1 - Diabetes mellitus, type 2 - Mortality - Cardiovascular mortality - Cardiovascular disease - Cardiovascular risk - Trend

4. T1D AND COMPLICATIONS

Chronic complications versus glycaemic variability, time in range and HbA_{1c} in people with type 1 diabetes: sub study of the RESCUE-trial

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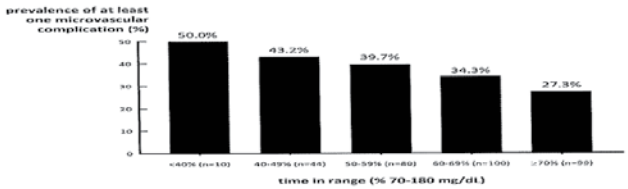
Abstract:
Background and aims: So far, HbA1c is the only metric of glucose control showing a strong association with chronic complications. However, it does not reflect short-term glycemic variability nor provides guidance in decreasing risk of hypoglycemia. More widespread use of continuous glucose monitoring (CGM) has changed the way people with type 1 diabetes (T1D) manage their glycemia by providing information about glycemic variability and time spent in different glucose ranges.
Materials and methods: Parameters that could have a link with diabetes complications were analyzed of 515 adults with T1D who entered the Belgian reimbursement system for real-time CGM (rtCGM): HbA1c, standard deviation (SD), coefficient of variation (%CV), time in range (TIR, 70–180 mg/dL), age, diabetes duration, BMI, and gender. Association between glucometrics from the first 2 weeks of rtCGM use and presence of the following diabetes complications at start were investigated with multiple logistic regression: composite microvascular complications (defined as presence of at least 1 of the following: peripheral or autonomic neuropathy, retinopathy, nephropathy), macrovascular complications, and hospitalization for hypoglycemia and ketoacidosis.
Results: Diabetes duration (OR=1.12, P<0.001) and TIR (OR=0.97, P=0.005) were independently correlated with composite microvascular complications. For nephropathy, diabetes duration (OR=1.08, P<0.001) and HbA1c (OR=1.65, P=0.012) were independently associated. For retinopathy it were diabetes duration (OR=1.14, P<0.001) and TIR (OR=0.96, P<0.001). For peripheral and autonomic neuropathy it were diabetes duration (OR=1.09, P<0.001; OR=1.08, P<0.001) and SD (OR=1.03, P=0.026; OR=1.035, P=0.015). Age (OR=1.08, P=0.003) and HbA1c (OR=1.80, P=0.044) were independently correlated with macrovascular complications. Only TIR (OR=0.97, P=0.021) was independently associated with hospitalization for hypoglycemia or ketoacidosis.
Conclusion: Shorter TIR was associated with the presence of composite microvascular complications, and with retinopathy in particular. A higher SD was linked to peripheral and autonomic neuropathy. For hospitalization due to hypoglycemia or ketoacidosis, TIR was the most important factor.



Garofolo et al. Cardiovasc Diabetol (2019) 18:159
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Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Microvascular complications burden (nephropathy, retinopathy and peripheral polyneuropathy) affects risk of major vascular events and all-cause mortality in type 1 diabetes: a 10-year follow-up study

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Abstract

Background: Microvascular complications (MC) have been claimed to increase the risk for cardiovascular disease in diabetic subjects. However, the effect of MC burden on the risk of major vascular outcomes and all-cause mortality in type 1 diabetes is still poorly explored. We evaluated the relationship between microvascular complications burden and incidence of major cardiovascular events and all-cause mortality in subjects with type 1 diabetes.

Methods: We recruited 774 participants with type 1 diabetes in a single-center observational study over a follow-up of 10.8 ± 2.5 years. Hazard ratios (HR) for cardiovascular outcomes and all-cause death associated with microvascular complications were determined by unadjusted and adjusted Cox regression analysis.

Results: Out of 774 individuals, 54.9% had no-MC, 32.3% 1 MC, 9.7% 2 MC and 3.1% 3 MC. A total of 54 deaths (7.0%) occurred. Death rate increased from no-MC 2.1% (Ref) to 1 MC 7.2% (HR 3.54 [95% CI 1.59–7.87]), 2 MC 14.7% (HR 6.41 [95% CI 2.65–15.49]) and 3 MC 66.7% (HR 41.73 [95% CI 18.42–94.57], p < 0.0001). After adjustments, HRs were: 1 MC 2.05 (95% CI 0.88–4.76), 2 MC 1.98 (95% CI 0.75–5.21), 3 MC 7.02 (95% CI 2.44–20.20, p = 0.002). Forty-nine subjects (6.7%) had at least one cardiovascular event, and cumulative incidence went from no-MC 2.2% (Ref) to 1 MC 5.0%; (HR 2.27 [95% CI 0.96–5.38]), 2 MC 26.8% (HR 12.88 [95% CI 5.82–28.50]) and 3 MC 40.9% (HR 29.34 [95% CI 11.59–74.25], p < 0.0001). Upon adjustments, HRs were: 1 MC 1.59 (95% CI 0.65–3.88), 2 MC 4.33 (95% CI 1.75–10.74), 3 MC 9.31 (95% CI 3.18–27.25, p < 0.0001). Thirty-five individuals (4.8%) had at least one coronary event, which cumulative incidence increased with MC burden (p < 0.0001).

Conclusions: In type 1 diabetes, microvascular complications burden increases in an independent dose-dependent manner the risk of major cardiovascular outcomes and all-cause mortality. The presence and number of microvascular complications should be considered in stratifying overall cardiovascular risk in type 1 diabetes.

Keywords: Type 1 diabetes mellitus, Microvascular complications, Microvascular burden, Diabetic kidney disease, Diabetic retinopathy, Peripheral diabetic polyneuropathy, All-cause mortality, Cardiovascular disease

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5. T1D AND PREGNANCY

Late Breaking Poster Presentations: Clinical Diabetes/Therapeutics

172-LB: Risk of Major Congenital Malformations, Perinatal or Neonatal Death with Insulin Detemir Compared with Other Basal Insulins in Pregnant Women with Preexisting Diabetes: The EVOLVE Study

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Abstract

Aim: The EVOLVE study examined the risk of major congenital malformations and perinatal or neonatal deaths when using insulin detemir (IDet) versus other basal insulins in pregnant women with pre-existing diabetes.

Materials and Methods: A prospective, non-interventional, multinational study in pregnant women with type 1 or type 2 diabetes treated with IDet or other insulin treatment. In the present analysis, 727 women using IDet during pregnancy were compared with 730 women using other basal insulin, mainly insulin glargine. The primary endpoint was the number of women completing ≥22 weeks of gestation without any of the following events: major congenital malformations, perinatal or neonatal deaths.

Results: At enrolment 86% of subjects had type 1 diabetes (mean age: 31 years; BMI: 26 kg/m^2) and mean A1C was 7.1%. There was no difference between treatment groups in crude or adjusted risk difference for pregnancies without major congenital malformations, perinatal or neonatal deaths (Table).

Conclusion: In pregnant women with pre-existing diabetes, IDet was not associated with excess risk of major congenital malformations, perinatal or neonatal deaths vs. other basal insulin.

DIABETICMedicine

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Research: Pregnancy

Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes

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Accepted 3 June 2019

Abstract

Aim To investigate potential cost savings associated with the use of real-time continuous glucose monitoring (RT-CGM) throughout pregnancy in women with Type 1 diabetes.

Methods A budget impact model was developed to estimate, from the perspective of National Health Service England, the total costs of managing pregnancy and delivery in women with Type 1 diabetes using self-monitoring of blood glucose (SMBG) with and without RT-CGM. It was assumed that the entire modelled cohort ($n = 1441$) would use RT-CGM from 10 to 38 weeks' gestation (7 months). Data on pregnancy and neonatal complication rates and related costs were derived from published literature, national tariffs, and device manufacturers.

Results The cost of glucose monitoring was £588 with SMBG alone and £1820 with RT-CGM. The total annual costs of managing pregnancy and delivery in women with Type 1 diabetes were £23 725 648 with SMBG alone, and £14 165 187 with SMBG and RT-CGM; indicating potential cost savings of approximately £9 560 461 from using RT-CGM. The principal drivers of cost savings were the daily cost of neonatal intensive care unit (NICU) admissions (£3743) and the shorter duration of NICU stay (mean 6.6 vs. 9.1 days respectively). Sensitivity analyses showed that RT-CGM remained cost saving, albeit to lesser extents, across a range of NICU costs and durations of hospital stay, and with varying numbers of daily SMBG measurements.

Conclusions Routine use of RT-CGM by pregnant women with Type 1 diabetes, would result in substantial cost savings, mainly through reductions in NICU admissions and shorter duration of NICU care.

Diabet. Med. 36, 1652–1658 (2019)

Type 1 Diabetes in Pregnancy

David R. McCance, MD*, Claire Casey, PhD

KEYWORDS

• Type 1 diabetes • Pregnancy • Glycemic control • Maternal/fetal outcomes

KEY POINTS

- Adverse maternal/fetal outcomes in type 1 diabetic pregnancy remain severalfold higher than in the background population.
- The benefits of pregnancy planning in improving outcomes are clear, but still only a minority of women plan their pregnancy, and education must remain a key priority.
- Recent advances in insulin delivery and glucose sensing offer promise, but elucidation of their relative roles and precise indication for use is urgently needed.

Disclosure: The authors have no conflicts of interest to declare.
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Diabetes Care Volume 43, Supplement 1, January 2020 S183

14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2020*

American Diabetes Association

Diabetes Care 2020;43(Suppl. 1):S183–S192 | https://doi.org/10.2337/dc20-S014

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc20-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc20-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

6. T1D PREVENTION

The NEW ENGLAND JOURNAL of MEDICINE

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An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

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ABSTRACT

BACKGROUND

Type 1 diabetes is a chronic autoimmune disease that leads to destruction of insulin-producing beta cells and dependence on exogenous insulin for survival. Some interventions have delayed the loss of insulin production in patients with type 1 diabetes, but interventions that might affect clinical progression before diagnosis are needed.

METHODS

We conducted a phase 2, randomized, placebo-controlled, double-blind trial of teplizumab (an Fc receptor–nonbinding anti-CD3 monoclonal antibody) involving relatives of patients with type 1 diabetes who did not have diabetes but were at high risk for development of clinical disease. Patients were randomly assigned to a single 14-day course of teplizumab or placebo, and follow-up for progression to clinical type 1 diabetes was performed with the use of oral glucose-tolerance tests at 6-month intervals.

RESULTS

A total of 76 participants (55 [72%] of whom were ≤18 years of age) underwent randomization — 44 to the teplizumab group and 32 to the placebo group. The median time to the diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group; the disease was diagnosed in 19 (43%) of the participants who received teplizumab and in 23 (72%) of those who received placebo. The hazard ratio for the diagnosis of type 1 diabetes (teplizumab vs. placebo) was 0.41 (95% confidence interval, 0.22 to 0.78; P=0.006 by adjusted Cox proportional-hazards model). The annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group. There were expected adverse events of rash and transient lymphopenia. KLRG1+TIGIT+CD8+ T cells were more common in the teplizumab group than in the placebo group. Among the participants who were HLA-DR3–negative, HLA-DR4–positive, or anti–zinc transporter 8 antibody–negative, fewer participants in the teplizumab group than in the placebo group had diabetes diagnosed.

CONCLUSIONS

Teplizumab delayed progression to clinical type 1 diabetes in high-risk participants. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT01030861.)

From the Departments of Immunobiology and Internal Medicine, Yale University, New Haven, CT (K.C.H.); the Departments of Epidemiology and Pediatrics, University of South Florida, Tampa (B.N.B., J.P.K., H.R.), the Department of Medicine, University of Miami, Miami (J.B.M., J.S.S.), and the Department of Pediatrics, University of Florida, Gainesville (D.S.) — all in Florida; Benaroya Research Institute, Seattle (S.A.L., M.J.D., P.S.L., C.J.G.); the Diabetes Center, University of California at San Francisco, San Francisco (J.A.B., S.E.G.); the Department of Pediatrics, Indiana University, Indianapolis (L.A.D.); the Barbara Davis Diabetes Center, University of Colorado, Anschultz (P.A.G.); Children's Mercy Hospital, Kansas City, MO (W.M.); the Department of Pediatrics, University of Minnesota, Minneapolis (A.M.); the Department of Pediatrics and Cell and Developmental Biology, Vanderbilt University, Nashville (W.E.R.); the Department of Pediatrics, University of Iowa, Iowa City (E.T.); the Hospital for Sick Children, University of Toronto, Toronto (D.K.W.); and Forschergruppe Diabetes, Technical University Munich, at Klinikum rechts der Isar, Munich, Germany (A.-G.Z.). Address reprint requests to Dr. Herold at Yale University, 300 George St., #353E, New Haven, CT 06520, or at kevan.herold@yale.edu.

*A complete list of investigators in the Type 1 Diabetes TrialNet Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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7. T1D + RISK OF PROGRESSION

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The risk of progression to type 1 diabetes is highly variable in individuals with multiple autoantibodies following screening

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Abstract

Aims/hypothesis—Young children who develop multiple autoantibodies (mAbs) are at very high risk for type 1 diabetes. We assessed whether a population with mAbs detected by screening is also at very high risk, and how risk varies according to age, type of autoantibodies and metabolic status.

8. T1D + COVID-19

Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study

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Summary

Background Diabetes has been associated with increased COVID-19-related mortality, but the association between modifiable risk factors, including hyperglycaemia and obesity, and COVID-19-related mortality among people with diabetes is unclear. We assessed associations between risk factors and COVID-19-related mortality in people with type 1 and type 2 diabetes.

Methods We did a population-based cohort study of people with diagnosed diabetes who were registered with a general practice in England. National population data on people with type 1 and type 2 diabetes collated by the National Diabetes Audit were linked to mortality records collated by the Office for National Statistics from Jan 2, 2017, to May 11, 2020. We identified the weekly number of deaths in people with type 1 and type 2 diabetes during the first 19 weeks of 2020 and calculated the percentage change from the mean number of deaths for the corresponding weeks in 2017, 2018, and 2019. The associations between risk factors (including sex, age, ethnicity, socioeconomic deprivation, HbA_{1c}, renal impairment [from estimated glomerular filtration rate (eGFR)], BMI, tobacco smoking status, and cardiovascular comorbidities) and COVID-19-related mortality (defined as International Classification of Diseases, version 10, code U07.1 or U07.2 as a primary or secondary cause of death) between Feb 16 and May 11, 2020, were investigated by use of Cox proportional hazards models.

Findings Weekly death registrations in the first 19 weeks of 2020 exceeded the corresponding 3-year weekly averages for 2017–19 by 672 (50·9%) in people with type 1 diabetes and 16 071 (64·3%) in people with type 2 diabetes. Between Feb 16 and May 11, 2020, among 264 390 people with type 1 diabetes and 2 874 020 people with type 2 diabetes, 1604 people with type 1 diabetes and 36 291 people with type 2 diabetes died from all causes. Of these total deaths, 464 in people with type 1 diabetes and 10 525 in people with type 2 diabetes were defined as COVID-19 related, of which 289 (62·3%) and 5833 (55·4%), respectively, occurred in people with a history of cardiovascular disease or with renal impairment (eGFR <60 mL/min per 1·73 m²). Male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes. Compared with people with an HbA_{1c} of 48–53 mmol/mol (6·5–7·0%), people with an HbA_{1c} of 86 mmol/mol (10·0%) or higher had increased COVID-19-related mortality (hazard ratio [HR] 2·23 [95% CI 1·50–3·30, p<0·0001] in type 1 diabetes and 1·61 [1·47–1·77, p<0·0001] in type 2 diabetes). In addition, in people with type 2 diabetes, COVID-19-related mortality was significantly higher in those with an HbA_{1c} of 59 mmol/mol (7·6%) or higher than in those with an HbA_{1c} of 48–53 mmol/mol (HR 1·22 [95% CI 1·15–1·30, p<0·0001] for 59–74 mmol/mol [7·6–8·9%] and 1·36 [1·24–1·50, p<0·0001] for 75–85 mmol/mol [9·0–9·9%]). The association between BMI and COVID-19-related mortality was U-shaped: in type 1 diabetes, compared with a BMI of 25·0–29·9 kg/m², a BMI of less than 20·0 kg/m² had an HR of 2·45 (95% CI 1·60–3·75, p<0·0001) and a BMI of 40·0 kg/m² or higher had an HR of 2·33 (1·53–3·56, p<0·0001); the corresponding HRs for type 2 diabetes were 2·33 (2·11–2·56, p<0·0001) and 1·60 (1·47–1·75, p<0·0001).

Interpretation Deaths in people with type 1 and type 2 diabetes rose sharply during the initial COVID-19 pandemic in England. Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycaemic control and BMI.

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Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study

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Summary

Background Although diabetes has been associated with COVID-19-related mortality, the absolute and relative risks for type 1 and type 2 diabetes are unknown. We assessed the independent effects of diabetes status, by type, on in-hospital death in England in patients with COVID-19 during the period from March 1 to May 11, 2020.

Methods We did a whole-population study assessing risks of in-hospital death with COVID-19 between March 1 and May 11, 2020. We included all individuals registered with a general practice in England who were alive on Feb 16, 2020. We used multivariable logistic regression to examine the effect of diabetes status, by type, on in-hospital death with COVID-19, adjusting for demographic factors and cardiovascular comorbidities. Because of the absence of data on total numbers of people infected with COVID-19 during the observation period, we calculated mortality rates for the population as a whole, rather than the population who were infected.

Findings Of the 61 414 470 individuals who were alive and registered with a general practice on Feb 16, 2020, 263 830 (0·4%) had a recorded diagnosis of type 1 diabetes, 2 864 670 (4·7%) had a diagnosis of type 2 diabetes, 41 750 (0·1%) had other types of diabetes, and 58 244 220 (94·8%) had no diabetes. 23 698 in-hospital COVID-19-related deaths occurred during the study period. A third occurred in people with diabetes: 7434 (31·4%) in people with type 2 diabetes, 364 (1·5%) in those with type 1 diabetes, and 69 (0·3%) in people with other types of diabetes. Unadjusted mortality rates per 100 000 people over the 72-day period were 27 (95% CI 27–28) for those without diabetes, 138 (124–153) for those with type 1 diabetes, and 260 (254–265) for those with type 2 diabetes. Adjusted for age, sex, deprivation, ethnicity, and geographical region, compared with people without diabetes, the odds ratios (ORs) for in-hospital COVID-19-related death were 3·51 (95% CI 3·16–3·90) in people with type 1 diabetes and 2·03 (1·97–2·09) in people with type 2 diabetes. These effects were attenuated to ORs of 2·86 (2·58–3·18) for type 1 diabetes and 1·80 (1·75–1·86) for type 2 diabetes when also adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure.

Interpretation The results of this nationwide analysis in England show that type 1 and type 2 diabetes were both independently associated with a significant increased odds of in-hospital death with COVID-19.

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Review

MOLECULAR METABOLISM

Diabetes, infection risk and COVID-19

Suheda Erener [1,2,3,4]

ABSTRACT

Background: Individuals with diabetes are at a greater risk of hospitalization and mortality resulting from viral, bacterial, and fungal infections. The coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread quickly to more than 213 countries and claimed 395,779 lives as of June 7, 2020. Notably, in several studies, diabetes is one of the most reported comorbidities in patients with severe COVID-19.

Scope of review: In this review, I summarize the clinical data on the risk for infectious diseases in individuals with diabetes while highlighting the mechanisms for altered immune regulation. The focus is on coronaviruses. Based on the new clinical data obtained from COVID-19 patients, a discussion of mechanisms, such as cytokine storm, pulmonary and endothelial dysfunction, and hypercoagulation, that may render individuals with diabetes more vulnerable to COVID-19 is provided.

Major conclusions: Epidemiological studies show that poorly controlled diabetes is a risk factor for various infectious diseases. Given the global burden of diabetes and the pandemic nature of coronaviruses, understanding how diabetes affects COVID-19 severity is critical to designing tailored treatments and clinical management of individuals affected by diabetes.

Keywords Diabetes; Infection; Coronavirus; COVID-19; SARS-CoV-2

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COVID-19 and Type 1 Diabetes: Concerns and Challenges

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Summary: Due to the current COVID-19 pandemic, worldwide population's lifestyle has changed dramatically, causing psychosocial consequences. Patients presenting a preexisting chronic condition, as Type 1 Diabetes (T1D), are the ones suffering the most from this situation. Moreover, people affected by diabetes are the ones with the worst prognosis, if infected by SARS-CoV-2. We analyzed why patients with T1D were poorly represented between the subjects hospitalized for COVID-19 and why the cases of diabetic ketoacidosis (DKA) were fewer and more severe compared with the past years. Furthermore, literature has showed how patients of all ages with T1D did not experience a deterioration in their glucose control throughout the lockdown. Among other causes, this is also due to the surging use of telemedicine. Finally, we tried to understand how the coronavirus tropism for endocrine tissues could influence the future epidemiology of T1D, focusing on the effects they have on pancreatic β-cells.

Key words: COVID19, Type 1 Diabetes, Children, Telemedicine

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REVIEW ARTICLE

COVID-19 and type 1 diabetes: dealing with the difficult duo

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Received: 6 June 2020 / Accepted: 16 June 2020

Abstract

Background Coronavirus disease 2019 (COVID-19) has aroused global health concerns, particularly in relation to diabetes where it has been associated with poorer outcomes. The bulk of the evolving evidence in diabetes and COVID-19 relates to type 2 diabetes (T2D). Since there are a significant number of patients with type 1 diabetes (T1D) with unique concerns and challenges during the ongoing COVID-19 pandemic, we reviewed existing literature, relevant websites, and related guidelines to form this narrative review to help address key questions in this area.

Methods We systematically searched the PubMed database up to May 31, 2020, and retrieved all the articles published on T1D and COVID-19.

Results We found 18 relevant articles, each of which carried a part of the evidence regarding the risk of contracting COVID-19 in patients with T1D, effect of COVID-19 on development of T1D, outcomes in T1D with COVID-19, and special management issues in T1D in the light of COVID-19. These have been documented in the present review.

Conclusion COVID-19 with T1D presents special challenges. While the available evidence does shed some light, we need more evidence to deal with this difficult duo.

Keywords COVID-19 · SARS-CoV-2 · Type 1 diabetes · Diabetic ketoacidosis

Diabetes Care

Comparison of Diabetic Ketoacidosis in Adults During the SARS-CoV-2 Outbreak and Over the Same Time Period for the Preceding 3 Years

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ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Trulicity 0,75 mg ενέσιμο διάλυμα σε προγεμισμένη πένα.Trulicity 1,5 mg ενέσιμο διάλυμα σε προγεμισμένη πένα.Trulicity 3 mg ενέσιμο διάλυμα σε προγεμισμένη συσκευή τύπου πένας.Trulicity 4,5 mg ενέσιμο διάλυμα σε προγεμισμένη συσκευή τύπου πένας. **ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ** ΤΚάθε προγεμισμένη πένα περιέχει 0,75 mg ή 1,5 mg ή 3 mg ή 4,5 mg ντουλαγλουτίδη σε 0,5 ml διαλύματος. Παράγεται σε κύτταρα CHO μέσω της τεχνολογίας του ανασυνδυασμένου DNA. **Θεραπευτικές ενδείξεις** Το Trulicity ενδείκνυται για χρήση σε ενήλικες με σακχαρώδη διαβήτη τύπου 2 για τη βελτίωση του γλυκαιμικού ελέγχου ως: ***Μονοθεραπεία*** Όταν η διατροφή και η άσκηση μόνο δεν παρέχουν επαρκή γλυκαιμικό έλεγχο σε ασθενείς για τους οποίους η χρήση μετφορμίνης θεωρείται ακατάλληλη λόγω δυσανεξίας ή αντενδείξεων. ***Συμπληρωματική θεραπεία*** Σε συνδυασμό με άλλα φαρμακευτικά προϊόντα που προκαλούν μείωση των επιπέδων γλυκόζης, συμ περιλαμβανομένης της ινσουλίνης, όταν αυτά, σε συνδυασμό με διατροφή και άσκηση, δεν παρέχουν επαρκή γλυκαιμικό έλεγχο. **Δοσολογία και τρόπος χορήγησης:** Δοσολογία ***Μονοθεραπεία*** Η συνιστώμενη δόση είναι 0,75 mg μία φορά την εβδομάδα. Συμπληρωματική θεραπεία Η συνιστώμενη δόση είναι 1,5 mg μία φορά την εβδομάδα.Για δυνητικά ευαίσθητους πληθυσμούς μπορεί να εξεταστεί δόση 0,75 mg μία φορά την εβδομάδα ως αρχική δόση. Για επιπρόσθετο γλυκαιμικό έλεγχο, η δόση των 1,5 mg μπορεί να αυξηθεί, μετά από τουλάχιστον 4 εβδομάδες, στη δόση των 3 mg μια φορά την εβδομάδα.η δόση των 3 mg μπορεί να αυξηθεί, μετά από τουλάχιστον 4 εβδομάδες, στη δόση των 4,5 mg μια φορά την εβδομάδα.Η μέγιστη δόση είναι 4,5 mg μια φορά την εβδομάδα. Τρόπος χορήγησης: Το Trulicity θα πρέπει να χορηγείται με έγεση υποδορίως στην κοιλιακή χώρα, το μηρό ή τον άνω βραχίονα. **Αντενδείξεις.** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. **Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση.** Η ντουλαγλουτίδη δεν θα πρέπει να χρησιμοποιείται σε ασθενείς με σακχαρώδη διαβήτη τύπου 1 ή για τη θεραπεία της διαβητικής κετοξέωσης. Η ντουλαγλουτίδη δεν είναι υποκατάστατο της ινσουλίνης. Αφυδάτωση Σε ασθενείς που έλαβαν ντουλαγλουτίδη, ιδιαίτερα κατά την έναρξη της θεραπείας, έχει αναφερθεί αφυδάτωση, η οποία μερικές φορές έχει οδηγεί σε οξεία νεφρική ανεπάρκεια ή επιδείνωση της νεφρικής δυσλειτουργίας. Οξεία παγκρεατίτιδα. Η χρήση αγωνιστών του υποδοχέα του GLP-1 έχει σχετιστεί με κίνδυνο ανάπτυξης οξείας παγκρεατίτιδας. Εάν υπάρχει υποψία παγκρεατίτιδας, η χορήγηση της ντουλαγλουτίδης θα πρέπει να διακόπεται. Υπογλυκαιμία Οι ασθενείς που λαμβάνουν ντουλαγλουτίδη σε συνδυασμό με σουλφονυλουρία ή ινσουλίνη μπορεί να διατρέχουν αυξημένο κίνδυνο υπογλυκαιμίας. Ο κίνδυνος υπογλυκαιμίας μπορεί να μειωθεί με τη μείωση της δόσης της σουλφονυλουρίας ή της ινσουλίνης. Πληθυσμοί που δεν έχουν μελετηθεί Υπάρχει περιορισμένη εμπειρία σε ασθενείς με συμφορητική καρδιακή ανεπάρκεια. Περιεκτικότητα σε νάτριο Το φαρμακευτικό αυτό προϊόν περιέχει λιγότερο από 1 mmol νατρίου (23 mg) ανά δόση 1,5 mg, δηλ. ουσιαστικά είναι «ελεύθερο νατρίου». **Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης.** Η ντουλαγλουτίδη καθυστερεί τη γαστρική κένωση και υπάρχει το ενδεχόμενο να επηρεάσει τον ρυθμό απορρόφησης των από του στόματος συγχορηγούμενων φαρμακευτικών προϊόντων. **Γονιμότητα, κύηση και γαλουχία** Κύηση Η χρήση της ντουλαγλουτίδης δεν συνιστάται κατά τη διάρκεια της εγκυμοσύνης. Θηλασμός. Η ντουλαγλουτίδη δεν θα πρέπει να χρησιμοποιείται κατά τη διάρκεια του θηλασμού. Γονιμότητα Η επίδραση της ντουλαγλουτίδης στην ανθρώπινη γονιμότητα είναι άγνωστη. **Ανεπιθύμητες ενέργειες** Οι ακόλουθες ανεπιθύμητες ενέργειες έχουν ταυτοποιηθεί με βάση την αξιολόγηση των κλινικών μελετών φάσης **II** και φάσης **III** σε ολόκληρη τη διάρκειά τους και τις αναφορές μετά την κυκλοφορία του προϊόντος: **Πολύ Συχνές:** ≥ 1/10. Διαταραχές του μεταβολισμού και της θρέψης: Υπογλυκαιμία (όταν χρησιμοποιείται σε συνδυασμό με ινσουλίνη, γλιπεπιρίδη, μετφορμίνη ή μετφορμίνη και γλιμεπιρίδη). Διαταραχές του γαστρεντερικού συστήματος: Ναυτία, διάρροια, έμετος, κοιλιακό άλγος **Συχνές:** ≥1/100 έως <1/10. Διαταραχές του μεταβολισμού και της θρέψης: Υπογλυκαιμία* (όταν χρησιμοποιείται ως μονοθεραπεία ή σε συνδυασμό με μετφορμίνη και πιογλιταζόνη) Διαταραχές του γαστρεντερικού συστήματος: Μειωμένη όρεξη, δυσπεψία, δυσκοιλιότητα, μετεωρισμός, κοιλιακή διάταση, γαστροοισοφαγική παλινδρόμηση, ερυγές Γενικές διαταραχές και καταστάσεις της οδού χορήγησης: Κόπωση Παρακλινικές εξετάσεις: Φλεβοκομβική ταχυκαρδία, κολποκοιλιακός αποκλεισμός πρώτου βαθμού (AVB)΄**Οχι συχνές:** ≥1/1.000 έως <1/100. Γενικές διαταραχές και καταστάσεις της οδού χορήγησης: Αντιδράσεις στη θέση της ένεσης Διαταραχές του ανοσοποιητικού συστήματος: Υπερευαισθησία, Διαταραχές του ήπατος και των χοληφόρων: Χολολιθίαση, χολοκυστίτιδα Διαταραχές του μεταβολισμού και της θρέψης: Αφυδάτωση **Σπάνιες:** ≥ 1/10.000 έως < 1/1.000. Διαταραχές του γαστρεντερικού συστήματος: Οξεία παγκρεατίτιδα Διαταραχές του ανοσοποιητικού συστήματος: Αναφυλακτική αντίδραση. Διαταραχές του δέρματος και του υποδορίου ιστού: Αγγειοοίδημα **Μη γνωστές:** Διαταραχές του γαστρεντερικού: Μη μηχανική εντερική απόφραξη Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών. **Υπερδοσολογία** Οι επιδράσεις της υπερδοσολογίας ντουλαγλουτίδης στις κλινικές μελέτες περιλάμβαναν διαταραχές του γαστρεντερικού συστήματος και υπογλυκαιμία. **Φαρμακοδυναμικές ιδιότητες** Φαρμακοθεραπευτική κατηγορία: Φάρμακα χρησιμοποιούμενα στον διαβήτη, άλλα φάρμακα για τη μείωση του σακχάρου του αίματος, εξαιρουμένων των ινσουλινών. Κωδικός ATC: A10BX14 **Διάρκεια ζωής** 2 χρόνια. **ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, Ολλανδία. **ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ** EU/1/14/956/001 TRULICITY IN.SO. 0,75MG/0,5ML BTx2 PF.PEN, EU/1/14/956/006 TRULICITY IN.SO. 1,5MG/0,5ML BTx2 PF.PEN **ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ** Ημερομηνία πρώτης έγκρισης: 21 Νοεμβρίου 2014 **ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ** 18 Νοεμβρίου 2020 . Λεπτομερή πληροφοριακά στοιχεία για το παρόν φαρμακευτικό προϊόν είναι διαθέσιμα στον δικτυακό τόπο του Ευρωπαϊκού Οργανισμού Φαρμάκων http://www.ema.europa.eu και στην ιστοσελίδα της ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ, www.pharmaserve.gr. **ΤΡΟΠΟΣ ΔΙΑΘΕΣΗΣ ΤΟΥ ΠΡΟΪΟΝΤΟΣ:** Φαρμακευτικό προϊόν για το οποίο απαιτείται ιατρική συνταγή. **ΕΠΙΧΟΡΗΓΗΣΗ ΑΠΟ ΤΑ ΤΑΜΕΙΑ:** 90% για ασθενείς με ΣΔτ2. **ΜΟΡΦΕΣ/ΤΙΜΕΣ:** TRULICITY IN.SOL 0,75MG BTx2 PF.PEN ΧΤ: 40,15€ ΛΤ: 55,33€ ΝΤ: 38,27€ , TRULICITY IN.SOL 1,5MG BTx2 PF.PEN ΧΤ: 40,26€ ΛΤ: 55,48€ ΝΤ: 38,38€.

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CONSENSUS REPORT

Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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Published online: 19 June 2020

Abstract
The convergence of advances in medical science, human biology, data science and technology has enabled the generation of new insights into the phenotype known as 'diabetes'. Increased knowledge of this condition has emerged from populations around the world, illuminating the differences in how diabetes presents, its variable prevalence and how best practice in treatment varies between populations. In parallel, focus has been placed on the development of tools for the application of precision medicine to numerous conditions. This Consensus Report presents the American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative in partnership with the European Association for the Study of Diabetes (EASD), including its mission, the current state of the field and prospects for the future. Expert opinions are presented on areas of precision diagnostics and precision therapeutics (including prevention and treatment) and key barriers to and opportunities for implementation of precision diabetes medicine, with better care and outcomes around the globe, are highlighted. Cases where precision diagnosis is already feasible and effective (i.e. monogenic forms of diabetes) are presented, while the major hurdles to the global implementation of precision diagnosis of complex forms of diabetes are discussed. The situation is similar for precision therapeutics, in which the appropriate therapy will often change over time owing to the manner in which diabetes evolves within individual patients. This Consensus Report describes a foundation for precision diabetes medicine, while highlighting what remains to be done to realise its potential. This, combined with a subsequent, detailed evidence-based review (due 2022), will provide a roadmap for precision medicine in diabetes that helps improve the quality of life for all those with diabetes.

Keywords Diabetes · Precision diagnostics · Precision medicine · Precision prevention · Precision therapeutics · Precision treatment · Prediction · Prognosis

Abbreviations

ADME	Absorption, distribution, metabolism, excretion
ADOPT	A Diabetes Outcome Progression Trial
DPP	Diabetes Prevention Program
DPP4i	Dipeptidyl peptidase 4 inhibitor
FDA	Food and Drug Administration
GDM	Gestational diabetes mellitus
GWAS	Genome-wide association studies
LADA	Latent autoimmune diabetes in adults
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
PMDI	Precision Medicine in Diabetes Initiative
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes
T1D-GRS	Type 1 diabetes genetic risk score

Stephen S. Rich and Paul W. Franks contributed equally to this Consensus Report and are co-chairs of the Precision Medicine in Diabetes Initiative.

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Subtypes of Type 2 Diabetes Determined From Clinical Parameters

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Type 2 diabetes (T2D) is defined by a single metabolite, glucose, but is increasingly recognized as a highly heterogeneous disease, including individuals with varying clinical characteristics, disease progression, drug response, and risk of complications. Identification of subtypes with differing risk profiles and disease etiologies at diagnosis could open up avenues for personalized medicine and allow clinical resources to be focused to the patients who would be most likely to develop diabetic complications, thereby both improving patient health and reducing costs for the health sector. More homogeneous populations also offer increased power in experimental, genetic, and clinical studies. Clinical parameters are easily available and reflect relevant disease pathways, including the effects of both genetic and environmental exposures. We used six clinical parameters (GAD autoantibodies, age at diabetes onset, HbA_{1c}, BMI, and measures of insulin resistance and insulin secretion) to cluster adult-onset diabetes patients into five subtypes. These subtypes have been robustly reproduced in several populations and associated with different risks of complications, comorbidities, genetics, and response to treatment. Importantly, the group with severe insulin-deficient diabetes (SIDD) had increased risk of retinopathy and neuropathy, whereas the severe insulin-resistant diabetes (SIRD) group had the highest risk for diabetic kidney disease (DKD) and fatty liver, emphasizing the importance of insulin resistance for DKD and hepatosteatosis in T2D. In conclusion, we believe that subclassification using these highly relevant parameters could provide a framework for personalized medicine in diabetes.

Heterogeneity of Diabetes

Current Classifications for Diabetes

Diabetes is a heterogeneous disease with varying manifestation and risk of complications (1). While diabetes is diagnosed on the basis of a single metabolite, glucose, hyperglycemia can arise due to multiple complex etiological processes that can vary between individuals (2). These processes influence the clinical characteristics, progression, drug response, and development of complications. Diabetes is therefore traditionally divided into different types (Fig. 1*A*). Type 1 diabetes (T1D) and latent autoimmune diabetes of the adult (LADA) both result from autoimmune destruction of β-cells, often, but not always, reflected by presence of pancreatic autoantibodies in the blood that can be used as a diagnostic marker (3). Identification of such antibodies is a strong indicator that the patient will eventually need insulin treatment to maintain glucose homeostasis (4). Rare monogenic diabetes types, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes, account for about 3% of diabetes diagnosed in individuals <30 years of age. Diagnosis requires sequencing of known monogenic diabetes genes, and the consequences for those affected are life changing, since a correct diagnosis has major implications on choice of treatment (5).

After exclusion of these and a few other subtypes, such as diabetes secondary to steroid use, cystic fibrosis, and hemochromatosis, the remaining patients, 75–85%, are considered to have type 2 diabetes (T2D). Because autoantibodies are not always measured and genetic diagnostics are often not available, the T2D group may include patients with undiagnosed autoimmune or monogenic diabetes. While the two main types of diabetes have been recognized for thousands of years, the names and definitions have changed and there is still no clear-cut definition that will allow all patients to be classified as either T1D or T2D (2). Some patients show signs of both autoimmune destruction of β-cells and profound insulin resistance with features of the "insulin resistance syndrome." The large remaining group of true T2D is still highly heterogeneous

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Articles

Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86)

Ernesto Maddaloni, Ruth L Coleman, Olorunsola Agbaje, Raffaella Buzzetti, Rury R Holman

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See Comment page 177

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Summary

Background Latent autoimmune diabetes of adulthood (LADA) differs in clinical features from type 2 diabetes. Whether this difference translates into different risks of complications remains controversial. We examined the long-term risk of microvascular complications in people enrolled in the UK Prospective Diabetes Study (UKPDS), according to their diabetes autoimmunity status.

Methods We did a post-hoc analysis of 30-year follow-up data from UKPDS (UKPDS 86). UKPDS participants with diabetes autoantibody measurements available and without previous microvascular events were included. Participants with at least one detectable autoantibody were identified as having latent autoimmune diabetes, and those who tested negative for all autoantibodies were identified as having type 2 diabetes. The incidence of the primary composite microvascular outcome (first occurrence of renal failure, renal death, blindness, vitreous haemorrhage, or retinal photocoagulation) was compared between adults with latent autoimmune diabetes and those with type 2 diabetes. The follow-up ended on Sept 30, 2007. Baseline and updated 9-year mean values of potential confounders were tested in Cox models to adjust hazard ratios (HRs). UKPDS is registered at the ISRCTN registry, 75451837.

Findings Among the 5028 participants included, 564 had latent autoimmune diabetes and 4464 had type 2 diabetes. After median 17·3 years (IQR 12·6–20·7) of follow-up, the composite microvascular outcome occurred in 1041 (21%) participants. The incidence for the composite microvascular outcome was 15·8 (95% CI 13·4–18·7) per 1000 person-years in latent autoimmune diabetes and 14·2 (13·3–15·2) per 1000 person-years in type 2 diabetes. Adults with latent autoimmune diabetes had a lower risk of the composite outcome during the first 9 years of follow-up than those with type 2 diabetes (adjusted HR 0·45 [95% CI 0·30–0·68], p<0·0001), whereas in subsequent years their risk was higher than for those with type 2 diabetes (1·25 [1·01–1·54], p=0·047). Correcting for the higher updated 9-year mean HbA_{1c} seen in adults with latent autoimmune diabetes than in those with type 2 diabetes explained entirely their subsequent increased risk for the composite microvascular outcome (adjusted HR 0·99 [95% CI 0·80–1·23], p=0·93).

Interpretation At diabetes onset, adults with latent autoimmune diabetes have a lower risk of microvascular complications followed by a later higher risk of complications than do adults with type 2 diabetes, secondary to worse glycaemic control. Implementing strict glycaemic control from the time of diagnosis could reduce the later risk of microvascular complications in adults with latent autoimmune diabetes.

Funding European Foundation for the Study of Diabetes Mentorship Programme (AstraZeneca).

Introduction

Diabetes-related autoantibodies are detectable in 2–12% of adults with a clinical diagnosis of type 2 diabetes.[1–3] These people are affected by a mild form of autoimmune diabetes known as latent autoimmune diabetes of adulthood (LADA). An overlap in the pathogenesis and clinical features of type 2 diabetes and type 1 diabetes has been hypothesised in latent autoimmune diabetes.[4]

Diabetic microvascular complications are a major cause of end-stage renal disease and blindness worldwide.[5,6] We have previously shown a similar risk of major cardiovascular events in latent autoimmune diabetes and type 2 diabetes.[7] However, the prevalence of microvascular complications might differ among diabetes types because of different pathogenesis and prevalence of risk factors, but data in this regard are scarce. The comparative evaluation of vascular complications between different forms of diabetes could aid in risk stratification, which is essential to help promote individualised prevention of complications and treatment strategies. Furthermore, it might show crucial differences in risk factors, which could have an impact on the understanding of the pathogenesis of complications in the different forms of diabetes. In this regard,

Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel

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A substantial proportion of patients with adult-onset diabetes share features of both type 1 diabetes (T1D) and type 2 diabetes (T2D). These individuals, at diagnosis, clinically resemble T2D patients by not requiring insulin treatment, yet they have immunogenetic markers associated with T1D. Such a slowly evolving form of autoimmune diabetes, described as latent autoimmune diabetes of adults (LADA), accounts for 2–12% of all patients with adult-onset diabetes, though they show considerable variability according to their demographics and mode of ascertainment. While therapeutic strategies aim for metabolic control and preservation of residual insulin secretory capacity, endotype heterogeneity within LADA implies a personalized approach to treatment. Faced with a paucity of large-scale clinical trials in LADA, an expert panel reviewed data and delineated one therapeutic approach. Building on the 2020 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus for T2D and heterogeneity within autoimmune diabetes, we propose "deviations" for LADA from those guidelines. Within LADA, C-peptide values, proxy for β-cell function, drive therapeutic decisions. Three broad categories of random C-peptide levels were introduced by the panel: *1*) C-peptide levels <0.3 nmol/L: a multiple-insulin regimen recommended as for T1D; *2*) C-peptide values ≥0.3 and ≤0.7 nmol/L: defined by the panel as a "gray area" in which a modified ADA/EASD algorithm for T2D is recommended; consider insulin in combination with other therapies to modulate β-cell failure and limit diabetic complications; *3*) C-peptide values >0.7 nmol/L: suggests a modified ADA/EASD algorithm as for T2D but allowing for the potentially progressive nature of LADA by monitoring C-peptide to adjust treatment. The panel concluded by advising general screening for LADA in newly diagnosed non–insulin-requiring diabetes and, importantly, that large randomized clinical trials are warranted.

Both type 1 diabetes (T1D) and type 2 diabetes (T2D) are complex heterogeneous diseases with a highly variable clinical course given that not all patients fit into the current binary classification. A substantial subgroup of patients, mostly with onset in adulthood, share several characteristics of both T1D and T2D as described over 30 years ago (1–3). These patients are considered to have a slowly progressive form of autoimmune diabetes with serum immune markers of T1D but not requiring insulin at diagnosis. Such patients identified as having latent autoimmune diabetes of adults (LADA) account for 2–12% of all patients with diabetes, with considerable variability according to ethnicity, type of autoantibody used for screening (most often autoantibody against glutamic acid

The Diabetes EDUCATOR

Diabetes Self-management Education and Support in Adults With Type 2 Diabetes

A Consensus Report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

METHODS

In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

RESULTS

During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Packer at Baylor Heart and Vascular Institute, 621 N. Hall St., Dallas, TX 75226, or at milton.packer@baylorhealth.edu.

*A complete list of the EMPEROR-Reduced investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Cardiovascular Benefit of Empagliflozin Across the Spectrum of Cardiovascular Risk Factor Control in the EMPA-REG OUTCOME Trial

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Context: Control of multiple cardiovascular (CV) risk factors reduces CV events in individuals with type 2 diabetes.

Objective: To investigate this association in a contemporary clinical trial population, including how CV risk factor control affects the CV benefits of empagliflozin, a sodium-glucose cotransporter-2 inhibitor.

Design: Post hoc analysis.

Setting: Randomized CV outcome trial (EMPA-REG OUTCOME).

Participants: Type 2 diabetes patients with established CV disease.

Intervention: Empagliflozin or placebo.

Main Outcome Measures: Risk of CV outcomes—including the treatment effect of empagliflozin—by achieving 7 goals for CV risk factor control at baseline: (1) glycated hemoglobin <7.5%, (2) low-density lipoprotein cholesterol <100 mg/dL or statin use, (3) systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, (4) pharmacological renin-angiotensin-aldosterone system blockade, (5) normoalbuminuria, (6) aspirin use, (7) nonsmoking.

Results: In the placebo group, the hazard ratio (HR) for CV death was 4.00 (95% CI, 2.26–7.11) and 2.48 (95% CI, 1.52–4.06) for patients achieving only 0–3 or 4–5 risk factor goals at baseline, respectively, compared with those achieving 6–7 goals. Participants achieving 0–3 or 4–5 goals also had increased risk for the composite outcome of hospitalization for heart failure or CV death (excluding fatal stroke) (HR 2.89 [1.82–4.57] and 1.90 [1.31–2.78], respectively) and 3-point major adverse CV events (HR 2.21 [1.53–3.19] and 1.42 [1.06–1.89]). Empagliflozin significantly

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EXPERT CONSENSUS DECISION PATHWAY

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the American Diabetes Association

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Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials

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See Comment page 353

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Summary

Background In our 2015 systematic review and meta-analysis of cardiovascular outcome trials for glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes, we reported a modest reduction in atherosclerotic cardiovascular events and an increased risk of heart failure, but with heterogeneous effects by drug or intervention type. In view of the completion of many large cardiovascular outcome trials since our previous analysis, including trials of novel drugs that have shown beneficial effects on cardiovascular outcomes, we aimed to update our analysis to incorporate these findings.

Methods We did an updated systematic review and meta-analysis of large cardiovascular outcome trials of glucose-lowering drugs or strategies in people with or at risk of type 2 diabetes. We searched Ovid MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials databases for reports of trials published from Nov 15, 2013 to Nov 20, 2019. We included randomised controlled trials with a minimum of 1000 adults (aged ≥19 years) with or at risk of type 2 diabetes, with major adverse cardiovascular events (MACE) as an outcome, and with follow-up of at least 12 months. We excluded trials with patients enrolled with an acute cardiovascular event. The main outcomes of interest were MACE (generally defined as a composite of cardiovascular death, myocardial infarction, or stroke) and heart failure. We calculated pooled risk ratios (RRs) and 95% CIs with inverse-variance random-effects models, did meta-regression to analyse treatment effects per difference in bodyweight achieved, and explored results stratified by baseline subgroups.

Findings Our updated search yielded 30 eligible trials (n=225 305). The mean age of participants was 63·0 years (SD 8·4) and mean duration of diabetes was 9·4 years (6·6). After a mean follow-up of 3·8 years (1·8), 23 016 (10·2%) participants had MACE and 8169 (3·6%) had a heart failure event. Glucose-lowering drugs or strategies lowered the risk of MACE compared with standard care or placebo (RR 0·92, 95% CI 0·89–0·95, p<0·0001), with no overall effect on the risk of heart failure (0·98, 0·90–1·08, p=0·71). However, across drug classes or strategies, the magnitude and directionality of RR for heart failure varied ($p_{interaction}$<0·0001), with meta-regression showing that a decrease in bodyweight of 1 kg was associated with a 5·9% (3·9–8·0) relative decrease in the risk of heart failure (p<0·0001). Among trials that assessed drug classes or strategies associated with weight loss (intensive lifestyle changes, GLP-1 receptor agonists, or SGLT2 inhibitors), the risk reduction for MACE was consistent among participants with (0·87, 0·83–0·92) and without (0·92, 0·83–1·02) established cardiovascular disease at baseline ($p_{interaction}$=0·33). For heart failure, the RR for drug classes or strategies associated with weight loss was consistent among participants with (0·80, 0·73–0·89) and without (0·84, 0·74–0·95) cardiovascular disease at baseline ($p_{interaction}$=0·63).

Interpretation Glucose-lowering drugs or strategies overall reduced the risk of fatal and non-fatal atherosclerotic events. The effect on heart failure was neutral overall but varied substantially by intervention type, with interventions associated with weight loss showing a beneficial effect. The cardiovascular and heart failure benefits of interventions associated with weight loss might extend to patients without established cardiovascular disease.

Funding None.

Introduction

Two classes of diabetes drugs, GLP-1 receptor agonists and SGLT2 inhibitors, have shown efficacy in reducing cardiovascular risk among patients with type 2 diabetes. Broadly considered to have varying effects, GLP-1 receptor agonists have mainly been shown to reduce atherosclerotic cardiovascular events, whereas SGLT2 inhibitors seem to affect the cardiorenal axis, reducing hospital admission for heart failure and showing renoprotection, with both drug classes having varying effects on cardiovascular death.[1,2] The mechanisms driving cardiovascular risk reduction for either drug class remain elusive without a clear understanding of whether the heterogeneity in observed effects is due to

Prescribing Paradigm Shift? Applying the 2019 European Society of Cardiology–Led Guidelines on Diabetes, Prediabetes, and Cardiovascular Disease to Assess Eligibility for Sodium–Glucose Cotransporter 2 Inhibitors or Glucagon-Like Peptide 1 Receptor Agonists as First-Line Monotherapy (or Add-on to Metformin Monotherapy) in Type 2 Diabetes in Scotland

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OBJECTIVE

In 2019, the European Society of Cardiology led and released new guidelines for diabetes cardiovascular (CV) risk management, reflecting recent evidence of CV disease (CVD) reduction with sodium–glucose cotransporter 2 inhibitors (SGLT-2is) and some glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes (T2D). A key recommendation is that all those with T2D who are (antihyperglycemic) drug naïve or on metformin monotherapy should be CVD risk stratified and an SGLT-2i or a GLP-1RA initiated in all those at high or very-high risk, irrespective of glycated hemoglobin. We assessed the impact of these guidelines in Scotland were they introduced as is.

RESEARCH DESIGN AND METHODS

Using a nationwide diabetes register in Scotland, we did a cross-sectional analysis, using variables in our register for risk stratification at 1 January 2019. We were conservative in our definitions, assuming the absence of a risk factor where data were not available. The risk classifications were applied to people who were drug naïve or on metformin monotherapy and the anticipated prescribing change calculated.

RESULTS

Of the 265,774 people with T2D in Scotland, 53,194 (20.0% of T2D) were drug naïve, and 56,906 (21.4%) were on metformin monotherapy. Of these, 74.5% and 72.4%, respectively, were estimated as at least high risk given the guideline risk definitions.

CONCLUSIONS

Thus, 80,830 (30.4%) of all those with T2D (n = 265,774) would start one of these drug classes according to table 7 and figure 3 of the guideline. The sizeable impact on drug budgets, enhanced clinical monitoring, and the trade-off with reduced CVD-related health care costs will need careful consideration.

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ARTICLE

Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses

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Abstract

Aims/hypothesis Few studies examine the association between age at diagnosis and subsequent complications from type 2 diabetes. This paper aims to summarise the risk of mortality, macrovascular complications and microvascular complications associated with age at diagnosis of type 2 diabetes.

Methods Data were sourced from MEDLINE and All EBM (Evidence Based Medicine) databases from inception to July 2018. Observational studies, investigating the effect of age at diabetes diagnosis on macrovascular and microvascular diabetes complications in adults with type 2 diabetes were selected according to pre-specified criteria. Two investigators independently extracted data and evaluated all studies. If data were not reported in a comparable format, data were obtained from authors, presented as minimally adjusted ORs (and 95% CIs) per 1 year increase in age at diabetes diagnosis, adjusted for current age for each outcome of interest. The study protocol was recorded with PROSPERO International Prospective Register of Systematic Reviews (CRD42016043593).

Results Data from 26 observational studies comprising 1,325,493 individuals from 30 countries were included. Random-effects meta-analyses with inverse variance weighting were used to obtain the pooled ORs. Age at diabetes diagnosis was inversely associated with risk of all-cause mortality and macrovascular and microvascular disease (all $p < 0.001$). Each 1 year increase in

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ARTICLE

Association of early-onset diabetes, prediabetes and early glycaemic recovery with the risk of all-cause and cardiovascular mortality

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Abstract

Aims/hypothesis The increasing incidence of diabetes among young adults is a disease burden; however, the effects of early-onset diabetes, prediabetes and glycaemic recovery on CVD or mortality remain unclear. We aimed to investigate the association of these factors with 10 year all-cause mortality, CVD mortality and CVD incidence in Korean young adults.

Methods This large and longitudinal cohort study included data from the Korean National Health Insurance Service-National Health Information Database; 2,502,375 young adults aged 20–39 years without diabetes mellitus and CVD at baseline were included. Glycaemic status was measured twice, first in 2002–2003 and second in 2004–2005. Changes in fasting glucose levels were evaluated according to fasting glucose status: normal fasting glucose (NFG; <5.5 mmol/l), impaired fasting glucose (IFG; 5.5–6.9 mmol/l), and diabetic fasting glucose (DFG; ≥7.0 mmol/l). Primary outcomes were all-cause and CVD mortality risk. The secondary outcome was incidence of CVD, including acute myocardial infarction and stroke. All outcomes arose from the 10 year follow-up period 1 Jan 2006 to 31 December 2015.

Results Individuals with NFG at baseline, who were subsequently newly diagnosed with diabetes and prediabetes (IFG), had increased all-cause mortality (HR [95% CI] 1.60 [1.44, 1.78] and 1.13 [1.09, 1.18], respectively) and CVD incidence (1.13 [1.05, 1.23] and 1.04 [1.01, 1.07], respectively). In those with DFG at baseline, early recovery to NFG and IFG was associated with decreased all-cause mortality (0.57 [0.46, 0.70] and 0.65 [0.53, 0.81], respectively) and CVD incidence (0.70 [0.60, 0.81] and 0.78 [0.66, 0.91], respectively). Among patients with IFG at baseline, early recovery to NFG was associated with decreased CVD mortality (0.74 [0.59, 0.93]).

Conclusions/interpretation Early-onset diabetes or prediabetes increased CVD risks and all-cause mortality after the 10 year follow-up. Furthermore, recovery of hyperglycaemia could reduce the subsequent 10 year risk for CVD incidence and all-cause mortality.

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Association of the Mediterranean Diet With Onset of Diabetes in the Women's Health Study

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Abstract

IMPORTANCE Higher Mediterranean diet (MED) intake has been associated with reduced risk of type 2 diabetes, but underlying biological mechanisms are unclear.

OBJECTIVE To characterize the relative contribution of conventional and novel biomarkers in MED-associated type 2 diabetes risk reduction in a US population.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted among 25 317 apparently healthy women. The participants with missing information regarding all traditional and novel metabolic biomarkers or those with baseline diabetes were excluded. Participants were invited for baseline assessment between September 1992 and May 1995. Data were collected from November 1992 to December 2017 and analyzed from December 2018 to December 2019.

EXPOSURES MED intake score (range, 0 to 9) was computed from self-reported dietary intake, representing adherence to Mediterranean diet intake.

MAIN OUTCOMES AND MEASURES Incident cases of type 2 diabetes, identified through annual questionnaires; reported cases were confirmed by either telephone interview or supplemental questionnaire. Proportion of reduced risk of type 2 diabetes explained by clinical risk factors and a panel of 40 biomarkers that represent different physiological pathways was estimated.

RESULTS The mean (SD) age of the 25 317 female participants was 52.9 (9.9) years, and they were followed up for a mean (SD) of 19.8 (5.8) years. Higher baseline MED intake (score ≥6 vs ≤3) was associated with as much as a 30% lower type 2 diabetes risk (age-adjusted and energy-adjusted hazard ratio, 0.70; 95% CI, 0.62-0.79; when regression models were additionally adjusted with body mass index [BMI]: hazard ratio, 0.85; 95% CI, 0.76-0.96). Biomarkers of insulin resistance made the largest contribution to lower risk (accounting for 65.5% of the MED–type 2 diabetes association), followed by BMI (55.5%), high-density lipoprotein measures (53.0%), and inflammation (52.5%), with lesser contributions from branched-chain amino acids (34.5%), very low-density lipoprotein measures (32.0%), low-density lipoprotein measures (31.0%), blood pressure (29.0%), and apolipoproteins (23.5%), and minimal contribution (≤2%) from hemoglobin A_{1c}. In post hoc subgroup analyses, the inverse association of MED diet with type 2 diabetes was seen only among women who had BMI of at least 25 at baseline but not those who had BMI of less than 25 (eg, women with BMI <25, age- and energy-adjusted HR for MED score ≥6 vs ≤3, 1.01; 95% CI, 0.77-1.33; *P* for trend = .92; women with BMI ≥25: HR, 0.76; 95% CI, 0.67-0.87; *P* for trend < .001).

CONCLUSIONS AND RELEVANCE In this cohort study, higher MED intake scores were associated with a 30% relative risk reduction in type 2 diabetes during a 20-year period, which could be

(continued)

Key Points

Question Is the Mediterranean (MED) diet associated with reduced risk of diabetes in a US population, and if so, what are possible underlying biological mechanistic pathways?

Findings Among 25 317 women followed up for 20 years in a prospective epidemiological cohort study, 2307 developed type 2 diabetes. Higher baseline MED intake was associated with a 30% reduction in future risk of diabetes; biomarkers of insulin resistance, adiposity, high-density lipoprotein, and inflammation contributed most to explaining this inverse association.

Meaning These findings suggest that the MED diet may be protective against diabetes by improving insulin resistance, lipoprotein metabolism, and inflammation.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial

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Summary

Background Type 2 diabetes is affecting people at an increasingly younger age, particularly in the Middle East and in north Africa. We aimed to assess whether an intensive lifestyle intervention would lead to significant weight loss and improved glycaemia in young individuals with early diabetes.

Methods This open-label, parallel-group, randomised controlled trial (DIADEM-I), done in primary care and community settings in Qatar, compared the effects of an intensive lifestyle intervention with usual medical care on weight loss and glycaemic outcomes in individuals with type 2 diabetes, aged 18–50 years, with a short diabetes duration (≤3 years), had a BMI of 27·0 kg/m² or more, and who were from the Middle East and north Africa region. Participants were randomly allocated (1:1) either to the intensive lifestyle intervention group or the usual medical care control group by a computer-generated sequence and an online randomisation service. The intensive lifestyle intervention comprised a total diet replacement phase, in which participants were given formula low-energy diet meal replacement products followed by gradual food reintroduction combined with physical activity support, and a weight-loss maintenance phase, involving structured lifestyle support. Participants in the control group received usual diabetes care, which was based on clinical guidelines. The primary outcome was weight loss at 12 months after receiving the assigned intervention. Our analysis was based on the intention-to-treat principle. Key secondary outcomes included diabetes control and remission. The trial was registered with the ISRCTN registry, ISRCTN20754766, and ClinicalTrials.gov, NCT03225339.

Findings Between July 16, 2017, and Sept 30, 2018, we enrolled and randomly assigned 158 participants (n=79 in each group) to the study. 147 participants (70 in the intervention group and 77 in the control group) were included in the final intention-to-treat analysis population. Between baseline and 12 months, the mean bodyweight of participants in the intervention group reduced by 11·98 kg (95% CI 9·72 to 14·23) compared with 3·98 kg (2·78 to 5·18) in the control group (adjusted mean difference −6·08 kg [95% CI −8·37 to −3·79], p<0·0001). In the intervention group, 21% of participants achieved more than 15% weight loss between baseline and 12 months compared with 1% of participants in the control group (p<0·0001). Diabetes remission occurred in 61% of participants in the intervention group compared with 12% of those in the control group (odds ratio [OR] 12·03 [95% CI 5·17 to 28·03], p<0·0001). 33% of participants in the intervention group had normoglycaemia compared with 4% of participants in the control group (OR 12·07 [3·43 to 42·45], p<0·0001). Five serious adverse events were reported in four participants in the control group; four admissions to hospital because of unanticipated events (supraventricular tachycardia, abdominal pain, pneumonia, and epididymo-orchitis), and one admission to hospital for an anticipanted event (hyperglycaemia).

Interpretation Our findings show that the intensive lifestyle intervention led to significant weight loss at 12 months, and was associated with diabetes remission in over 60% of participants and normoglycaemia in over 30% of participants. The provision of this lifestyle intervention could allow a large proportion of young individuals with early diabetes to achieve improvements in key cardiometabolic outcomes, with potential long-term benefits for health and wellbeing.

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Introduction

The prevalence of type 2 diabetes is increasing worldwide, creating a major global health challenge.[1] Type 2 diabetes is associated with serious complications that contribute to reduced quality of life and increased mortality. Over time, an increasing number of young individuals (ie, those aged 18–50 years) are being affected by type 2 diabetes, and these individuals have earlier and more severe diabetes-related complications and reduced longevity.[2] Current recommendations for diabetes management focus strongly on the use of medications to control blood glucose, blood lipids, and blood pressure.[3]

Με εστίαση στην εξατομικευμένη αντιμετώπιση του Διαβήτη τύπου 2[1]

EMPA (10/2019) PC-GR-100560

ΒΙΒΛΙΟΓΡΑΦΙΑ: 1. Περιλήψεις των Χαρακτηριστικών των προϊόντων (Π.Χ.Π.)

Για περισσότερες πληροφορίες συμβουλευθείτε την Περίληψη Χαρακτηριστικών των Προϊόντων ή απευθυνθείτε στο ιατρικό τμήμα της εταιρείας Boehringer Ingelheim Ελλάς Α.Ε.

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Weight Loss Improves β-Cell Function in People With Severe Obesity and Impaired Fasting Glucose: A Window of Opportunity

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Background: In people with obesity, β-cell function may adapt to insulin resistance. We describe β-cell function in people with severe obesity and normal fasting glucose (NFG), impaired fasting glucose (IFG), and type 2 diabetes (T2DM), as assessed before, 3 to 6 months after, and 2 years after medical weight loss to describe its effects on insulin sensitivity, insulin secretion, and β-cell function.

Methods: Fifty-eight participants with body mass index (BMI) ≥ 35 kg/m^2 (14 with NFG, 24 with IFG, and 20 with T2DM) and 13 normal weight participants with NFG underwent mixed meal tolerance tests to estimate insulin sensitivity (S[I]), insulin secretion (Φ), and β-cell function assessed as model-based Φ adjusted for S(I). All 58 obese participants were restudied at 3 to 6 months and 27 were restudied at 2 years.

Results: At 3 to 6 months, after a 20-kg weight loss and a decrease in BMI of 6 kg/m^2, S(I) improved in all obese participants, Φ decreased in obese participants with NFG and IFG and tended to decrease in obese participants with T2DM, and β-cell function improved in obese participants with NFG and tended to improve in obese participants with IFG. At 2 years, β-cell function deteriorated in participants with NFG and T2DM but remained significantly better in participants with IFG compared to baseline.

Conclusions: Short-term weight loss improves β-cell function in participants with NFG and IFG, but β-cell function tends to deteriorate over 2 years. In participants with IFG, weight loss improves longer-term β-cell function relative to baseline and likely relative to no intervention, suggesting that obese people with IFG are a subpopulation whose β-cell function is most likely to benefit from weight loss. **(*J Clin Endocrinol Metab* 105: e1621–e1630, 2020)**

Key Words: type 2 diabetes, insulin sensitivity, insulin secretion, weight loss

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Insulin resistance is a hallmark of obesity (1, 2). Pancreatic β-cells normally adapt to the insulin resistance of obesity by increasing insulin secretion in

Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; BMI, body mass index; FPG, fasting plasma glucose; IFG, impaired fasting glucose;NFG, normal fasting glucose; T2DM, type 2 diabetes;VLED, very-low-energy diet;WMP, Weight Management Program.

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ARTICLE

An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study

Shuai Yuan [1] · Susanna C. Larsson [1,2]

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Abstract

Aims/hypothesis The aim of this study was to use Mendelian randomisation (MR) to identify the causal risk factors for type 2 diabetes.

Methods We first conducted a review of meta-analyses and review articles to pinpoint possible risk factors for type 2 diabetes. Around 170 possible risk factors were identified of which 97 risk factors with available genetic instrumental variables were included in MR analyses. To reveal more risk factors that were not included in our MR analyses, we conducted a review of published MR studies of type 2 diabetes. For our MR analyses, we used summary-level data from the DIAbetes Genetics Replication And Meta-analysis consortium (74,124 type 2 diabetes cases and 824,006 controls of European ancestry). Potential causal associations were replicated using the FinnGen consortium (11,006 type 2 diabetes cases and 82,655 controls of European ancestry). The inverse-variance weighted method was used as the main analysis. Multivariable MR analysis was used to assess whether the observed associations with type 2 diabetes were mediated by BMI. We used the Benjamini–Hochberg method that controls false discovery rate for multiple testing.

Results We found evidence of causal associations between 34 exposures (19 risk factors and 15 protective factors) and type 2 diabetes. Insomnia was identified as a novel risk factor (OR 1.17 [95% CI 1.11, 1.23]). The other 18 risk factors were depression, systolic BP, smoking initiation, lifetime smoking, coffee (caffeine) consumption, plasma isoleucine, valine and leucine, liver alanine aminotransferase, childhood and adulthood BMI, body fat percentage, visceral fat mass, resting heart rate, and four plasma fatty acids. The 15 exposures associated with a decreased risk of type 2 diabetes were plasma alanine, HDL- and total cholesterol, age at menarche, testosterone levels, sex hormone binding globulin levels (adjusted for BMI), birthweight, adulthood height, lean body mass (for women), four plasma fatty acids, circulating 25-hydroxyvitamin D and education years. Eight associations remained after adjustment for adulthood BMI. We additionally identified 21 suggestive risk factors ($p < 0.05$), such as alcohol consumption, breakfast skipping, daytime napping, short sleep, urinary sodium, and certain amino acids and inflammatory factors.

Conclusions/interpretation The present study verified several previously reported risk factors and identified novel potential risk factors for type 2 diabetes. Prevention strategies for type 2 diabetes should be considered from multiple perspectives on obesity, mental health, sleep quality, education level, birthweight and smoking.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-020-05253-x) contains supplementary material, which is available to authorised users.

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ARTICLE

Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study

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Abstract

Aims/hypothesis We aimed to investigate whether the impact of obesity and unfavourable lifestyle on type 2 diabetes risk is accentuated by genetic predisposition.

Methods We examined the joint association of genetic predisposition, obesity and unfavourable lifestyle with incident type 2 diabetes using a case-cohort study nested within the Diet, Cancer and Health cohort in Denmark. The study sample included 4729 individuals who developed type 2 diabetes during a median 14.7 years of follow-up, and a randomly selected cohort sample of 5402 individuals. Genetic predisposition was quantified using a genetic risk score (GRS) comprising 193 known type 2 diabetes-associated loci (excluding known BMI loci) and stratified into low (quintile 1), intermediate and high (quintile 5) genetic risk groups. Lifestyle was assessed by a lifestyle score composed of smoking, alcohol consumption, physical activity and diet. We used Prentice-weighted Cox proportional-hazards models to test the associations of the GRS, obesity and lifestyle score with incident type 2 diabetes, as well as the interactions of the GRS with obesity and unfavourable lifestyle in relation to incident type 2 diabetes.

Results Obesity (BMI ≥ 30 kg/m^2) and unfavourable lifestyle were associated with higher risk for incident type 2 diabetes regardless of genetic predisposition ($p > 0.05$ for GRS–obesity and GRS–lifestyle interaction). The effect of obesity on type 2 diabetes risk (HR 5.81 [95% CI 5.16, 6.55]) was high, whereas the effects of high genetic risk (HR 2.00 [95% CI 1.76, 2.27]) and unfavourable lifestyle (HR 1.18 [95% CI 1.06, 1.30]) were relatively modest. Even among individuals with low GRS and favourable lifestyle, obesity was associated with a >8-fold risk of type 2 diabetes compared with normal-weight individuals in the same GRS and lifestyle stratum.

Conclusions/interpretation Having normal body weight is crucial in the prevention of type 2 diabetes, regardless of genetic predisposition.

RESEARCH

Intrauterine exposure to diabetes and risk of cardiovascular disease in adolescence and early adulthood: a population-based birth cohort study

Laetitia Guillemette PhD, Brandy Wicklow MD, Elizabeth A.C. Sellers MD, Allison Dart MD, Garry X. Shen MD, Vernon W. Dolinsky PhD, Joseph W. Gordon PhD, Davinder S. Jassal MD, Nathan Nickel PhD, Todd A. Duhamel PhD, Dan Chateau PhD, Heather J. Prior MSc, Jonathan McGavock PhD

■ Cite as: *CMAJ* 2020 September 28;192:E1104-13. doi: 10.1503/cmaj.190797

ABSTRACT

BACKGROUND: It is unclear whether intrauterine exposure to maternal diabetes is associated with risk factors for cardiovascular disease and related end points in adulthood. We examined this potential association in a population-based birth cohort followed up to age 35 years.

METHODS: We performed a cohort study of offspring born between 1979 and 2005 (n = 293 546) and followed until March 2015 in Manitoba, Canada, using registry-based administrative data. The primary exposures were intrauterine exposure to gestational diabetes and type 2 diabetes mellitus. The primary outcome was a composite measure of incident cardiovascular disease events, and the secondary outcome was a composite of risk factors for cardiovascular disease in offspring followed up to age 35 years.

RESULTS: The cohort provided 3 628 576 person-years of data (mean age at latest follow-up 20.5 [standard deviation 6.4] years, 49.3% female); 2765 (0.9%) of the offspring experienced a cardiovascular disease end point, and 12 673 (4.3%) experienced a cardiovascular disease risk factor. After propensity score matching, the hazard for cardiovascular disease end points was elevated in offspring exposed to gestational diabetes (adjusted hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.12–1.79) but not type 2 diabetes (adjusted HR 1.40, 95% CI 0.98–2.01). A similar association was observed for cardiovascular disease risk factors (gestational diabetes: adjusted HR 1.92, 95% CI 1.75–2.11; type 2 diabetes: adjusted HR 3.40, 95% CI 3.00–3.85).

INTERPRETATION: Intrauterine exposure to maternal diabetes was associated with higher morbidity and risk related to cardiovascular disease among offspring up to 35 years of age.

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Clinical Research Article

Clinical Research Article

Physical Activity, Genetic Susceptibility, and the Risk of Latent Autoimmune Diabetes in Adults and Type 2 Diabetes

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Abbreviations: ANDIS, All New Diabetics in Scania; ANDiU, All New Diabetics in Uppsala; BMI, body mass index; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; ESTRID, Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes; FHD, family history of diabetes; FTO, fat mass and obesity-associated gene; GADA, glutamic acid decarboxylase antibody; HLA, human leukocyte antigen; HOMA-β, homeostasis model assessment–estimating β-cell function; HOMA-IR, homeostasis model assessment–insulin resistance;HUNT, Nord-Trøndelag Health Study; LADA, latent autoimmune diabetes in adults; PA, physical activity; RR, relative risk; SNV, single-nucleotide variation; TCF7L2, transcription factor 7-like 2 gene.

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Purpose: Physical activity (PA) has been linked to a reduced risk of type 2 diabetes by reducing weight and improving insulin sensitivity. We investigated whether PA is associated with a lower incidence of latent autoimmune diabetes in adults (LADA) and whether the association is modified by genotypes of human leukocyte antigen (HLA), transcription factor 7-like 2 (*TCF7L2*)-rs7903146, or the fat mass and obesity-associated gene, *FTO*-rs9939609.

Methods: We combined data from a Swedish case-control study and a Norwegian prospective study including 621 incident cases of LADA and 3596 cases of type 2 diabetes. We estimated adjusted pooled relative risks (RRs) and 95% CI of diabetes in relation to high (≥ 30 minutes of moderate activity 3 times/week) self-reported leisure time PA, compared to sedentariness.

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2-year remission of type 2 diabetes and pancreas morphology: a post-hoc analysis of the DiRECT open-label, cluster-randomised trial

*Ahmad Al-Mrabeh, Kieren G Hollingsworth, James A M Shaw, Alex McConnachie, Naveed Sattar, Michael E J Lean, Roy Taylor**

Summary

Background The pancreas is small and irregular in shape in people with type 2 diabetes. If these abnormalities are caused by the disease state itself rather than being a predisposing factor, remission of type 2 diabetes should restore normal pancreas morphology. The objective of this study was to determine whether changes in pancreas volume and shape occurred during 2 years of remission.

Methods For this post-hoc analysis, we included a subset of adult participants of the Diabetes Remission Clinical Trial (DiRECT), who had type 2 diabetes and were randomly assigned to a weight management intervention or routine diabetes management. Intervention group participants were categorised as responders (HbA_{1c} <6·5% [48 mmol/mol] and fasting blood glucose <7·0 mmol/L, off all anti-diabetes medication) and non-responders, who were classified as remaining diabetic. Data on pancreas volume and irregularity of pancreas border at baseline, 5 months, 12 months, and 24 months after intervention were compared between responders and non-responders; additional comparisons were made between control group participants with type 2 diabetes and a non-diabetic comparator (NDC) group, who were matched to the intervention group by age, sex, and post-weight-loss weight, to determine the extent of any normalisation. We used a mixed-effects regression model based on repeated measures ANOVA with correction for potential confounding. Magnetic resonance techniques were employed to quantify pancreas volume, the irregularity of the pancreas borders, and intrapancreatic fat content. β-cell function and biomarkers of tissue growth were also measured.

Findings Between July 25, 2015, and Aug 5, 2016, 90 participants with type 2 diabetes in the DiRECT subset were randomly assigned to intervention (n=64) or control (n=26) and were assessed at baseline; a further 25 non-diabetic participants were enrolled into the NDC group. At baseline, mean pancreas volume was 61·7 cm³ (SD 16·0) in all participants with type 2 diabetes and 79·8 cm³ (14·3) in the NDC group (p<0·0001). At 24 months, pancreas volume had increased by 9·4 cm³ (95% CI 6·1 to 12·8) in responders compared with 6·4 cm³ (2·5 to 10·3) in non-responders (p=0·0008). Pancreas borders at baseline were more irregular in participants with type 2 diabetes than in the NDC group (fractal dimension 1·138 [SD 0·027] *vs* 1·097 [0·025]; p<0·0001) and had normalised by 24 months in responders only (1·099 [0·028]). Intrapancreatic fat declined by 1·02 percentage points (95% CI 0·53 to 1·51) in 32 responders and 0·51% (–0·17 to 1·19) in 13 non-responders (p=0·23).

Interpretation These data show for the first time, to our knowledge, reversibility of the abnormal pancreas morphology of type 2 diabetes by weight loss-induced remission.

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Diabetes Care Volume 43, November 2020

Replacement of Red and Processed Meat With Other Food Sources of Protein and the Risk of Type 2 Diabetes in European Populations: The EPIC-InterAct Study

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OBJECTIVE

There is sparse evidence for the association of suitable food substitutions for red and processed meat on the risk of type 2 diabetes. We modeled the association between replacing red and processed meat with other protein sources and the risk of type 2 diabetes and estimated its population impact.

RESEARCH DESIGN AND METHODS

The European Prospective Investigation into Cancer (EPIC)-InterAct case cohort included 11,741 individuals with type 2 diabetes and a subcohort of 15,450 participants in eight countries. We modeled the replacement of self-reported red and processed meat with poultry, fish, eggs, legumes, cheese, cereals, yogurt, milk, and nuts. Country-specific hazard ratios (HRs) for incident type 2 diabetes were estimated by Prentice-weighted Cox regression and pooled using random-effects meta-analysis.

RESULTS

There was a lower hazard for type 2 diabetes for the modeled replacement of red and processed meat (50 g/day) with cheese (HR 0.90, 95% CI 0.83–0.97) (30 g/day), yogurt (0.90, 0.86–0.95) (70 g/day), nuts (0.90, 0.84–0.96) (10 g/day), or cereals (0.92, 0.88–0.96) (30 g/day) but not for replacements with poultry, fish, eggs, legumes, or milk. If a causal association is assumed, replacing red and processed meat with cheese, yogurt, or nuts could prevent 8.8%, 8.3%, or 7.5%, respectively, of new cases of type 2 diabetes.

CONCLUSIONS

Replacement of red and processed meat with cheese, yogurt, nuts, or cereals was associated with a lower rate of type 2 diabetes. Substituting red and processed meat by other protein sources may contribute to the prevention of incident type 2 diabetes in European populations.

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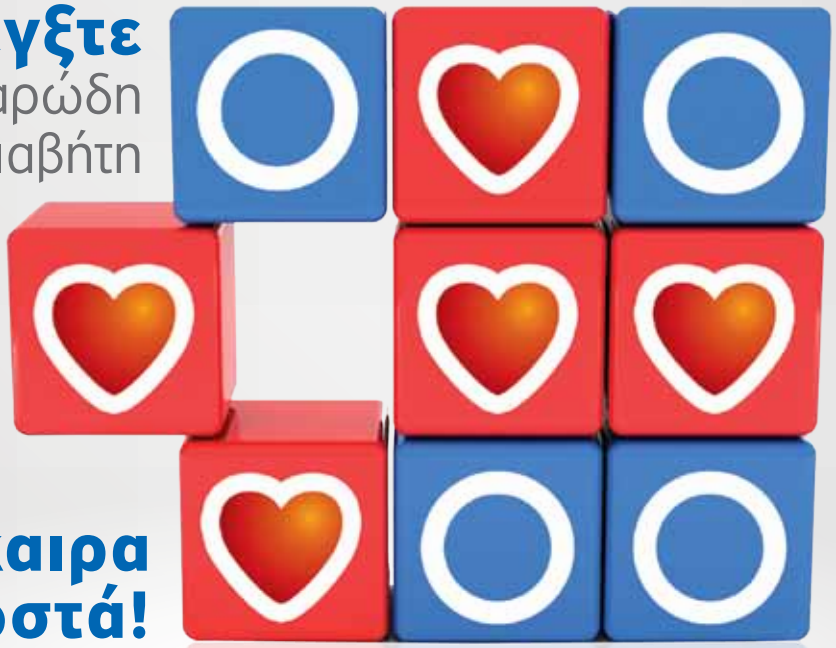

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ARTICLE

Pregnancy loss is associated with type 2 diabetes: a nationwide case–control study

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Abstract

Aims/hypothesis Type 2 diabetes is killing more people than ever, and early-life predictors remain critical for the development of effective preventive strategies. Pregnancy loss is a common event associated with later atherosclerotic disease and ischaemic heart failure and might constitute a predictor for type 2 diabetes. The objective of this study was to investigate whether pregnancy loss is associated with later development of type 2 diabetes.

Methods Using a Danish nationwide cohort, we identified all women born from 1957 through to 1997 and who had a diagnosis of type 2 diabetes during the period 1977 to 2017. The women were matched 1:10 on year of birth and educational level to women without diabetes in the general Danish population. Conditional logistic regression models provided odds ratios for type 2 diabetes with different numbers of pregnancy losses.

Results We identified 24,774 women with type 2 diabetes and selected 247,740 controls without diabetes. Women who had ever been pregnant (ever-pregnant women) with 1, 2 and ≥3 pregnancy losses had ORs of type 2 diabetes of 1.18 (95% CI 1.13, 1.23), 1.38 (95% CI 1.27, 1.49) and 1.71 (95% CI 1.53, 1.92) compared with ever-pregnant women with no pregnancy losses, respectively. Women who never achieved a pregnancy had an OR of type 2 diabetes of 1.56 (95% CI 1.51, 1.61) compared with ever-pregnant women with any number of losses. Similar results were found after adjustment for obesity and gestational diabetes.

Conclusions/interpretation We found a significant and consistent association between pregnancy loss and later type 2 diabetes that increased with increasing number of losses. Thus, pregnancy loss and recurrent pregnancy loss are significant risk factors for later type 2 diabetes. Future studies should explore whether this association is due to common background factors or whether prediabetic metabolic conditions are responsible for this association.

Keywords Miscarriage · Pregnancy loss · Recurrent pregnancy loss · Reproduction · Type 2 diabetes

ORIGINAL RESEARCH

Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies

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JY and QH are joint first authors.

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ABSTRACT

Objective The association between the regular use of proton pump inhibitors (PPIs) and the risk of type 2 diabetes remains unclear, although a recent randomised controlled trial showed a trend towards increased risk. This study was undertaken to evaluate the regular use of PPIs and risk of type 2 diabetes.

Method This is a prospective analysis of 204 689 participants free of diabetes in the Nurses' Health Study (NHS), NHS II and Health Professionals Follow-up Study (HPFS). Type 2 diabetes was confirmed using American Diabetes Association (ADA) diagnostic criteria. We evaluated hazard ratios (HRs) adjusting for demographic factors, lifestyle habits, the presence of comorbidities, use of other medications and clinical indications.

Results We documented 10 105 incident cases of diabetes over 2 127 471 person-years of follow-up. Regular PPI users had a 24% higher risk of diabetes than non-users (HR 1.24, 95% CI 1.17 to 1.31). The risk of diabetes increased with duration of PPI use. Fully adjusted HRs were 1.05 (95% CI 0.93 to 1.19) for participants who used PPIs for >0–2 years and 1.26 (95% CI 1.18 to 1.35) for participants who used PPIs for >2 years compared with non-users.

Conclusions Regular use of PPIs was associated with a higher risk of type 2 diabetes and the risk increased with longer duration of use. Physicians should therefore exercise caution when prescribing PPIs, particularly for long-term use.

Significance of this study

What is already known about this subject?
- Despite the irreplaceable role of proton pump inhibitors (PPIs) in clinical practice, long-term use of PPIs has been linked to a series of health problems such as bone fracture and enteric infections.
- PPIs have a major impact on gut microbiome which, in turn, may increase the risk of type 2 diabetes, but epidemiological evidence remains unclear.

What are the new findings?
- In this prospective analysis of 204 689 participants free of diabetes from three ongoing US cohorts, regular use of PPIs was associated with a 24% increased risk of diabetes even after adjusting for putative risk factors and indications for use, with a higher risk observed in individuals with a longer duration of PPI use.

How might it impact on clinical practice in the foreseeable future?
- Physicians should be aware of the potential risk of type 2 diabetes when prescribing PPIs, particularly for long-term treatment.
- Screening for abnormal blood glucose and type 2 diabetes may be required for regular PPI users, particularly for high-risk populations.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the top 10 most commonly used medications worldwide.[1] PPIs are routinely recommended for acid-related disorders such as gastro-oesophageal reflux disease, peptic ulcer disease and non-ulcer dyspepsia.[2] It is generally accepted that short-term use of PPIs for valid indications is safe. However, long-term use of PPIs has been linked to various adverse effects such as bone fractures, chronic kidney disease, enteric infections and gastric cancer.[2–5] Recent studies have shown that PPIs can affect gut microbial communities by shifting the native gastrointestinal tract milieu.[6 7] At a population level, PPIs may have an even more pronounced effect on gut microbiome than other commonly used drugs such as antibiotics, leading to warnings of overuse of PPIs and calls for further investigation into the sequelae of long-term PPI consumption.[6]

Type 2 diabetes has become a global epidemic with a worldwide prevalence of 8.5% in 2014.[8] The aetiology of type 2 diabetes is complex, involving multiple genetic, behavioural and environmental factors.[9] In recent years, researchers have turned their attention to the role of human gut microbiota, which is essential for expanding the repertoire of host metabolic processes, in the development of diabetes.[10 11] Accumulating studies support a causal role for alterations in the gut microbiota in the pathogenesis of metabolic diseases.[12 13]

Given the pronounced effect of PPIs on the gut microbiome, its use may be associated with an

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Diabetes Care

Combination Therapy With Canagliflozin Plus Liraglutide Exerts Additive Effect on Weight Loss, but Not on HbA_{1c}, in Patients With Type 2 Diabetes

Ali Muhammed Ali, Robert Martinez, Hussein Al-Jobori, John Adams, Curtis Triplitt, Ralph DeFronzo, Eugenio Cersosimo, and Muhammad Abdul-Ghani

https://doi.org/10.2337/dc18-2460

OBJECTIVE

To examine the effect of combination therapy with canagliflozin plus liraglutide on HbA_{1c}, endogenous glucose production (EGP), and body weight versus each therapy alone.

RESEARCH DESIGN AND METHODS

Forty-five patients with poorly controlled (HbA_{1c} 7–11%) type 2 diabetes mellitus (T2DM) on metformin with or without sulfonylurea received a 9-h measurement of EGP with [3-^{3}H]glucose infusion, after which they were randomized to receive *1*) liraglutide 1.2 mg/day (LIRA); *2*) canagliflozin 100 mg/day (CANA); or *3*) liraglutide 1.2 mg plus canagliflozin 100 mg (CANA/LIRA) for 16 weeks. At 16 weeks, the EGP measurement was repeated.

RESULTS

The mean decrease from baseline to 16 weeks in HbA_{1c} was −1.67 ± 0.29% (P = 0.0001), −0.89 ± 0.24% (P = 0.002), and −1.44 ± 0.39% (P = 0.004) in patients receiving CANA/LIRA, CANA, and LIRA, respectively. The decrease in body weight was −6.0 ± 0.8 kg (P < 0.0001), −3.5 ± 0.5 kg (P < 0.0001), and −1.9 ± 0.8 kg (P = 0.03), respectively. CANA monotherapy caused a 9% increase in basal rate of EGP (P < 0.05), which was accompanied by a 50% increase (P < 0.05) in plasma glucagon-to-insulin ratio. LIRA monotherapy reduced plasma glucagon concentration and inhibited EGP. In CANA/LIRA-treated patients, EGP increased by 15% (P < 0.05), even though the plasma insulin response was maintained at baseline and the CANA-induced rise in plasma glucagon concentration was blocked.

CONCLUSIONS

These results demonstrate that liraglutide failed to block the increase in EGP caused by canagliflozin despite blocking the rise in plasma glucagon and preventing the decrease in plasma insulin concentration caused by canagliflozin. The failure of liraglutide to prevent the increase in EGP caused by canagliflozin explains the lack of additive effect of these two agents on HbA_{1c}.

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ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

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*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study

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Summary

Background Cardiovascular and kidney outcome trials have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors slow progression of chronic kidney disease in patients with type 2 diabetes with or without chronic kidney disease. The aim of this study was to assess whether these benefits extend to patients with type 2 diabetes treated in routine clinical practice.

Methods CVD-REAL 3 was a multinational observational cohort study in which new users of SGLT2 inhibitors and other glucose-lowering drugs with measurements of estimated glomerular filtration rate (eGFR) before and after (within 180 days) initiation were identified via claims, medical records, and national registries in Israel, Italy, Japan, Taiwan, and the UK. Propensity scores for SGLT2 inhibitor initiation were developed in each country, with 1:1 matching with initiators of other glucose-lowering drugs. Propensity score included (in addition to other clinical and demographic variables) baseline eGFR and eGFR slope before SGLT2 inhibitor or other glucose-lowering drug initiation. The main outcome measure was rate of eGFR decline (slope) calculated with a linear mixed regression model. Differences in eGFR slope between SGLT2 inhibitors and other glucose-lowering drugs were calculated and pooled. We also assessed a composite outcome of 50% eGFR decline or end-stage kidney disease.

Findings After propensity matching, there were 35 561 episodes of treatment initiation in each group, from 65 231 individual patients. Dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin accounted for 57·9%, 34·1%, 5·7%, 1·4%, 0·5%, and 0·4% of SGLT2 inhibitor initiation episodes, respectively. At baseline, 29 363 (41·3%) of 71 122 initiations were in women, mean age was 61·3 years, mean HbA_{1c} was 72 mmol/mol (8·71%), and mean eGFR was 90·7 mL/min per 1·73 m². During follow-up, SGLT2 inhibitor initiation was associated with reduced eGFR decline (difference in slope for SGLT2 inhibitors *vs* other glucose-lowering drugs 1·53 mL/min per 1·73 m² per year, 95% CI 1·34–1·72, p<0·0001). During a mean follow-up of 14·9 months, 351 composite kidney outcomes occurred: 114 (3·0 events per 10 000 patient-years) among initiators of SGLT2 inhibitors and 237 (6·3 events per 10 000 patient-years) among initiators of other glucose-lowering drugs (hazard ratio 0·49, 95% CI 0·35–0·67; p<0·0001). These findings were consistent across countries ($p_{heterogeneity}$ 0·10) and prespecified subgroups.

Interpretation In this large, international, real-world study of patients with type 2 diabetes, initiation of SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared with initiation of other glucose-lowering drugs. These data suggest that the benefits of SGLT2 inhibitors on kidney function identified in clinical trials seem to be largely generalisable to clinical practice.

Funding AstraZeneca.

Introduction

Since the introduction of the regulatory requirement to test the cardiovascular safety of new glucose-lowering drugs for marketing authorisation, many large clinical trials in patients with type 2 diabetes have been completed. These trials showed that sodium-glucose co-transporter-2 (SGLT2) inhibitors substantially reduced the risk of hospital admission for heart failure and slowed the progression of kidney function decline in patients with type 2 diabetes with or without chronic kidney disease.[1–4]

Assessing whether the results of these clinical trials are applicable to the broader range of patient populations treated in clinical practice is of importance to determine the magnitude of effectiveness of SGLT2 inhibitor use. The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors) study showed that the benefits of SGLT2 inhibitors in reducing the risk of cardiovascular events and heart failure extend to a large, broad patient population with type 2 diabetes treated in clinical practice, with findings consistent in various parts of the world.[5–7] However,

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.

METHODS

In this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m^2 of body-surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2. All the patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).

CONCLUSIONS

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

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*A complete list of the FIDELIO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial

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*A list of collaborators in the MiTy trial is provided in the appendix (pp 4–10)

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Summary

Background Although metformin is increasingly being used in women with type 2 diabetes during pregnancy, little data exist on the benefits and harms of metformin use on pregnancy outcomes in these women. We aimed to investigate the effects of the addition of metformin to a standard regimen of insulin on neonatal morbidity and mortality in pregnant women with type 2 diabetes.

Methods In this prospective, multicentre, international, randomised, parallel, double-masked, placebo-controlled trial, women with type 2 diabetes during pregnancy were randomly assigned from 25 centres in Canada and four in Australia to receive either metformin 1000 mg twice daily or placebo, added to insulin. Randomisation was done via a web-based computerised randomisation service and stratified by centre and pre-pregnancy BMI (<30 kg/m² or ≥30 kg/m²) in a ratio of 1:1 using random block sizes of 4 and 6. Women were eligible if they had type 2 diabetes, were on insulin, had a singleton viable pregnancy, and were between 6 and 22 weeks plus 6 days' gestation. Participants were asked to check their fasting blood glucose level before the first meal of the day, before the last meal of the day, and 2 h after each meal. Insulin doses were adjusted aiming for identical glucose targets (fasting glucose <5·3 mmol/L [95 mg/dL], 2-h postprandial glucose <6·7 mmol/L [120 mg/dL]). Study visits were done monthly and patients were seen every 1–4 weeks as was needed for standard clinical care. At study visits blood pressure and bodyweight were measured; patients were asked about tolerance to their pills, any hospitalisations, insulin doses, and severe hypoglycaemia events; and glucometer readings were downloaded to the central coordinating centre. Participants, caregivers, and outcome assessors were masked to the intervention. The primary outcome was a composite of fetal and neonatal outcomes, for which we calculated the relative risk and 95% CI between groups, stratifying by site and BMI using a log-binomial regression model with an intention-to-treat analysis. Secondary outcomes included several relevant maternal and neonatal outcomes. The trial was registered with ClinicalTrials.gov, NCT01353391.

Findings Between May 25, 2011, and Oct 11, 2018, we randomly assigned 502 women, 253 (50%) to metformin and 249 (50%) to placebo. Complete data were available for 233 (92%) participants in the metformin group and 240 (96%) in the placebo group for the primary outcome. We found no significant difference in the primary composite neonatal outcome between the two groups (40% *vs* 40%; p=0·86; relative risk [RR] 1·02 [0·83 to 1·26]). Compared with women in the placebo group, metformin-treated women achieved better glycaemic control (HbA_{1c} at 34 weeks' gestation 41·0 mmol/mol [SD 8·5] *vs* 43·2 mmol/mol [–10]; 5·90% *vs* 6·10%; p=0·015; mean glucose 6·05 [0·93] mmol/L *vs* 6·27 [0·90] mmol/L; difference –0·2 [–0·4 to 0·0]), required less insulin (1·1 units per kg per day *vs* 1·5 units per kg per day; difference –0·4 [95% CI –0·5 to –0·2]; p<0·0001), gained less weight (7·2 kg *vs* 9·0 kg; difference –1·8 [–2·7 to –0·9]; p<0·0001) and had fewer caesarean births (125 [53%] of 234 in the metformin group *vs* 148 [63%] of 236 in the placebo group; relative risk [RR] 0·85 [95% CI 0·73 to 0·99]; p=0·031). We found no significant difference between the groups in hypertensive disorders (55 [23%] in the metformin group *vs* 56 [23%] in the placebo group; p=0·93; RR 0·99 [0·72 to 1·35]). Compared with those in the placebo group, metformin-exposed infants weighed less (mean birthweight 3156 g [SD 742] *vs* 3375 g [742]; difference –218 [–353 to –82]; p=0·002), fewer were above the 97th centile for birthweight (20 [9%] in the metformin group *vs* 34 [15%] in the placebo group; RR 0·58 [0·34 to 0·97]; p=0·041), fewer weighed 4000 g or more at birth (28 [12%] in the metformin group *vs* 44 [19%] in the placebo group; RR 0·65 [0·43 to 0·99]; p=0·046), and metformin-exposed infants had reduced adiposity measures (mean sum of skinfolds 16·0 mm [SD 5·0] *vs* 17·4 [6·2] mm; difference –1·41 [–2·6 to –0·2]; p=0·024; mean neonatal fat mass 13·2 [SD 6·2] *vs* 14·6 [5·0]; p=0·017). 30 (13%) infants in the metformin group and 15 (7%) in the placebo group were small for gestational age (RR 1·96 [1·10 to 3·64]; p=0·026). We found no significant difference in the cord c-peptide between groups (673 pmol/L [435] in the metformin group *vs* 758 pmol/L [595] in the placebo group; p=0·10; ratio of means 0·88 [0·72 to 1·02]). The most common adverse event reported was gastrointestinal (38 [27%] events in the metformin group and 38 [22%] events in the placebo group).

Interpretation We found several maternal glycaemic and neonatal adiposity benefits in the metformin group. Along with reduced maternal weight gain, insulin dosage, and rate of caesarean sections, and improved glyacaemic

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

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ABSTRACT

BACKGROUND

It is thought that a reduction in the frequency of basal insulin injections might facilitate treatment acceptance and adherence among patients with type 2 diabetes. Insulin icodec is a basal insulin analogue designed for once-weekly administration that is in development for the treatment of diabetes.

METHODS

We conducted a 26-week, randomized, double-blind, double-dummy, phase 2 trial to investigate the efficacy and safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100 in patients who had not previously received long-term insulin treatment and whose type 2 diabetes was inadequately controlled (glycated hemoglobin level, 7.0 to 9.5%) while taking metformin with or without a dipeptidyl peptidase 4 inhibitor. The primary end point was the change in glycated hemoglobin level from baseline to week 26. Safety end points, including episodes of hypoglycemia and insulin-related adverse events, were also evaluated.

RESULTS

A total of 247 participants were randomly assigned (1:1) to receive icodec or glargine. Baseline characteristics were similar in the two groups; the mean baseline glycated hemoglobin level was 8.09% in the icodec group and 7.96% in the glargine group. The estimated mean change from baseline in the glycated hemoglobin level was −1.33 percentage points in the icodec group and −1.15 percentage points in the glargine group, to estimated means of 6.69% and 6.87%, respectively, at week 26; the estimated between-group difference in the change from baseline was −0.18 percentage points (95% CI, −0.38 to 0.02, P=0.08). The observed rates of hypoglycemia with severity of level 2 (blood glucose level, <54 mg per deciliter) or level 3 (severe cognitive impairment) were low (icodec group, 0.53 events per patient-year; glargine group, 0.46 events per patient-year; estimated rate ratio, 1.09; 95% CI, 0.45 to 2.65). There was no between-group difference in insulin-related key adverse events, and rates of hypersensitivity and injection-site reactions were low. Most adverse events were mild, and no serious events were deemed to be related to the trial medications.

CONCLUSIONS

Once-weekly treatment with insulin icodec had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine U100 in patients with type 2 diabetes. (Funded by Novo Nordisk; NN1436-4383 ClinicalTrials.gov number, NCT03751657.)

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*A list of principal investigators in this trial is available in the Supplementary Appendix, available at NEJM.org.

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FROM RESEARCH TO PRACTICE

Diabetes, Therapeutic Inertia, and Patients' Medication Experience

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Factors contributing to therapeutic inertia related to patients' medication experiences include concerns about side effects and out-of-pocket costs, stigmatization for having diabetes, confusion about frequent changes in evidence-based guidelines, low health literacy, and social determinants of health. A variety of solutions to this multifactorial problem may be necessary, including integrating pharmacists into interprofessional care teams, using medication refill synchronization programs, maximizing time with patients to discuss fears and concerns, being cognizant of language used to discuss diabetes-related topics, and avoiding stigmatizing patients. Managing diabetes successfully is a team effort, and the full commitment of all team members (including patients) is required to achieve desired outcomes through an individualized approach.

Despite decades of research investigating the importance of achieving diabetes-related goals and countless innovations introduced in the field of diabetes, slightly less than half of adults living with diabetes in the United States met recommended goals for comprehensive diabetes care in 2010 (1). A subsequent analysis looking at individualized A1C targets noted a slight decline in patients achieving their glycemic goals from 2003 to 2014, with only 64% of adults with diabetes achieving their individualized A1C goal (2). The factors contributing to this phenomenon are various, ranging from patient-level decisions to the current landscape of the U.S. health care delivery system (3). Regardless, therapeutic inertia is one of the most significant reasons for this phenomenon. To complement the perspectives of other articles in this *Diabetes Spectrum* From Research to Practice section, this article focuses on therapeutic inertia directly related to patients' medication experiences.

Relevant Definitions

"Clinical inertia" has been defined previously as "the failure of health care providers to initiate or intensify therapy when indicated, caused by overestimation of care provided, use of 'soft' reasons to avoid intensification of therapy, and/or lack of education, training, and practice organization aimed at achieving therapeutic goals" (4). Unfortunately, this definition only speaks to the actions of health care providers, and multiple other factors also contribute to delays in helping patients achieve their diabetes-related goals, including patient- and health system–related factors (5,6). Therefore, the term "therapeutic inertia" will be used in this article to encompass this broader range of factors (7).

Another important term to introduce is the "medication experience," a practice concept that refers to seeking to understand patients' experiences with medications and medication-taking behaviors to meet their medication-related needs (8). This concept has four general constructs: a meaningful encounter, bodily effects, unremitting nature, and exerting control. A meaningful encounter is any initial exposure to the medication, ranging from a discussion with a provider or friend about a new medication to administering the first dose of a new medication. The construct of bodily effects encompasses the gamut of outcomes patients experience after initiating a medication, from the positive (e.g., improved glucose levels) to the negative (e.g., adverse effects). The unremitting nature construct speaks to the nature of living with a chronic condition, the importance of medications to help manage that condition, and the psychological toll that having a chronic condition can have on a person. Finally, the construct of exerting control describes how patients may begin to self-adjust their medications to better suit their symptoms or daily routine, mostly for the better (e.g., timing medications around daily activities), but sometimes for the worse (e.g., intentionally omitting doses).

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Διατροφή

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ΟΜΙΛΗΤΗΣ: Άννα Παπαγεωργίου

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Clinical Nutrition

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Original article

Low carbohydrate diet and all cause and cause-specific mortality

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SUMMARY

Background: Evidence is limited regarding the association between low-carbohydrate diet (LCD) score and mortality among Asians, a population that consumes a large amount of carbohydrates.
Objective: The present study examined the association between low-carbohydrate diet (LCD) score (based on percentage of energy as carbohydrate, fat, and protein) and the risk of total and cause-specific mortality among Asians.
Design: This study was a prospective cohort study in Japan with follow-up for a median of 16.9 years involving 43008 men and 50646 women aged 45–75 years. Association of LCD score, LCD score based on animal sources of protein and fat, and LCD score based on plant sources of protein and fat with risk of mortality was assessed using Cox proportional hazards model.
Results: A U-shaped association was observed between LCD score and total mortality: the multivariable-adjusted hazard ratios (HRs) (95% CI) of total mortality for lowest through highest scores were 1.00, 0.95 (0.91, 1.01), 0.93 (0.88, 0.98), 0.93 (0.88, 0.98), and 1.01 (0.95, 1.07) (P-non-linearity <0.01). A similar association was found for mortality from cardiovascular disease (CVD) and heart disease. LCD score based on carbohydrate, animal protein, and animal fat also showed a U-shaped association for total mortality (P-non-linearity <0.01). In contrast, LCD score based on carbohydrate, plant protein, and plant fat was linearly associated with lower total (HR, 0.89; 95% CI: 0.83, 0.94 for highest versus lowest quintile), CVD [0.82 (0.73, 0.92)], heart disease [0.83 (0.71, 0.98)], and cerebrovascular disease [0.75 (0.62, 0.91) mortality.
Conclusions: Both LCD with high animal protein and fat and high-carbohydrate diet with low animal protein and fat were associated with higher risk of mortality. Meanwhile, LCD high in plant-based sources of protein and fat was associated with a lower risk of total and CVD mortality.

Results

As shown in Table 1, participants with higher scores of all LCD were less likely to be male but more likely to have higher BMI and a history of diabetes and consumed higher amount of green tea. Participants with higher score of total and animal-based protein and fat scores were more likely to be alcohol drinkers. In addition, participants with higher plant-based protein and fat score were less likely to be alcohol drinker and smoker. With respect to specific nutrients, all LCD scores were positively associated with animal fat, plant fat, and animal protein intake but inversely associated with plant protein intake (except LCD score based on plant protein and plant fat). During the median follow-up of 16.9 years, the number of deaths from all-causes, cancer, CVD, heart disease, and cerebrovascular disease were 13179,

5246, 3450, 1811, and 1358, respectively. LCD score was nonlinearly associated with the risk of total mortality (Table 2). After adjustment for age, sex, study area, BMI, smoking status, alcohol consumption, physical activity, history of hypertension, history of diabetes, history of dyslipidemia, occupation, energy intake, coffee, and green tea consumption, the HRs (95% CI) of mortality for the lowest through highest quintiles of the score were 1.00 (reference), 0.95 (0.91e1.01), 0.93 (0.88e0.98), 0.93 (0.88e0.98), and 1.01 (0.95e1.07) (P for trend ¼ 0.52 and P for nonlinearity

Table 1
Age- and sex-adjusted baseline characteristics of the study participants by quintile categories of low-carbohydrate diet score.

	Low-carbohydrate diet score			Low-carbohydrate score based on animal sources of protein and fat			Low-carbohydrate diet score based on plant sources of protein and fat		
	Q1(Low)	Q3	Q5(High)	Q1(Low)	Q3	Q5(High)	Q1(Low)	Q3	Q5(High)
N	22204	18823	16480	20796	21203	18134	21651	17522	15952
Median score	5	15	26	4	15	27	8	15	23
Age (years)	57.1 ± 0.05[a]	56.0 ± 0.06	56.7 ± 0.06	57.3 ± 0.05	56.0 ± 0.05	56.4 ± 0.06	56.8 ± 0.05	56.2 ± 0.06	56.7 ± 0.06
Sex (men, %)	54.6	46.8	33.0	47.4	47.0	40.0	61.8	44.7	29.1
BMI (kg/m^2)	23.4 ± 0.02	23.5 ± 0.02	23.6 ± 0.02	23.4 ± 0.02	23.5 ± 0.02	23.6 ± 0.02	23.4 ± 0.02	23.5 ± 0.02	23.6 ± 0.02
Current smoker (%)	18.0	16.8	15.4	16.8	16.9	16.8	20.4	16.3	14.0
Alcohol drinker (≥1 d/week, %)	31.7	40.0	33.9	27.4	40.6	38.4	38.7	36.7	33.3
Total physical activity (MET-h/day)	33.1 ± 0.05	33.05 ± 0.05	33.1 ± 0.05	33.2 ± 0.05	33.1 ± 0.05	33.1 ± 0.05	33.0 ± 0.05	33.1 ± 0.05	33.2 ± 0.05
History of hypertension (%)	16.2	17.3	16.4	16.6	17.4	16.4	15.7	16.7	17.3
History of diabetes (%)	3.6	4.7	5.5	3.7	4.6	5.2	3.9	4.3	5.9
History of dyslipidaemia (%)	4.4	5.1	4.1	4.6	5.0	3.9	3.9	4.6	5.0
Occupation (agriculture, forestry, or fishery, %)	19.0	16.2	17.6	19.4	16.3	17.6	18.1	16.9	16.8
Nutrient intake									
Energy (kcal/day)	1715.2 ± 4.5	2013.8 ± 4.8	2440.6 ± 5.2	1749.8 ± 4.7	2010.3 ± 4.6	2406.6 ± 5.0	1800.4 ± 4.7	2050.5 ± 5.2	2238.2 ± 5.5
Carbohydrate (% energy/day)	65.2 ± 0.04	54.2 ± 0.04	42.8 ± 0.05	65.4 ± 0.04	53.7 ± 0.04	43.0 ± 0.04	59.6 ± 0.06	54.1 ± 0.07	49.2 ± 0.07
Fat (% energy/day)	17.6 ± 0.03	25.4 ± 0.03	35.4 ± 0.03	18.1 ± 0.03	25.4 ± 0.03	34.8 ± 0.03	20.1 ± 0.04	26.0 ± 0.05	30.8 ± 0.05
Animal fat (% energy/day)	8.4 ± 0.03	13.7 ± 0.03	22.0 ± 0.03	7.7 ± 0.02	13.7 ± 0.02	22.7 ± 0.02	12.5 ± 0.04	14.7 ± 0.04	14.6 ± 0.05
Plant fat (% energy/day)	9.2 ± 0.02	11.7 ± 0.02	13.4 ± 0.02	10.4 ± 0.02	11.7 ± 0.02	12.1 ± 0.03	7.5 ± 0.01	11.3 ± 0.01	16.2 ± 0.02
Protein (% energy/day)	11.9 ± 0.01	14.3 ± 0.01	17.6 ± 0.01	12.1 ± 0.01	14.3 ± 0.01	17.0 ± 0.01	12.6 ± 0.02	14.5 ± 0.02	16.0 ± 0.02
Animal protein (% energy/day)	4.7 ± 0.01	7.6 ± 0.01	11.6 ± 0.01	4.5 ± 0.01	7.6 ± 0.01	11.5 ± 0.01	6.6 ± 0.02	7.9 ± 0.02	8.2 ± 0.02
Plant protein (% energy/day)	7.2 ± 0.01	6.7 ± 0.01	6.0 ± 0.01	7.6 ± 0.01	6.6 ± 0.01	5.5 ± 0.01	6.0 ± 0.01	6.6 ± 0.01	7.8 ± 0.01
Green tea (≥1 cup/d, %)	75.5	81.1	81.9	76.6	80.7	80.0	72.6	81.2	83.6
Coffee consumption (≥1 cup/d, %)	31.7	36.3	35.8	30.4	36.8	36.9	35.2	34.8	34.5

Abbreviation: MET, metabolic equivalent; BMI, body mass index.
[a] Mean ± S.E. (all such values).

Table 2
Multivariate-adjusted hazard ratios (95% CI) for mortality across quintiles of low-carbohydrate diet score.

	Q1	Q2	Q3	Q4	Q5	P trend[a]	P for non-linearity[b]
N	22204	15625	18823	20522	16480		
Median score (range)	5 (0–8)	10 (9–12)	15 (13–17)	20 (18–23)	26 (24–30)		
Person years	355495	250601	304448	334542	268123		
Total mortality							
No of deaths	3626	2309	2481	2550	2213		
Rate/1000 person years	10.2	9.2	8.1	7.6	8.2		
Model 1[c]	1.00	0.97 (0.92–1.03)	**0.91 (0.86 to 0.96)**	**0.88 (0.83 to 0.92)**	0.96 (0.91–1.01)	0.001	<0.001
Model 2[d]	1.00	0.95 (0.91–1.01)	**0.93 (0.88 to 0.98)**	**0.93 (0.88 to 0.98)**	1.01 (0.95–1.07)	0.52	<0.001
Cancer mortality							
No of deaths	1369	930	1019	1063	865		
Rate/1000 person years	3.8	3.7	3.3	3.2	3.2		
Model 1[c]	1.00	1.02 (0.94–1.11)	0.98 (0.90–1.06)	0.97 (0.89–1.05)	1.00 (0.92–1.09)	0.61	0.56
Model 2[d]	1.00	0.98 (0.90–1.07)	0.98 (0.90–1.07)	0.99 (0.91–1.08)	1.04 (0.95–1.14)	0.53	0.21
Cardiovascular disease mortality							
No of deaths	983	599	631	660	577		
Rate/1000 person years	2.8	2.4	2.1	2.0	2.1		
Model 1[c]	1.00	0.95 (0.85–1.05)	**0.86 (0.77 to 0.95)**	**0.84 (0.76 to 0.92)**	0.90 (0.81–1.00)	0.003	0.01
Model 2[d]	1.00	0.94 (0.85–1.04)	**0.90 (0.81 to 0.99)**	0.90 (0.81–1.00)	0.96 (0.86–1.08)	0.24	0.03
Heart disease mortality							
No of deaths	539	294	320	355	303		
Rate/1000 person years	1.5	1.2	1.0	1.1	1.1		
Model 1[c]	1.00	**0.84 (0.73 to 0.97)**	**0.79 (0.69 to 0.91)**	**0.82 (0.72 to 0.94)**	**0.86 (0.74 to 0.99)**	0.01	0.01
Model 2[d]	1.00	**0.85 (0.73 to 0.98)**	**0.84 (0.73 to 0.97)**	0.89 (0.78–1.03)	0.92 (0.79–1.07)	0.27	0.03
Cerebrovascular disease mortality							
No of deaths	369	254	255	260	220		
Rate/1000 person years	1.04	1.01	0.84	0.78	0.82		
Model 1[c]	1.00	1.07 (0.91–1.26)	0.92 (0.78–1.08)	0.88 (0.75–1.03)	0.92 (0.78–1.09)	0.068	0.68
Model 2[d]	1.00	1.05 (0.89–1.23)	0.95 (0.80–1.12)	0.94 (0.79–1.11)	0.97 (0.81–1.17)	0.45	0.69

[a] Linear trend across quintiles of low-carbohydrate score was tested by entering the median values of each quintile into the Cox proportional hazards model.
[b] P for quadratic trend across quintiles of low-carbohydrate, high total protein, and total fat score was tested by using orthogonal polynomial contrasts.
[c] Adjusted for age, sex, and public health center area.
[d] Additionally adjusted for BMI, smoking status, alcohol consumption, total physical activity levels, history of hypertension, history of diabetes, history of hyperlipidemia, occupation, energy intake, coffee, and green tea consumption.

Discussion

In this large population-based prospective cohort study in Japan, we observed a U-shaped association between LCD score and risk of total mortality. A similar association was evident for mortality from CVD. When the score was separated for animal and for plant sources of protein and fat, a U-shaped association was found for LCD score based on carbohydrate and animal sources of protein and fat and risk of mortality. In contrast, LCD score based on carbohydrate and plant sources of protein and fat was inversely associated with risk of total mortality and cause-specific mortality including CVD mortality, heart disease mortality, and cerebrovascular disease mortality. Our study suggests that both LCD with high animal protein and fat and high-carbohydrate diet with low animal protein and fat can increase the risk of mortality, whereas an LCD with mostly plant sources of protein and fat can decrease the risk of mortality. To our best knowledge, the present study is one of the few to investigate the association between LCD score and mortality.

Carbohydrate intake was relatively higher in the present study compared to the US studies. The mean carbohydrate intake in the lowest and highest quintile of LCD score based on animal sources of protein and fat were 65.4 and 43.0% energy, respectively in the present study. In contrast, the corresponding values were approximately 60e61 and 35e38% in the US studies [11,13]. In addition, the major sources of carbohydrate in Japan are rice and processed rice [22], while they are soft drinks and soda, yeast bread and rolls, and cake, cookies, pastry, and pie in the US rice and cooked grains contributed only 3.1% of total carbohydrate intake [23]. Moreover, the main sources of animal fat and protein was red meat in the US, whereas it is fish in Japan. Total meat intake (excluding fish) is much higher in the US than in Japan (per capita meat intake: 122.8 kg/year in US vs 55.9 kg/year in Japan) [24] and, of total per capita consumption of total meat (including fish), the percentage of red meat (beef and pork) and fish/sea food consumption was 53% and 15%, respectively in US versus 26% and 60% in Japan [24]. The

meat intake mortality association appears to vary by region. In a meta-analyses by study region, high intake of red and processed meat was associated with an increased risk of all-cause and CVD mortality in the US populations but not in Asian populations [25,26]. Several studies from US and Europe reported that moderate red meat or total meat consumption (up to 100 g/d) was not associated with increased risk of stroke [27,28] and ischemic heart disease [29], but large consumption was [27,29]. Meanwhile, two cohort studies from Japan and Korea reported that moderate red meat consumption (up to 100 g/d) was associated with decreased risk of CVD.

in line with our finding, a recent multi-country study suggested that very low intake of saturated fat (less than 7% of energy) might have an adverse effect on mortality [32]. In addition, animal proteins are rich in iron, and low iron intake is associated with anemia [33], which is a risk factor for CVD [34]. In contrast, excessive dietary iron intake is associated with increased risk of coronary heart disease [35]. Along with these findings, the present study suggests that moderate consumption of carbohydrate with animal protein and fat is beneficial for long-term health than extremely low or high consumption. The clear inverse association of LCD score based on plant protein and plant fat score with total mortality and CVD mortality including heart disease and cerebrovascular disease mortality in the present study is consistent with the findings from the US study [11]. It is also in line with our previous report from the JPHC cohort study showing a clear inverse association between plant protein intake and risk of total and CVD-related mortality [36]. High plant protein intake has been associated with favorable cardiometabolic profile: waist circumference [37], body weight [37], blood pressure [38,39], low-density lipoproteins [40,41], triglycerides [41], insulin resistance [42], and type 2 diabetes [42,43]. Intakes of nuts and grains/ legumes, a rich source of plant protein and fat, was associated with lower risk of all-cause and cardiovascular disease mortality [44,45]. Plant-based mono-unsaturated fatty acids were also associated with lower risk of mortality [46] and individual polyunsaturated fatty acids from plant-based sources such as alpha-linolenic acids are associated with decreased risk of CVD [47]. Collectively, the available data suggest that diets lower in carbohydrate and higher in plant-based protein and fat is associated with a lower risk of total and CVD mortality.

Table 3
Multivariate-adjusted hazard ratios (95% CI) for mortality across quintiles of low-carbohydrate diet score based on carbohydrate and animal sources of protein and fat.

	Q1	Q2	Q3	Q4	Q5	P trend[a]	P for non-linearity[b]
N	20796	17147	21203	16374	18134		
Median score (range)	4 (0–7)	10 (8–12)	15 (13–18)	21 (19–23)	27 (24–30)		
Person years	334908	276285	342098	264992	294925		
Total mortality							
No of deaths	3303	2422	2824	2124	2506		
Rate/1000 person years	9.9	8.8	8.2	8.0	8.5		
Model 1[c]	1.00	**0.94 (0.90 to 0.99)**	**0.93 (0.89 to 0.98)**	**0.93 (0.89 to 0.98)**	0.98 (0.93–1.03)	0.20	<0.01
Model 2[d]	1.00	**0.93 (0.89 to 0.99)**	0.95 (0.90–1.00)	0.96 (0.91–1.01)	1.01 (0.95–1.06)	0.74	<0.01
Cancer mortality							
No of deaths	1233	994	1143	860	1016		
Rate/1000 person years	3.6	3.6	3.3	3.2	3.4		
Model 1[c]	1.00	1.02 (0.94–1.11)	0.99 (0.92–1.08)	0.99 (0.91–1.08)	1.06 (0.97–1.15)	0.39	0.33
Model 2[d]	1.00	0.99 (0.91–1.08)	0.98 (0.90–1.06)	0.99 (0.90–1.08)	1.06 (0.97–1.16)	0.25	0.10
Cardiovascular disease mortality							
No of deaths	907	603	743	553	644		
Rate/1000 person years	2.7	2.2	2.2	2.1	2.2		
Model 1[c]	1.00	**0.87 (0.79 to 0.97)**	0.91 (0.82–1.00)	**0.89 (0.80 to 0.99)**	0.92 (0.83–1.02)	0.13	0.05
Model 2[d]	1.00	**0.87 (0.78 to 0.97)**	0.94 (0.85–1.04)	0.94 (0.84–1.05)	0.95 (0.86–1.06)	0.66	0.10
Heart disease mortality							
No of deaths	486	316	381	292	336		
Rate/1000 person years	1.5	1.1	1.1	1.1	1.1		
Model 1[c]	1.00	**0.85 (0.74 to 0.98)**	**0.87 (0.76 to 0.99)**	0.87 (0.76–1.01)	0.88 (0.77–1.01)	0.10	0.09
Model 2[d]	1.00	0.86 (0.75–1.00)	0.92 (0.80–1.05)	0.94 (0.81–1.09)	0.93 (0.80–1.08)	0.54	0.22
Cerebrovascular disease mortality							
No of deaths	355	231	295	232	245		
Rate/1000 person years	1.1	0.8	0.9	0.9	0.8		
Model 1[c]	1.00	0.86 (0.72–1.01)	0.93 (0.79–1.08)	0.97 (0.82–1.14)	0.91 (0.77–1.07)	0.54	0.09
Model 2[d]	1.00	**0.83 (0.70 to 0.99)**	0.93 (0.79–1.09)	0.99 (0.83–1.17)	0.92 (0.77–1.09)	0.82	0.22

[a] Linear trend across quintiles of low-carbohydrate score based on carbohydrate and animal sources of protein and fat was tested by entering the median values of each quintile into the Cox proportional hazards model.
[b] P for quadratic trend across quintiles of low-carbohydrate, high animal protein, and animal fat score was tested by using orthogonal polynomial contrasts.
[c] Adjusted for age, sex, and public health center area.
[d] Additionally adjusted for BMI, smoking status, alcohol consumption, total physical activity levels, history of hypertension, history of diabetes, history of hyperlipidemia, occupation, energy intake, coffee, and green tea consumption.

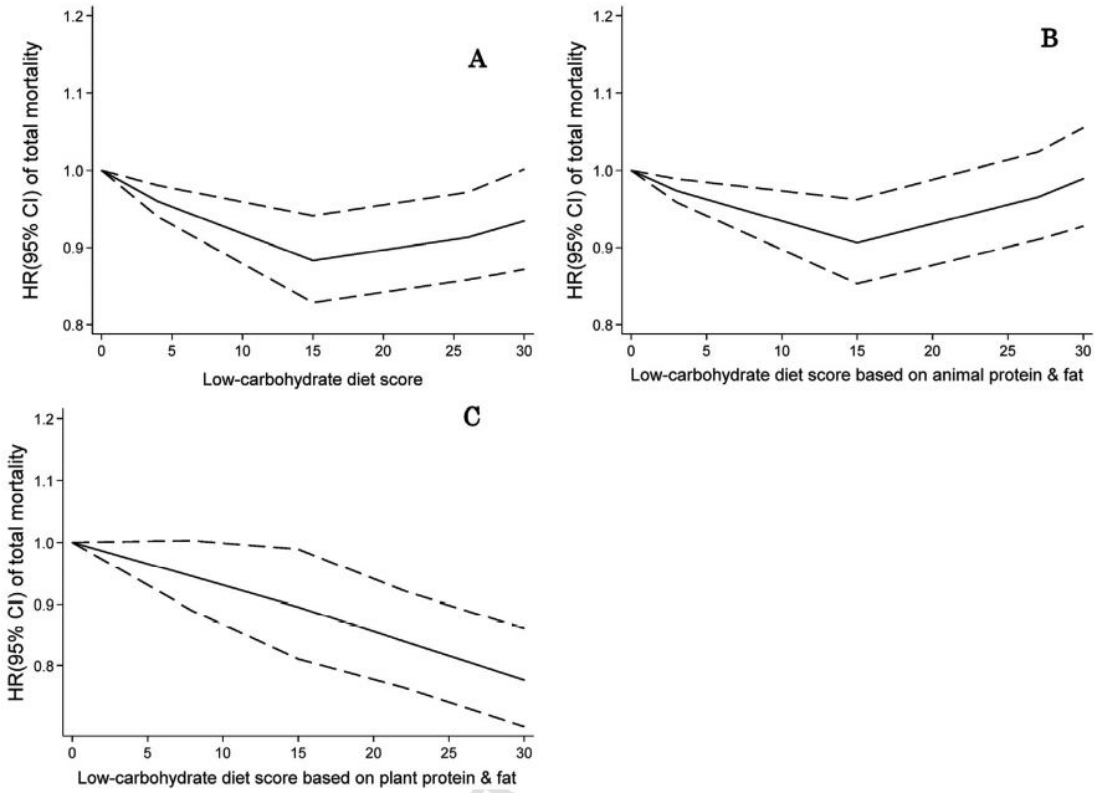

Fig. 1. Hazard ratios (HR, solid line) and 95% confidence interval (CI, dashed lines) for total mortality associated with (A) low-carbohydrate diet score, (B) low-carbohydrate diet score based on carbohydrate and animal sources of protein and fat, and (C) low-carbohydrate diet score based on carbohydrate and plant sources of protein and fat. The scores were modelled using restricted cubic spline with three knots placed at the 10th, 50th, and 90th percentiles. The reference value was 0. The model was adjusted for age, sex, public health center area, BMI, smoking status, alcohol consumption, total physical activity levels, history of hypertension, history of diabetes mellitus, history of dyslipidemia, occupation, energy intake, coffee, and green tea consumption.

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Critical Review

Nutrition in Cancer: Evidence and Equality

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Abstract

Purpose: Poor nutrition is highly implicated in the pathogenesis of cancer and affects the survival of patients during and after completion of definitive therapies. Mechanistic evidence accumulated over the last century now firmly places dysregulated cellular energetics within the emerging hallmarks of cancer. Nutritional intervention studies often aim to either enhance treatment effect or treat nutritional deficiencies that portend poor prognoses. Patients living within food priority areas have a high risk of nutritional need and are more likely to develop comorbidities, including diabetes, hypertension, renal disease, and cardiovascular risk factors. Unfortunately, there is currently a paucity of data analyzing the impact of food priority areas on cancer outcomes.

Methods: Therefore, we performed a review of the literature focusing on the molecular and clinical interplay of cancer and nutrition, the importance of clinical trials in elucidating how to intervene in this setting and the significance of including citizens who live in food priority areas in these future prospective studies.

Conclusions: Given the importance of nutrition as an emerging hallmark of cancer, further research must be aimed at directing the optimal nutrition strategy throughout oncologic treatments, including the supplementation of nutritious foods to those that are otherwise unable to attain them

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According to recent estimates, 80,000 cancer cases per year could be prevented with an adequate diet alone.3 The importance of nutrition is broadly implicated in cancer incidence, outcomes, and mitigation of long-term comorbidities after treatment.3-5 Unfortunately, nutrition recommendations in oncology remain vague and often contradictory.6 Epidemiologic studies throughout the 20th and 21st centuries associate high-calorie diets and obesity with the incidence of many types of cancer. Indeed, morbidities of obesity, including insulin resistance and diabetes mellitus type 2, are both independently recognized to increase cancer risk.

Mechanistically, studies have revealed that the chronic consumption of excess calories promotes an increase in the insulin-like growth factor-1 (IGF-1) mammalian target of rapamycin (mTOR) signaling pathway, which is paramount to nutrient sensing and subsequent cell growth. Various methods of dietary interventions to mitigate this pathway are under active exploration, including caloric restriction, intermittentfasting, and specific macronutrient restriction.

Most nutrition data are gathered using food surveys aimed at analyzing adherence to specific diets or eating within different macronutrient or micronutrient profiles. Owing to the intrinsic heterogeneity encountered within such studies, results are often mixed and generally considered fundamentally biased, resulting in inconsistent findings.24 Furthermore, intervention bias plagues many of these analyses. A recent meta-analysis including 31 studies reported that patients who followed diets that scored high on the Dietary Approaches to Stop Hypertension, the Alternative Healthy Eating Index, and the Healthy Eating Index had significantly decreased cancer incidence, mortality, and allcause mortality.25 Adherence to a Mediterranean diet was also inversely associated with cancer mortality, including significant risk reductions in colorectal, breast, gastric, liver, head and neck, and prostate cancers, which the authors attributed to higher intakes of fruit, vegetables, and whole grains.26 However, data evaluating vegetarian diets on cancer incidence and mortality are inconsistent. A large analysis of 96 vegetarian and vegan studies showed a significant decrease in the incidence of cancer (relative risk: 0.92; confidence interval, 0.87-0.98), but not cancer mortality.27 Yet another meta-analysis that included 9 studies of vegetarian diets and evaluated the subsequent risk of breast, colorectal, and prostate cancers found no significant association between diet and cancer risk.

Many studies show that patients who lose significant weight during cancer treatment have poorer outcomes and a reduced quality of life.4,13,58 These effects are multifactorial. The development of cachexia, defined as skeletal muscle loss with or without anorexia and not reversible with nutritional intervention, portends a poor prognosis.59 Cachexia is poorly understood, likely resulting from a mixture of systemic inflammation, increased resting energy expenditure, and decreased protein synthesis.58-60 Therefore, the potential benefits of caloric restriction while preventing the incidence of cachexia are difficult to glean. In addition, long-term caloric restriction was shown to decrease immune function in animal models.37 Given these challenges, time-restricted feeding, which includes short-term fasting, intermittent fasting, and shortterm extreme caloric restriction, have been studied. Cellular adaptions to starvation, conserved from yeast to mammals, repeatedly show increases in stress resistance by reducing nutrients and growth signals, such as IGF-1, and thus downregulating the PI3k/AKT/mTOR pathway.61,62 Reductions in IGF-1 signaling have been shown to induce cell cycle arrest as normal cells partition cellular processes toward survival while tumor cells are largely immune to this regulation.55,63 This difference, termed differential stress resistance,63 allows normal but not tumor cell survival in response to high doses of chemotherapeutic agents.55,64 Indeed, short-term fasting in just 48 to 72 hours induced a 70% reduction in circulating IGF-1 levels and protected mice to lethal doses of chemotherapeutic agents.55 Cycles of fasting proved effective at delaying cancer progression in multiple tumor mouse models, reducing toxicities to chemotherapy and promoting long-term survival, particularly when combined with chemotherapy.65,66 In humans, short-term fasts have been shown to be safe and may decrease chemotherapeutic side effects.67,68 Additional studies are ongoing and promising. Finally, other dietary interventions under active investigation in oncology aim to restrict specific nutrients. The ketogenic diet (KD), defined by the presence of ketone bodies in systemic circulation, aims to restrict both carbohydrates and protein. The KD was originally developed in the

1920s as a treatment for intractable pediatric epilepsy.69 At very low carbohydrate intakes, such as those with fasting, the liver produces betahydroxybutyrate from fatty acids, which is a ketone body that is able to cross the blood-brain barrier and provide an additional energy source for the brain. The KD may provide a selective advantage against cancer cells because beta-hydroxybutyrate bypasses the Warburg metabolism while providing adequate energy via the tricarboxylic acid cycle in normal tissues. In addition, the KD induces significant reductions in both insulin and IGF-1,70,71 and acts as signaling molecules to inhibit histone deacetylase and gene expression.72 Preclinical studies show that the KD significantly slowed tumor growth, sensitized tumor cells to both chemotherapy and radiation therapy, decreased cachexia, and increased survival.73-78 Preliminary clinical studies show the safety and feasibility of the KD in the clinic,64,70,79-82 and current clinical trials are ongoing.

long-term side effects in cancer survivors, lead to reduced physical activity and loss of muscle mass, promoting sarcopenic obesity.88 Cancer survivors with sarcopenic obesity, which is the replacement of muscle mass with fat, are at a high risk for posttreatment mortality.89 Therefore, maintaining a healthy, nutritious diet at all timepoints during cancer care is critical, especially in cancer survivors who received curative treatment. As such, 1 in 3 patients with cancer inquire about dietary intake. Unfortunately, current recommendations from National Comprehensive Cancer Networke designated cancer institutions remain vague.6 From the aforementioned investigational interventions, the preferred diet from an oncologic perspective is uncertain. Yet, there is a role for nutritional intercession as can be deduced from the data discussed. Despite the potential benefits of dietary changes in all patients with cancer, the greatest advantage would most likely be observed in those who have little access to healthy, nutritious foods. One in 10 Americans live within a food priority area (FPA), defined as an area encompassing low quantity and quality of grocers, and adequate transportation to get there.21,90 In some inner cities, the proportion increases to 1 in 4 Americans.91 Although the effects of residence within a FPA on various health issues, such as diabetes,92 hypertension,93 renal disease,94 and cardiovascular risks,95 have been well-characterized in the literature, data reporting the effects of residing in FPAs on cancer treatment and outcomes is nonexistent.

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American Cancer Society Guideline for Diet and Physical Activity for Cancer Prevention

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Abstract: The American Cancer Society (ACS) publishes the Diet and Physical Activity Guideline to serve as a foundation for its communication, policy, and community strategies and, ultimately, to affect dietary and physical activity patterns among Americans. This guideline is developed by a national panel of experts in cancer research, prevention, epidemiology, public health, and policy, and they reflect the most current scientific evidence related to dietary and activity patterns and cancer risk. The ACS

guideline focus on recommendations for individual choices regarding diet and physical activity patterns, but those choices occur within a community context that either facilitates or creates barriers to healthy behaviors. Therefore, this committee presents recommendations for community action to accompany the 4 recommendations for individual choices to reduce cancer risk. These recommendations for community action recognize that a supportive social and physical environment is indispensable if individuals at all levels of society are to have genuine opportunities to choose healthy behaviors. This 2020 ACS guideline is consistent with guidelines from the American Heart Association and the American Diabetes Association for the prevention of coronary heart disease and diabetes as well as for general health promotion, as defined by the 2015 to 2020 Dietary Guidelines for Americans and the 2018 Physical Activity Guidelines for Americans. CA Cancer J Clin 2020;0:1-27. © 2020 American Cancer Society.

TABLE 1. 2020 American Cancer Society Guideline on Diet and Physical Activity for Cancer Prevention

Recommendations for individuals
1. Achieve and maintain a healthy body weight throughout life.
• Keep body weight within the healthy range and avoid weight gain in adult life.
2. Be physically active.
• Adults should engage in 150-300 min of moderate-intensity physical activity per wk, or 75-150 min of vigorous-intensity physical activity, or an equivalent combination; achieving or exceeding the upper limit of 300 min is optimal. • Children and adolescents should engage in at least 1 hr of moderate- or vigorous-intensity activity each day. • Limit sedentary behavior, such as sitting, lying down, and watching television, and other forms of screen-based entertainment.
3. Follow a healthy eating pattern at all ages.
• A healthy eating pattern includes: o Foods that are high in nutrients in amounts that help achieve and maintain a healthy body weight; o A variety of vegetables—dark green, red, and orange, fiber-rich legumes (beans and peas), and others; o Fruits, especially whole fruits with a variety of colors; and o Whole grains. • A healthy eating pattern limits or does not include: o Red and processed meats; o Sugar-sweetened beverages; or o Highly processed foods and refined grain products.
4. It is best not to drink alcohol.
• People who do choose to drink alcohol should limit their consumption to no more than 1 drink per day for women and 2 drinks per day for men.
Recommendation for Community Action
• Public, private, and community organizations should work collaboratively at national, state, and local levels to develop, advocate for, and implement policy and environmental changes that increase access to affordable, nutritious foods; provide safe, enjoyable, and accessible opportunities for physical activity; and limit alcohol for all individuals.

Narrative Review

Low-carbohydrate diets: Effects on metabolism and exercise – A comprehensive literature review

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summary Background & aims: Low-carbohydrate diets (LCD) have gained substantial attention in recent years for their potential in health promotion and treatment of diseases, but they remain controversial in nutrition guidelines and exercise performance. Herein, through a literature review, we discuss the current evidence base by considering management of LCD and potential coupling of these dietary regiments with physical exercise. Methods: We performed a comprehensive literature review with no date limits as a means of including seminal to current studies. Results: Reduction of CHO intake decreases muscle glycogen, yielding greater fat oxidation and associated metabolic benefits. LCD may promote fat mass loss and regulation of biochemical parameters, such as lipid and glycemic biomarkers. The therapeutic potential of LCD towards noncommunicable diseases, particularly obesity and its comorbidities, is therefore reasonable as a dietary candidate in this context. Potential benefits to this approach are linked to enhancement of mitochondrial gene expression and mitochondrial biogenesis. As such, LCD may be a feasible tool in a 'periodized nutrition' for athletes and within clinical scenarios. Long-term observational follow-up studies have demonstrated increased mortality and cardiovascular implications of LCD. However, harmful associations may depend on the food source (e.g., animal-based vs. plant-based foods). Conclusion: LCD may decrease body mass, waist circumference, and improve fat and carbohydrate metabolism. When combined with exercise, LCD seems to be an effective strategy in regulating metabolic factors of cardiovascular diseases. Conversely, LCD may be associated with higher mortality and metabolic dysregulations if it contains large amounts of animal-based foods, particularly saturated fat.

Obesity in patients with COVID-19: a systematic review and meta-analysis

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ABSTRACT

Background: Obesity is common in patients with coronavirus disease 2019 (COVID-19). The effects of obesity on clinical outcomes of COVID-19 warrant systematical investigation.
Objective: This study explores the effects of obesity with the risk of severe disease among patients with COVID-19.
Methods: Body mass index (BMI) and degree of visceral adipose tissue (VAT) accumulation were used as indicators for obesity status. Publication databases including preprints were searched up to August 10, 2020. Clinical outcomes of severe COVID-19 included hospitalization, a requirement for treatment in an intensive care unit (ICU), invasive mechanical ventilation (IMV), and mortality. Risks for severe COVID-19 outcomes are presented as odds ratios (OR) and 95% confidence interval (95%CI) for cohort studies with BMI-defined obesity, and standardized mean difference (SMD) and 95%CI for controlled studies with VAT-defined excessive adiposity.
Results: A total of 45, 650 participants from 30 studies with BMI-defined obesity and 3 controlled studies with VAT-defined adiposity were included for assessing the risk of severe COVID-19. Univariate analyses showed significantly higher ORs of severe COVID-19 with higher BMI: 1.76 (95%: 1.21, 2.56, $P = 0.003$) for hospitalization, 1.67 (95%CI: 1.26, 2.21, $P<0.001$) for ICU admission, 2.19 (95%CI: 1.56, 3.07, $P<0.001$) for IMV requirement, and 1.37 (95%CI: 1.06, 1.75, $P = 0.014$) for death, giving an overall OR for severe COVID-19 of 1.67 (95%CI: 1.43, 1.96; $P<0.001$). Multivariate analyses revealed increased ORs of severe COVID-19 associated with higher BMI: 2.36 (95%CI: 1.37, 4.07, $P = 0.002$) for hospitalization, 2.32 (95%CI: 1.38, 3.90, $P = 0.001$) for requiring ICU admission, 2.63 (95%CI: 1.32, 5.25, $P = 0.006$) for IMV support, and 1.49 (95%CI: 1.20, 1.85, $P<0.001$) for mortality, giving an overall OR for severe COVID-19 of 2.09 (95%CI: 1.67, 2.62; $P<0.001$). Compared to non-severe COVID-19 patients, severe COVID-19 cases showed significantly higher VAT accumulation with a SMD of 0.49 for hospitalization (95% CI: 0.11, 0.87; $P = 0.011$), 0.57 (95% CI: 0.33, 0.81; $P<0.001$) for requiring ICU admission and 0.37 (95% CI: 0.03, 0.71; $P = 0.035$) for IMV support. The overall SMD for severe COVID-19 was 0.50 (95% CI: 0.33, 0.68; $P<0.001$).
Conclusions: Obesity increases risk for hospitalization, ICU admission, IMV requirement and death among patients with COVID-19. Further, excessive visceral adiposity appears to be associated with severe COVID-19 outcomes. These findings emphasize the need for effective actions by individuals, the public and governments to increase awareness of the risks resulting from obesity and how these are heightened in the current global pandemic.

The included studies involved 9 countries over the world including USA, Italy, China, Spain, The state of Kuwait, Mexico, France, Switzerland and Greece. A total of 45, 650 participants were finally included into analysis. Nearly two third of the studies (18/33) were from USA, the current epicenter of the coronavirus pandemic.

Patients mainly participated in these studies between February to May. The participants in 20 studies were all adults, over 18 years of age, while 11 studies did not report the age range of their participants in detail. Only one study included exclusively children with a median age of 13.1 (0.4–19.3) [21]. Except for this study, the median age of participants ranges from 40.5 (31.5–52.1) to 72 (60–80) years, with fourteen studies reporting a mean age or no statistical description for their age range. Obesity criteria among 24 studies were defined as a level of BMI of 30 kg/m2 or more. One study from China defined a BMI of 28 kg/m2 or more as obesity in accordance to obesity criteria of Chinese adults [9], another study from Italy defined a BMI of over 29 kg/m2 as obesity [22]. It should be noted that one study emphasized that the World Health Organization defined obesity as abnormal or excessive fat accumulation that presents a risk to health condition issues .

Compared to younger patients, older COVID-19 patients with BMI ≥ 30 kg/m2 appeared to develop a less severe condition. Nevertheless, it's worth noting that the gradient of risk of severe COVID-19 in relation to BMI might be more gradual among older patients when compared to younger individuals . This may be attributed to the fact that BMI is a less accurate predictor of excess fat in older adults with

lower muscle mass, together with a shift from subcutaneous fat to VAT and increased relative fat mass among them [14]. A more precise measurement of excess fat may help predict more reliable health risks in this group with obesity. The positive relationship between VAT and severe COVID-19 in our meta-analysis may provide an important insight. The underlying mechanism by which obesity increases the risk of severe covid-19 remains unknown. Previous research has shown that obesity was related to a worse outcome as a result of infection and disease progression for certain kinds of infectious virus diseases, such as influenza in the 1918 “Spanish” influenza pandemic [42,43], the 1957 pandemic, the 1968 pandemic and the 2009 Influenza A virus (IAV) H1N1 pandemic [44,45]. People with obesity tend to have respiratory dysfunction at various levels [46] and may be mildly hypoxaemic [47]. A greater oxygen cost of breathing was needed for patients with obesity when compared to those without obesity, even at rest [47]. In a recently published meta-analysis, dyspnea rather than fever was shown to be significantly associated with the risk of mortality among COVID-19 patients [48]. One study we included found that BMI ≥ 30 kg/m2 were associated with the risk of hypoxemia upon hospital admission among patients with COVID-19 (OR: 1.7, 95%CI: 1.3, 2.1; P < 0.0005) [35]. A BMI ≥ 35 kg/m2 was even a significant predictor for increasing oxygenation requirement in a cohort of COVID-19 patients in the Bronx borough of New York City [12].

Obesity also increases the risk of many common non-communicable diseases such as diabetes mellitus, cardiovascular disorders, cancers and non-alcoholic fatty liver disease, and often co-exists with them in a single individual. These co-existing co-morbidities are considered to increase the likelihood of severe illness from COVID-19 for people with obesity [50–52]. Excessive adipose tissue including ectopic fat may serve as reservoirs for angiotensin-converting enzyme 2 (ACE2) and microbes such as coronavirus, influenza A virus and Mycobacterium tuberculosis [53]. Beyond disease severity, obesity increased the duration of influenza A virus shedding to hasten virus spreading mainly for person-to-person transmission

To the best of our knowledge, this is the first meta-analysis to identify a positive relationship between high VAT accumulation and severe COVID-19

Above all, combined adipose tissue-mediated immune and metabolic dysfunctions might play a key role in the pathophysiological pathways that lead obesity to influence COVID-19 prognosis [46,56,57]. Low-grade systemic inflammation and increasing insulin resistance commonly exists in people with obesity [58,59]. and this immune and metabolic phenomena is strongly associated with presence of excess VAT [60]. Excess VAT is believed to be the main culprit in the inflammatory diseases of obesity [60], which in turn might induce severe complications on top of the viral infection itself, such as development of thrombosis [56]. Visceral obesity-related impaired immune response can also lead to systemic metabolic dysfunction [43,56] and increase risks of metabolic disorders and cardiovascular diseases, as well as their complications [61–63]. Furthermore, while BMI on its own does not reflects any particular distribution of body fat, VAT is a marker of increased ectopic fat that might contribute to increased atherosclerosis and cardiometabolic risk [64]. Excessive visceral adiposity may provide additional important information about COVID-19 risk, which is not captured in BMI. Evidence of value from two recent studies, which were not included in our analysis due to our study design and eligibility criteria, suggests that visceral adiposity increases the likelihood of severe COVID-19 [15,65]. Central obesity is defined as a state of excessive VAT accumulation [66]. Patients with central obesity evidenced by waist circumference or waist-to-hip ratio were also found to be more likely to develop severe COVID-19 (P

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Original article

Association between dietary fat intake and mortality from all-causes, cardiovascular disease, and cancer: A systematic review and meta-analysis of prospective cohort studies

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summary Background & aims: Low-carbohydrate diets (LCD) have gained substantial attention in recent years for their potential in health promotion and treatment of diseases, but they remain controversial in nutrition guidelines and exercise performance. Herein, through a literature review, we discuss the current evidence base by considering management of LCD and potential coupling of these dietary regiments with physical exercise. Methods: We performed a comprehensive literature review with no date limits as a means of including seminal to current studies. Results: Reduction of CHO intake decreases muscle glycogen, yielding greater fat oxidation and associated metabolic benefits. LCD may promote fat mass loss and regulation of biochemical parameters, such as lipid and glycemic biomarkers. The therapeutic potential of LCD towards noncommunicable diseases, particularly obesity and its comorbidities, is therefore reasonable as a dietary candidate in this context. Potential benefits to this approach are linked to enhancement of mitochondrial gene expression and mitochondrial biogenesis. As such, LCD may be a feasible tool in a 'periodized nutrition' for athletes and within clinical scenarios. Long-term observational follow-up studies have demonstrated increased mortality and cardiovascular implications of LCD. However, harmful associations may depend on the food source (e.g., animal-based vs. plant-based foods). Conclusion: LCD may decrease body mass, waist circumference, and improve fat and carbohydrate metabolism. When combined with exercise, LCD seems to be an effective strategy in regulating metabolic factors of cardiovascular diseases. Conversely, LCD may be associated with higher mortality and metabolic dysregulations if it contains large amounts of animal-based foods, particularly saturated fat.

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Meta-analysis

Association between sugar-sweetened beverages and waist circumference in adult populations: A meta-analysis of prospective cohort studies

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summary Background & aim: Based on previous studies, Sugar-Sweetened beverages (SSB) can increase the risk of obesity and obesity-related disorders. However, findings are conflicting. The aim of the present study was to summarize the association between the intake of SSB and waist circumference (WC) in adult populations. Methods: Four electronic databases including PubMed/Medline, Web of Knowledge, Scopus, and EMBASE were considered to collect eligible papers until 31 January 2019 with English language. Results: Finally, we reached 7 eligible cohort studies for both qualitative and quantitative synthesis. Based on the pooled 10 effect sizes, we found that the consumption of SSB can increase WC by 14%. However, it was not statistically significant and the between-study heterogeneity was high (95%CI: 0.86, 1.51; I2 : 90.8%). We also observed that soda drink can increase WC by 31% (95%CI: 1.03, 1.66; I2 :0%). Conclusion: The current systematic review and meta-analysis revealed that the consumption of SSB can increase WC by 14% in adult populations. However, this value was not statistically significant. However, more prospective studies are necessary to make a decision on the link between the consumption of SSB and abdominal obesity.

To the best of our knowledge, it is the first systematic review and meta-analysis in which the link between the consumption of various SSBs and adiposity in both children and adults were examined. In the recent meta-analysis on food groups and obesity, conducted by Schlesinger et al., only 3 studies on SSB and overweight were included. They reported that the intake of SSB can increase the risk of overweight/obesity by 20% [18]. In this study, due to limited studies classifications by age groups were not performed. In our study, although the effect of SSB on adiposity in younger individuals were greater than older, its effects were significant in no categories. In our meta-analysis, WC was considered as a measure of adiposity. Although we extracted the information related to fat mass, as a measure of adiposity, only limited studies examined this variable and we could not pool and perform a meta-

analysis on fat mass. Stern and colleagues reported that in overweight/obese women the impact of changes in sugar sweetened soda on body weight was stronger compared to those with normal weight [26]. However, in the present meta-analysis due to limited studies we could not do a subgroup analysis based on BMI to evaluate this issue. It is notable that some cohort studies assessed a particular sweetened beverage including soda, juice with added sugar or diet beverages, not sugar-sweetened beverages as a whole. Due to limited studies in each category, we only could report findings on soft drink, separately. We found that soft drink can increase the risk of adiposity by 31%. However, pooling studies on all SSBs showed odd ratio of 1.18 with adiposity. Therefore, types of SSB can affect the association. However based on current cohort studies, this issue remained unanswered. All the included cohort studies obtained minimum score of 5 for methodological quality. Accordingly, there is no bias on findings regarding high risk of bias. However, various categories were considered for comparisons the effects of high SSB intake verses low consumption and this point made it difficult to define a cut-off point and provide nutritional recommendations on this regard. On the other hands, sensitivity analysis showed that our findings were stable and two studies had decisive effect. Thus, findings must be interpreted by great caution.

SSBs can stimulate intake of other high glycemic foods that lead to the intake of greater total calorie. Furthermore, due to high glycemic loads of SSBs, repeated high insulin is demanded. An increase in insulin secretion can lead to fat accumulation and weight gain [29]. Based on evidence, high-fructose maize syrup that is used for some types of SSBs can also stimulate hepatic de novo lipogenesis and substantially increase the serum levels of triglyceride [19]. Although the association between SSBs and adiposity were not statistically significant, due to an increase of 14% in adiposity following SSBs intake and no robustness of findings, recommendation regarding limiting the consumption of SSBs by health providers seems reasonable. Among the weakness of the present meta-analysis we can point to the lack of dose-response analysis due to variation in cut-off points and comparison groups. In addition, only papers with English language were included. The strength points of the current systematic review and meta-analysis are as follows: i) examining the quality of studies based on a standard tool; and ii) including only cohort studies that can clarify the cause and effect relationships between SSB and adiposity. It is suggested to compare various types of SSB with different sweeteners including fructose and sucrose as well as beverages with various kinds of artificial sugar in the future prospective studies.

In our meta-analysis, WC was considered as a measure of adiposity. Although we extracted the information related to fat mass, as a measure of adiposity, only limited studies examined this variable and we could not pool and perform a meta-analysis on fat mass. Stern and colleagues reported that in overweight/obese women the impact of changes in sugar sweetened soda on body weight was stronger compared to those with normal weight [26]. However, in the present meta-analysis due to limited studies we could not do a subgroup analysis based on BMI to evaluate this issue. It is notable that some cohort studies assessed a particular sweetened beverage including soda, juice with added sugar or diet beverages, not sugar-sweetened beverages as a whole. Due to limited studies in each category, we only could report findings on soft drink, separately. We found that soft drink can increase the risk of adiposity by 31%

Journal Pre-proof

Diet and ovarian cancer risk: an umbrella review of systematic reviews and meta-analyses of cohort studies

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ABSTRACT 33 Background & Aims: Diet may play an important role in the etiology of ovarian 34 cancer (OC). We aimed to evaluate the strength and credibility of evidence pertaining 35 to dietary risk factors for OC. 36 Methods: We comprehensively searched PubMed, Web of Science, Cochrane, 37 CINAHL, JBI Database of Systematic Reviews and Implementation Reports, 38 PROSPERO and EMBASE databases to identify related systematic reviews and 39 meta-analyses of prospective cohort studies. This study had been registered at 40 PROSPERO. The registration number is CRD42020187651. For each association, we 41 estimated the summary effect size using fixed and random effects models, the 95% 42 confidence interval and the 95% prediction interval. We assessed heterogeneity, 43 evidence of small-study effects, and excess significance bias. 44 Results: A total of 22 systematic reviews and meta-analyses were included in the 45 present study. These previous reports evaluated 184 individual studies, which 46 proposed a total of 36 associations between dietary factors and OC risk. Out of the 36 47 associations, there were no strong, highly suggestive and suggestive evidence, only 48 four (black tea, skim/low-fat

milk, lactose, and calcium) were determined to be 49 supported by weak evidence. OC risk was inversely associated with intake of black 50 tea or calcium, and positively associated with intake of skim/low-fat milk or lactose. 51 Conclusions: Our studies revealed that four associations between OC risk and dietary 52 factors (black tea, skim/low-fat milk, lactose, and calcium) were supported by weak 53 evidence. The remaining 32 associations were not confirmed. Additional studies are 54 needed to carefully evaluate the relationship between dietary factors and OC risk.

Journal Pre-proof

The influence of fasting and energy-restricted diets on leptin and adiponectin levels in humans: A systematic review and meta-analysis

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Abstract Background and & aims: Fasting and energy-restricted diets have been evaluated in several studies as a means of improving cardiometabolic biomarkers related to body fat loss. However, further investigation is required to understand potential alterations of leptin and adiponectin concentrations. Thus, we performed a systematic review and meta-analysis to derive a more precise estimate of the influence of fasting and energy-restricted diets on leptin and adiponectin levels in humans, as well as to detect potential sources of heterogeneity in the available literature. Journal Pre-proof 3 Methods: A comprehensive systematic search was performed in Web of Science, PubMed/MEDLINE, Cochrane, SCOPUS and Embase from inception until June 2019. All clinical trials investigating the effects of fasting and energy-restricted diets on leptin and adiponectin in adults were included. Results: Twelve studies containing 17 arms and a total of 495 individuals (intervention = 249, control = 246) reported changes in serum leptin concentrations, and 10 studies containing 12 arms with a total of 438 individuals (intervention = 222, control = 216) reported changes in serum adiponectin concentrations. The combined effect sizes suggested a significant effect of fasting and energy-restricted diets on leptin concentrations (WMD: -3.690 ng/ml, 95% CI: - 5.190, -2.190, p ≤ 0.001; I2 = 84.9%). However, no significant effect of fasting and energyrestricted diets on adiponectin concentrations was found (WMD: -

159.520 ng/ml, 95% CI: - 689.491, 370.451, p = 0.555; I2 = 74.2%). Stratified analyses showed that energy-restricted regimens significantly increased adiponectin (WMD: 554.129 ng/ml, 95% CI: 150.295, 957.964; I 2 = 0.0%). In addition, subsequent subgroup analyses revealed that energy restriction, to ≤50% normal required daily energy intake, resulted in significantly reduced concentrations of leptin (WMD: -4.199 ng/ml, 95%CI: -7.279, -1.118; I2 = 83.9%) and significantly increased concentrations of adiponectin (WMD: 524.04 ng/ml, 95%CI: 115.618, 932.469: I2 = 0.0%). Conclusion: Fasting and energy-restricted diets elicit significant reductions in serum leptin concentrations. Increases in adiponectin may also be observed when energy intake is ≤50% of normal requirements, although limited data preclude definitive conclusions on this point.

Research

JAMA Internal Medicine | Original Investigation

Lifestyle Intervention With or Without Lay Volunteers to Prevent Type 2 Diabetes in People With Impaired Fasting Glucose and/or Nondiabetic Hyperglycemia
A Randomized Clinical Trial

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IMPORTANCE Nearly half of the older adult population has diabetes or a high-risk intermediate glycemic category, but we still lack trial evidence for effective type 2 diabetes prevention interventions in most of the current high-risk glycemic categories. OBJECTIVE To determine whether a group-based lifestyle intervention (with or without trained volunteers with type 2 diabetes) reduced the risk of progression to type 2 diabetes in populations with a high-risk glycemic category. DESIGN, SETTING, AND PARTICIPANTS The Norfolk Diabetes Prevention Study was a parallel, 3-arm, group-based, randomized clinical trial conducted with up to 46 months of follow-up from August 2011 to January 2019 at 135 primary care practices and 8 intervention sites in the East of England. We identified 141 973 people at increased risk of type 2 diabetes, screened 12 778 (9.0%), and randomized those with a high-risk glycemic category.

RESULTS In this study, 1028 participants were randomized (INT, 424 [41.2%] [166 women (39.2%)]; INT-DPM, 426 [41.4%] [147 women (34.5%)]; CON, 178 [17.3%] [70 women (%39.3)]) between January 1, 2011, and February 24, 2017. The mean (SD) age was 65.3 (10.0) years, mean (SD) body mass index 31.2 (5) (calculated as weight in kilograms divided by height in meters squared), and mean (SD) follow-up 24.7 (13.4) months. A total of 156 participants progressed to type 2 diabetes, which comprised 39 of 171 receiving CON (22.8%), 55 of 403 receiving INT (13.7%), and 62 of 414 receiving INT-DPM (15.0%). There was no significant difference between the intervention arms in the primary outcome (odds ratio [OR], 1.14; 95% CI, 0.77-1.7; P = .51), but each intervention arm had significantly lower odds of type 2 diabetes (INT: OR, 0.54; 95% CI, 0.34-0.85; P = .01; INT-DPM: OR, 0.61; 95% CI, 0.39-0.96; P = .033; combined: OR, 0.57; 95% CI, 0.38-0.87; P = .01). The effect size was similar in all glycemic, age, and social deprivation groups, and intervention costs per participant were low at $153 (£122).

CONCLUSIONS AND RELEVANCE The Norfolk Diabetes Prevention lifestyle intervention reduced the risk of type 2 diabetes in current high-risk glycemic categories. Enhancing the intervention with DPM did not further reduce diabetes risk. These translatable results are relevant for current diabetes prevention efforts.

Study Design The NDPS was a 7-year research program (UK National Institute for Health Research RP PG 0109-10013). The NDPS protocol35 (Supplement 1) and baseline publications35-38 summarize NDPS sample sizes, recruitment plans, training materials, and screening data. The NDPS identified people with high risk intermediate glycemic categories in the East of England and eligible participants entered a randomized clinical 3-arm parallel group trial with up to 46 months of follow-up that tested a group-delivered, theory-based lifestyle intervention with or without the support of trained lay volunteers (diabetes prevention mentors [DPM]) with type 2 diabetes. Screening Potential participants were screened with FPG levels, venous HbA1c levels, and biometric and clinical data collection. Participants with an eligible glycemic high-risk category on initial testing results had repeated testing a median of 40 days (interquartile range, 27-69 days) later. Trial randomization was offered if paired baseline tests were concordant for a high-risk intermediate glycemic category. The first screening appointment was August 22, 2011, and the last March 24, 2017. Protocol-driven screening was undertaken by NDPS program staff in 8 screening sites across the East of England.

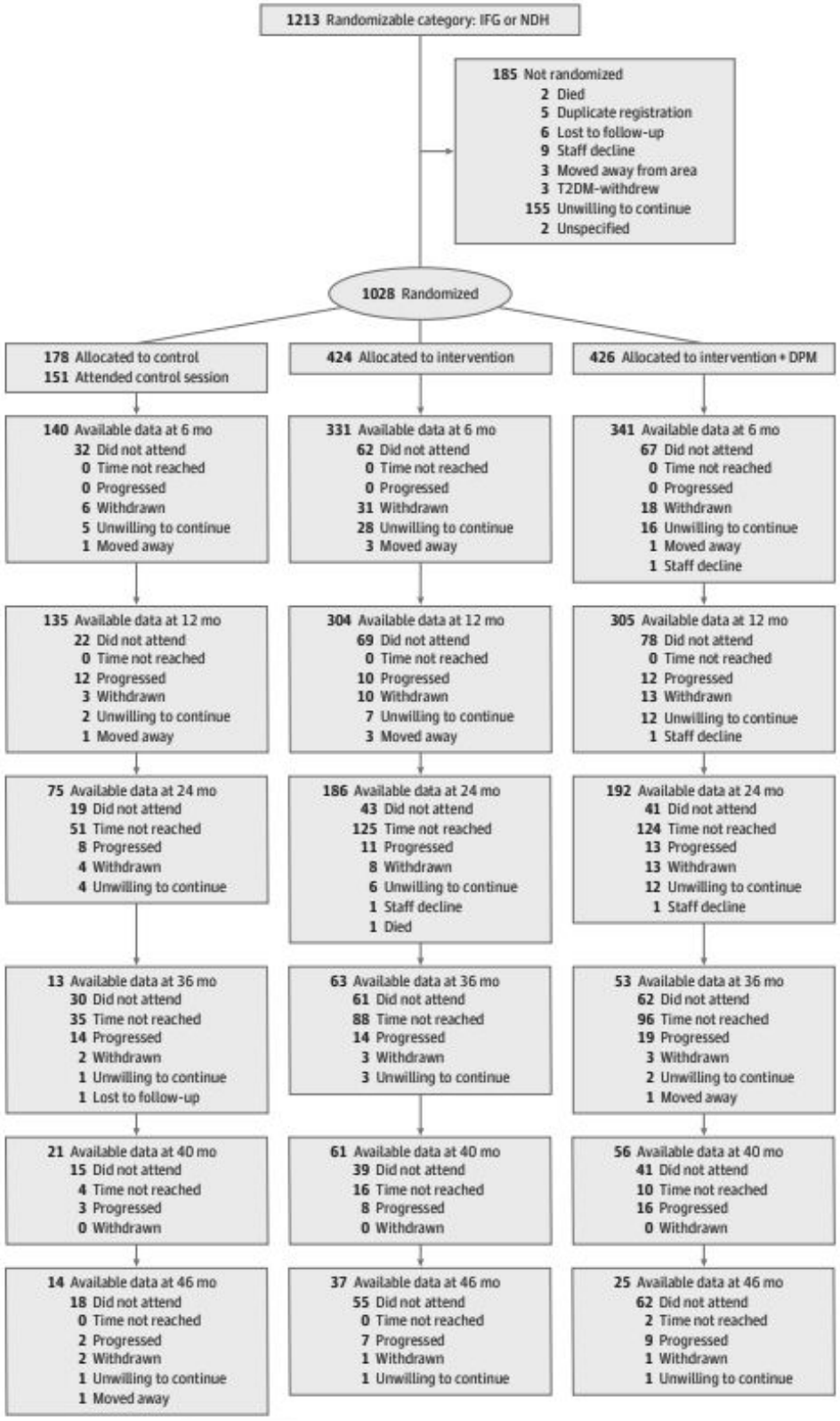
Interventions :The intervention was delivered by trained health care professionals alone (diabetes prevention facilitators [DPF]) or delivered jointly by DPFs and DPMs. The intervention theory aimed to support maintenance of changes in physical activity and diet using patient-centered counseling techniques to encourage decision-making about behavior changes; increase motivation to change; engage social support; aid individually tailored goal setting, action planning, and self-monitoring; and support problem solving. Behavior change targets were set by participants, who were encouraged to think about (and were presented with the health benefits of) a 7% weight loss if their BMI was greater than 30, achieving 150 minutes per week of moderate intensity physical activity over 5 days or more, 2 to 3 sessions of muscle-strengthening exercise per week, and reducing intake of total and saturated fat. The intervention comprised 6 2-hour educational group sessions of varying content for 12 weeks, followed by up to 15 maintenance sessions 8 weeks apart from month 4. Maintenance sessions were discussion based and followed the same format, including a 50-minute supervised physical activity/muscle strengthening exercise session. Sessions contained no more than 15 participants. The maximum contact time per participant was 49.5 hours. Participants randomized to the INTDPM arm received additional individual motivational telephone calls between sessions. The DPMs were assigned up to 7 participants, and telephone contacts were monthly for the first 3 months and then every 2 months. During these contacts, the DPM and participants discussed progress, goal achievement, action planning, and barriers to coping. The INT–DPM participants therefore received a contact from the study at least once every 4 weeks. The CON group received written information and discussion about the risk of diabetes and the effect of lifestyle modification on reducing this risk in line with then current local National Health Service (NHS) clinical policy. This was delivered in a single 2-hour session delivered by a DPF.

Results

We invited 141 973 people at increased risk of developing type 2 diabetes to participate, and 12 778 (9.0%) were screened. Between October 1, 2011, and June 1, 2017, we randomized 424 eligible participants into the standard INT arm, 426 into the INT-DPM arm, and 178 into the CON arm.

Baseline characteristics and flow through the trial are shown inTable 130,38-44 and Figure 1.Mean (SD) follow-upwas 742 (403) days (24.7months), and by arm was 727 (383) (CON), 744 (415) (INT), and 746 (402) days (INT-DPM). Between 75% and 78% were followed for at least 12months (CON, n = 135; INT, n = 304; INT-DPM, n = 305) in a rolling recruitment until the end of the recruitment period (Figure 1).

Figure 1. Trial Consolidated Standards of Reporting Trials Profile



Time not reached refers to the number of participants randomized as planned but not at a point during rolling recruitment that provided planned data collection at that later time. DPM indicates diabetes prevention mentors; IFG, impaired fasting glucose; NDH, nondiabetic hyperglycemia; T2DM, type 2

To our knowledge, NDPS is the largest type 2 diabetes prevention trial since the US Diabetes Prevention Program more than 20 years ago19-22 and now extends the prevention evidence base to contemporary high-risk glycemic categories. Nearly all of the earlier landmark trial evidence on diabetes prevention is drawn from people categorized as having IGT using an oral glucose tolerance test. The assumption that this earlier evidence can simply be translated with similar expected benefit to IFG or NDH populations with a different phenotype may not be valid. The NDPS affirms that a low-cost group-based lifestyle intervention in these high risk groups does have a substantial effect in preventing type 2 diabetes. The glycemic criteria we used are those now recognized as identifying individuals with a high risk of diabetes in UK prevention policy, in the NHS England diabetes prevention program, and in US prevention programs. Our results are therefore translatable to the current clinical and policy context. A meta-analysis of 11 similar trials with a diet and physical activity intervention of more than 2 years in high-risk glycemic categories20 described a similar composite effect size of a risk ratio of 0.57 (95% CI, 0.5-.64; P > .001). In that analysis of 9 trials20 exclusively randomized based on oral glucose tolerance test data, 1 included IFG or IGT, and 1 included people with a fasting glucose level of 95-124 mg/dL.

Discussion In this trial, people with a current high-risk intermediate glycemic category of IFG and/or NDH were 40% to 47% less likely to develop type 2 diabetes in the intervention groups compared with controls over an average 24 months. Broadly, 1 person was prevented from developing type 2 diabetes for every 11 who received the intervention. The enhanced intervention with trained DPMs did not

further reduce the risk of type 2 diabetes

Table 1. Baseline Characteristics of CON, INT, and INT-DPM

Characteristic	CON	INT	INT-DPM
No.	178	424	426
Age, mean (SD), y	65.3 (10.0)	66.5 (8.6)	66.7 (9.5)
Ethnicity, %			
White	96.0	97.1	97.1
South Asian	1.7	1.7	1.2
Black	0.6	0	0
Other	1.7	1.2	1.7
Sex, No. (%)			
Women	70 (39.3)	166 (39.2)	147 (34.5)
Men	108 (60.7)	258 (60.8)	279 (65.5)
Family history			
Type 2 diabetes, No. (%)	67 (37.6)	173 (40.8)	167 (39.2)
Cardiovascular disease, No. (%)	22 (12.4)	63 (14.9)	57 (13.4)
Previous gestational diabetes, No. (%)[a]	4 (5.7)	12 (7.2)	18 (12.2)
Social deprivation score, mean (SD)[b]	15.5 (10.6)	15.4 (10.2)	16.2 (10.7)
Weight, mean (SD), kg	90.5 (17.8)	90.2 (18.2)	89.8 (17.4)
BMI, mean (SD)	31.2 (5.0)	31.1 (5.6)	30.9 (5.6)
Waist circumference, mean (SD), cm	105.1 (13.1)	105.1 (13.5)	105.2 (13.0)
Body fat mass, mean (SD), kg[c]	35.2 (8.8)	34.0 (9.0)	33.6 (8.9)
IFG, No. (%)[d]	114 (64.0)	261 (61.6)	256 (60.1)
NDH, No. (%)[d]	64 (36.0)	163 (38.4)	170 (39.9)
HbA_{1c}, mean (SD), %	6.1 (0.3)	6.1 (0.3)	6.1 (0.3)
Fasting, mean (SD)			
Plasma glucose, mg/dL	112 (7.2)	112 (7.2)	113 (7.2)
HDL cholesterol, mg/dL	49.5 (13)	38.7 (13)	38.7 (13)
LDL cholesterol, mg/dL	119.1 (35)	117 (34)	118 (35)
Plasma insulin, pmol/l	108.3 (72.5)	95.7 (54.4)	91.0(57.1)
HOMA, mean (SD)			
Insulin sensitivity, (%)[e]	68.5 (41.9)	73.2 (51.5)	77.6 (47.2)
β cell function, (%)[e]	98.1 (44.0)	90.6 (35.6)	88.2 (36.3)
Physical activity, mean (SD)			
MET min per wk[f]	2507 (2761)	2701 (2640)	2660 (2748)
Min sitting per wk[f]	442 (269)	463 (263)	431 (241)
Low physical activity category, No. (%)[f]	42 (32.3)	91 (29.4)	98 (32.3)
Dietary fat intake scale, mean (SD)[g]	2.3 (0.3)	2.3 (0.3)	2.3 (0.3)
W-BQ12, mean (SD)[h]	24.8 (6.1)	25.1 (6.5)	25.0 (6.1)
EQ-5D, mean (SD)[h]	0. 8 (0.2)	0.8 (0.2)	0.8 (0.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CON, control arm; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; INT, standard intervention arm; INT-DPM, intervention arm with diabetes prevention mentors; LDL, low-density lipoprotein; MET, metabolic equivalent of task; NDH, nondiabetic hyperglycemia.

SI conversion factors: To convert total, HDL and LDL cholesterol to mmol/L, multiply by 0.0259; plasma glucose to mmol/L, multiply by 0.0555.

[a] Female participants.

[b] Indices of multiple deprivation social deprivation score.[30]

[c] Body fat by Tanita body composition analyzer.[30]

[d] Impaired fasting glucose–paired baseline fasting plasma glucose levels of 110 or greater to less than 126 mg/dL. Nondiabetic hyperglycemia–paired baseline HbA1c levels of 6.0% or greater to less than 6.5% with an IFG fasting plasma glucose level of 100 or greater to less than 110 mg/dL.

[e] Homeostasis model assessment of baseline insulin sensitivity and β cell function expressed as percentage of standard reference range, from fasting plasma insulin and glucose data.[38]

[f] Physical activity scales, energy expenditure during physical activity (MET minutes per week), low physical activity category, and sedentary time derived from the international physical activity questionnaire.[39,40]

[g] Dietary fat and fiber scores based on self-reported Diet Behavior Questionnaire.[41]

[h] Well-being score questionnaire, EQ-5D questionnaire.[30,42-44]

The combined intervention group at 12 months had a significantly lower mean weight (−1.76 kg), waist circumference (−2.48 cm), and BMI. Despite relatively low levels of weight loss, compared with the landmark studies in the field, the maintenance of behavior changes or area under the curve generated may be partly responsible for the marked effect on diabetes incidence. For the subgroup who attained a high intervention dose, weight loss was significant even at 2 years into the program (−3.47 kg) compared with those attaining a low dose. These weight changes are similar to that seen in a systematic analysis of weight loss in intervention arms in translational and controlled trial prevention studies.28 It is also similar to the observed mean weight loss in high attenders in the NHS England diabetes prevention program.12 The longer-term legacy effect of the NDPS intervention on type 2 diabetes incidence and maintained weight loss is unknown, but some short-term regain of lost weight after an intensive lifestyle intervention is a common observation in people with obesity, type 2 diabetes, or high-risk glycemic categories, particularly in those with the least initial weight loss.49-52 We also observed a significant

increase in energy expenditure in the intervention groups (eTables 3-7 in Supplement 2). There is a direct consistent association between reduced type 2 diabetes risk and an increase in almost all type of physical activity and energy expenditure that is only partially mediated through changes in adiposity.53 The DPM-supplemented intervention group (INT- DPM) did not differ significantly from the INT group in the risk of type 2 diabetes, any secondary outcome, or in participant adherence to the intervention. The use of lay volunteer health workers to deliver lifestyle modification interventions for people at high risk of type 2 diabetes, or with established type 2 diabetes, is well recognized 30-32 but this study's model did not add value.30-32,37 To our knowledge, only 1 other study has used people with type 2 diabetes in this role to prevent diabetes,53 with significant improvement in risk markers, although it is unknown if this translated into a lower type 2 diabetes incidence. The effect of lay or peer volunteers on type 2 diabetes prevention in high-risk groups has been reviewed, with 30 studies (including 10 randomized clinical trials) largely delivered in high-income countries to largely minority populations of color and studies of between 20 and 2369 participants.30 None of these reported a diabetes prevention benefit with diabetes as an end point or were powered to detect such an outcome, although there were commonly improvements in surrogate markers for diabetes risk.30 Cluster randomized clinical trials in high-risk groups using generic lay trainer programs to support or deliver the intervention have also shown no significant effect in diabetes prevention in community or primary care settings.

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Perspective

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A HALF-CENTURY OF PROGRESS IN HEALTH: THE NATIONAL ACADEMY OF MEDICINE AT 50

Solving Population-wide Obesity — Progress and Future Prospects

Shiriki Kumanyika, Ph.D., M.P.H., and William H. Dietz, M.D., Ph.D.

124 million children and adolescents have obesity. Globally, obesity is responsible for 41% of uterine cancers; more than 10% of gallbladder, kidney, liver, and colon cancers; 40% of cases of cardiovascular disease1 ; and most cases of type 2 diabetes. SARSCoV-2 infection is more likely to cause serious illness or death in people with obesity than in those with a healthier body-mass index (BMI).2 The prevalence of obesity is higher in the United States than in other member countries of the Organization for Economic Cooperation and Development: nationwide, about 42% of adults, 14% of children 2 to 5 years of age, and 20% of children 6 to 19 years of age have obesity. Obesity disproportionately affects racial and ethnic minority groups and rural and low-income populations in the United States. Obesity rates have increased during the past two decades in all age groups except the youngest children.

The Lancet Commission on Obesity has suggested confronting obesity globally within a syndemic framework that views obesity, undernutrition, and climate change as pandemics that interact with and have adverse effects on each other.5 The overproduction and overconsumption that drive obesity also increase the release of greenhouse gases that exacerbate global warming, increase the risk of catastrophic weather events, and reduce crop yields and the micronutrient content of crops, thereby leading to food insecurity and undernutrition, particularly in low- and middle-income countries. Powerful societal, political, socioeconomic, and commercial drivers underpin and sustain these pandemics, and all three of them disproportionately affect less advantaged populations.

Efforts to curb the obesity epidemic must include strengthening and scaling up the most effective strategies, combining complementary interventions, and giving these strategies time to work. This approach assumes that the fundamental drivers of obesity can be allowed to remain in place — that we can work around them. But experts emphasize that obesity on a global scale is embedded in societal structures driven by the forces of globalization, urbanization, and technology. Moreover, disparities will be exacerbated if strategies don’t reach racial and ethnic minority, low-income, and other high-risk communities, and there is some evidence that gaps are already widening. The Healthy Communities Study found that implementation of the CDC’s recommended obesity-prevention strategies was associated with favorable BMI trajectories among White children and in higher-income communities in the Northeast, but not in other regions or among Black or Hispanic children or lower-income communities. Reducing obesity disparities will require strategies that address the underlying societal structures that lead to health disparities more broadly. Reports from the IOM and the U.K. Government Office for Science have called for systems-level transformation to address the structures that foster and sustain population-wide obesity. It will be necessary to reimagine and reengineer systems that define modern life and to move away from the contexts that people often take for granted: an overabundance and the normative overconsumption of highly palatable processed and high-calorie convenience foods, motorized transportation, sedentary work and learning environments and entertainment, and companies whose profits depend on perpetuating these circumstances in both the general and highest-risk populations.

World Health Organization 2020 guidelines on physical activity and sedentary behaviour

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ABSTRACT Objectives To describe new WHO 2020 guidelines on physical activity and sedentary behaviour. Methods The guidelines were developed in accordance with WHO protocols. An expert Guideline Development Group reviewed evidence to assess associations between physical activity and sedentary behaviour for an agreed set of health outcomes and population groups. The assessment used and systematically updated recent relevant systematic reviews; new primary reviews addressed additional health outcomes or subpopulations. Results The new guidelines address children, adolescents, adults, older adults and include new specific recommendations for pregnant and postpartum women and people living with chronic conditions or disability. All adults should undertake 150–300min of moderateintensity, or 75–150min of vigorous-intensity physical activity, or some equivalent combination of moderateintensity and vigorous-intensity aerobic physical activity, per week. Among children and adolescents, an average of 60min/day of moderate-to-vigorous intensity aerobic physical activity across the week provides health benefits. The guidelines recommend regular muscle-strengthening activity for all age groups. Additionally, reducing sedentary behaviours is recommended across all age groups and abilities, although evidence was insufficient to quantify a sedentary behaviour threshold. Conclusion These 2020 WHO guidelines update previous WHO recommendations released in 2010. They reaffirm messages that some physical activity is better than none, that more physical activity is better for optimal health outcomes and provide a new recommendation on reducing sedentary behaviours. These guidelines highlight the importance of regularly undertaking both aerobic and muscle strengthening activities and for the first time, there are specific recommendations for specific populations including for pregnant and postpartum women and people living with chronic conditions or disability. These guidelines should be used to inform national health policies aligned with the WHO Global Action Plan on Physical Activity 2018– 2030 and to strengthen surveillance systems that track progress towards national and global targets.

This paper reports on the development of new WHO guidelines on physical activity and sedentary behaviour.5 These guidelines provide evidencebased public health recommendations concerning the amount (frequency, intensity, duration) and types of physical activity that offer significant health

This paper reports on the development of new WHO guidelines on physical activity and sedentary behaviour.5 These guidelines provide evidencebased public health recommendations concerning the amount (frequency, intensity, duration) and types of physical activity that offer significant health benefits and mitigate health risks (for definitions see table 1). These guidelines have been developed for children, adolescents, adults, older adults and, for the first time, include specific recommendations on physical activity for pregnant and postpartum women and people living with chronic conditions or disability. In addition, for the first time, these WHO guidelines address the health impact of sedentary behaviour. The new WHO guidelines update previous WHO recommendations on physical activity for health released in 20102 with the most recent advances in the evidence base for these behaviours and associated selected health consequences. These new guidelines, together with the Guidelines on Physical Activity, Sedentary Behaviour and Sleep for Children Under 5 Years of Age, 6 provide evidence-updated recommendations for physical activity and sedentary behavior across the life course.

Children and adolescents ***(aged 5–17 years), including those living with disability***	In children and adolescents, physical activity confers benefits for the following health outcomes: physical fitness (cardiorespiratory and muscular fitness), cardiometabolic health (blood pressure, dyslipidaemia, glucose and insulin resistance), bone health, cognitive outcomes (academic performance, executive function) and mental health (reduced symptoms of depression) and reduced adiposity. It is recommended that: ► Children and adolescents should do at least an average of 60 min/day of moderate-to-vigorous intensity, mostly aerobic, physical activity, across the week; ► Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone should be incorporated at least 3 days a week. *Strong recommendation*	In children and adolescents, higher amounts of sedentary behaviour are associated with detrimental effects on the following health outcomes: fitness and cardiometabolic health, adiposity, behavioural conduct/pro-social behaviour and sleep duration. It is recommended that: ► Children and adolescents should limit the amount of time spent being sedentary, particularly the amount of recreational screen time. *Strong recommendation*
Adults ***(aged 18–64 years) including those with chronic conditions and those living with disability***	In adults, physical activity confers benefits for the following health outcomes: all-cause mortality, cardiovascular disease mortality, incident hypertension, incident type 2 diabetes, incident site-specific cancers,mental health (reduced symptoms of anxiety and depression), cognitive health and sleep ; measures of adiposity may also improve. It is recommended that: ► All adults should undertake regular physical activity; ► Adults should do at least 150–300 min of moderate-intensity aerobic physical activity, or at least 75–150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate-intensity and vigorous-intensity activity throughout the week for substantial health benefits; ► Adults should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits. *Strong recommendation* ► Adults may increase moderate-intensity aerobic physical activity to >300 min, or do >150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate-intensity and vigorous-intensity activity throughout the week for additional health benefits (when not contraindicated for those with chronic conditions). *Conditional recommendation*	In adults, higher amounts of sedentary behaviour are associated with detrimental effects on the following health outcomes: all-cause mortality, cardiovascular disease mortality and cancer mortality and incidence of cardiovascular disease, type 2 diabetes and cancer. It is recommended that: ► Adults should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits; ► To help reduce the detrimental effects of high levels of sedentary behaviour on health, adults should aim to do more than the recommended levels of moderate-to-vigorous physical activity. *Strong recommendation*
Older adults ***(aged 65 years and older) including those with chronic conditions and those living with disability***	In older adults, physical activity also helps prevent falls and falls-related injuries and declines in bone health and functional ability. It is recommended that: As for adults, plus ► As part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasises functional balance and strength training at moderate or greater intensity on 3 or more days a week, to enhance functional capacity and to prevent falls. *Strong recommendation*	As for adults *Strong recommendation*
Pregnant and postpartum women	In women, physical activity during pregnancy and the postpartum period confers benefits for the following maternal and fetal health outcomes: reduced risk of pre-eclampsia, gestational hypertension, gestational diabetes, excessive gestational weight gain, delivery complications and postpartum depression and no increase in risk of stillbirth, newborn complications or adverse effects on birth weight. It is recommended that all pregnant and postpartum women without contraindication should: ► undertake regular physical activity throughout pregnancy and post partum; ► do at least 150 min of moderate-intensity aerobic physical activity throughout the week for substantial health benefits; ► incorporate a variety of aerobic and muscle-strengthening activities. Adding gentle stretching may also be beneficial. In addition: Women who, before pregnancy, habitually engaged in vigorous-intensity aerobic activity or who were physically active can continue these activities during pregnancy and the postpartum period.	► Pregnant and postpartum women should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. *Strong recommendation*

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Original Investigation | Nutrition, Obesity, and Exercise

Effect of a Low-Fat Vegan Diet on Body Weight, Insulin Sensitivity, Postprandial Metabolism, and Intramyocellular and Hepatocellular Lipid Levels in Overweight Adults

A Randomized Clinical Trial

Hana Kahleova, MD, PhD; Kitt Falk Petersen, MD; Gerald I. Shulman, MD, PhD; Jihad Alwarith, BS; Emilie Rembert, BS; Andrea Tura, PhD; Martin Hill, PhD; Richard Holubkov, PhD; Neal D. Barnard, MD

Abstract IMPORTANCE Excess body weight and insulin resistance lead to type 2 diabetes and other major health problems. There is an urgent need for dietary interventions to address these conditions. OBJECTIVE To measure the effects of a low-fat vegan diet on body weight, insulin resistance, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults. DESIGN, SETTING, AND PARTICIPANTS This 16-week randomized clinical trial was conducted between January 2017 and February 2019 in Washington, DC. Of 3115 people who responded to flyers in medical offices and newspaper and radio advertisements, 244 met the participation criteria (age 25 to 75 years; body mass index of 28 to 40) after having been screened by telephone. INTERVENTIONS Participants were randomized in a 1:1 ratio. The intervention group (n = 122) was asked to follow a low-fat vegan diet and the control group (n = 122) to make no diet changes for 16 weeks. MAIN OUTCOMES AND MEASURES At weeks 0 and 16, body weight was assessed using a calibrated scale. Body composition and visceral fat were measured by dual x-ray absorptiometry. Insulin resistance was assessed with the homeostasis model assessment index and the predicted insulin sensitivity index (PREDIM). Thermic effect of food was measured by indirect calorimetry over 3 hours after a standard liquid breakfast (720 kcal). In a subset of participants (n = 44), hepatocellular and intramyocellular lipids were quantified by proton magnetic resonance spectroscopy. Repeated measure analysis of variance was used for statistical analysis.

RESULTS

Dietary Intake and Physical Activity Self-reported energy intake decreased in both groups but more so in the intervention group (treatment effect, −354.9 kcal/d; 95% CI, −519.0 to −190.8 kcal/d; P < .001) (Table 2). In the intervention group, mean intakes of carbohydrate and fiber increased, whereas mean fat, protein, and cholesterol intake decreased. These values did not change significantly in the control group. Physical activity decreased slightly in both groups (−709.8 metabolic equivalents [95% CI, −1346 to −73.9 metabolic equivalents] in the control group and −604.8 metabolic equivalents [95% CI, −1388 to −178.6 metabolic equivalents] in the intervention group; between-group P = .84).

Body Weight, Body Composition, and Blood Lipid Levels Mean body weight decreased by 6.4 kg in the intervention group compared with 0.5 kg in the control group (treatment effect, −5.9 kg; 95% CI, −6.7 to −5.0; interaction between group and time, P < .001). This difference was largely attributable to a reduction in body fat, as noted by significant decreases in fat mass and visceral fat volume in the intervention group participants. Total and low-density lipoprotein cholesterol levels decreased by 0.5 mmol/L and 0.4 mmol/L (to convert to milligrams per deciliter, divide by 0.0259), respectively, in the

intervention group, with no significant changes in the control group (0.1 mmol/L and 0.07 mmol/L, respectively) (P < .001 for both)

Insulin Sensitivity Fasting plasma insulin concentration decreased by 21.6 pmol/L (to convert to micro-IU per milliliter, divide by 6.945) in the intervention group, with no significant change in the control group (23.6 pmol/L; 95% CI, −5.0 to 54.3; between-group P = .006). The homeostasis model assessment index (a measure of insulin resistance) decreased significantly (−1.3; 95% CI, −2.2 to −0.3; P < .001), and PREDIM (a measure of insulin sensitivity) increased significantly in the intervention group (0.9; 95% CI, 0.5-1.2; P < .001); neither changed significantly in the control group (Table 2). Within the intervention group, the change in PREDIM correlated negatively with the change in body weight (r = −0.43; P < .001). Postprandial Metabolism Postprandial energy expenditure (the thermic effect of food) increased by 18.7% (95% CI, 4.4%-22.3%) in the intervention group from baseline to 16 weeks and did not change significantly in the control group (14.1%; 95% CI, 6.5%-20.4%) (interaction between group and time, P < .001) (Figure 2A). The F values were as follows: group, F = 1.7 (P = .19); week, F = 15.4 (P < .001); time, in thermic effect of food correlated negatively with changes in fat mass (r = −0.30; P < .05) and positively with changes in PREDIM (r = 0.36; P < .05). That is, as fat mass decreased and insulin sensitivity improved, postprandial metabolism increased (Table 2). A linear regression model for changes in reported energy intake and body weight showed that every 100 kcal/d change in energy intake was associated with a 0.15 kg change in body weight (eFigure 3 in Supplement 2). The mean (SD) reported energy reduction of 355 (617) kcal in the intervention group compared with the control group would therefore be associated with a mean (SD) weight loss of 0.53 (4.4) kg. For changes in postprandial energy expenditure and body weight, every change in postprandial energy expenditure of 10 000 U in area under the curve was associated with a change in body weight of 0.48 kg (eFigure 3 in Supplement 2). The mean (SD) decrease in postprandial energy expenditure of 8588 (34 020) U of area under the curve was associated with an mean (SD) weight loss of 0.41 (2.8) kg. Hepatocellular and Intramyocellular Lipid Levels In the 44 participants for whom hepatocellular and intramyocellular lipid levels were quantified, baseline hepatocellular lipid content was generally in the normal range.29,30 Nonetheless, hepatocellular lipid content decreased in the intervention group by 34.4% (from a mean [SD] of 3.2% [2.9%] to 2.4% [2.2%]; P = .03) and remained unchanged in the control group (from a mean [SD] of 3.3% [4.3%] to 3.6% [4.7%]) (group, F = 3.1 [P = .09]; week, F = 1.27 [P = .27]; group × week, F = 10.8 [P = .002]) (Figure 2B). Results were similar in models adjusted for age and race/ethnicity (eFigure 1 in Supplement 2) and for baseline BMI (eFigure 2 in Supplement 2). Within the intervention group, the decrease in hepatocellular lipid levels was significantly associated with change in body weight (r = 0.42; P = .04) but not with changes in reported energy intake (r = 0.24; P = .27) or fiber consumption (r = 0.07; P = .76). In both groups combined, changes in hepatocellular lipid levels correlated negatively with changes in PREDIM (r = −0.47; P < .05). That is, as hepatocellular lipid level decreased, insulin sensitivity increased.

Επινεφρίδια

ΠΡΟΕΔΡΟΣ: Αικατερίνη Σαριδάκη
ΟΜΙΛΗΤΗΣ: Γιάννης Ηλίας

CLINICAL RESEARCH ARTICLE

Perioperative Glucocorticoid Therapy for Patients with Adrenal Insufficiency: Dosing Based on Pharmacokinetic Data

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Background: Perioperative glucocorticoid therapy for patients with adrenal insufficiency (AI) is currently based on anecdotal reports, without supporting pharmacokinetic data.

Methods: We determined the half-life, clearance, and volume of distribution of 2 consecutive intravenously (IV)-administered doses of hydrocortisone (15 or 25 mg every 6 hours) to 22 dexamethasone-suppressed healthy individuals and used the data to develop a novel protocol to treat 68 patients with AI who required surgical procedures. Patients received 20 mg of hydrocortisone orally 2 to 4 hours before intubation and were started on 25 mg of IV hydrocortisone every 6 hours for 24 hours and 15 mg every 6 hours during the second day. Nadir cortisol concentrations were repeatedly measured during that period.

Results: In healthy individuals, cortisol half-life was longer when the higher hydrocortisone dose was administered (2.02 ± 0.15 vs 1.81 ± 0.11 hours; $P < 0.01$), and in patients with AI, the half-life was longer than in healthy individuals given the same hydrocortisone dose. In both populations, the cortisol half-life increased further with the second hormone injection. Prolongation of cortisol half-life was due to decreased hydrocortisone clearance and an increase in its volume of distribution. Nadir cortisol levels determined throughout the 48 postoperative hours were within the range of values and often exceeded those observed perioperatively in patients without adrenal dysfunction.

Conclusions: Cortisol pharmacokinetics are altered in the postoperative period and indicate that lower doses of hydrocortisone can be safely administered to patients with AI undergoing major surgery. The findings of this investigation call into question the current practice of administering excessive glucocorticoid supplementation during stress. **(*J Clin Endocrinol Metab* 105: e753–e761, 2020)**

Key Words: HPA function, adrenal insufficiency, stress doses of glucocorticoids

Activation of the hypothalamic-pituitary-adrenal (HPA) function is one of several characteristic features of the physiologic response to psychological or physical stressors such as trauma, infections, and surgery. The intensity of the stress stimulus often dictates the degree and duration of HPA activation (1, 2). While the importance of having adequate glucocorticoid secretion during and after major surgery has been well recognized for decades, the magnitude of perioperative HPA activation required during that period has been debated for

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Abbreviations: AI, adrenal insufficiency; AUC, area under the curve; BMI, body mass index; HC, hydrocortisone; HPA, hypothalamic-pituitary-adrenal; IV, intravenous.

Original Article

Comprehensive Analysis of Steroid Biomarkers for Guiding Primary Aldosteronism Subtyping

Adina F. Turcu, Taweesak Wannachalee, Alexander Tsodikov, Aya T. Nanba, Jianwei Ren, James J. Shields, Patrick J. O'Day, Donald Giacherio, William E. Rainey, Richard J. Auchus

Abstract—Adrenal vein sampling (AVS) is required to distinguish unilateral from bilateral aldosterone sources in primary aldosteronism (PA), and cortisol is used for AVS data interpretation, but cortisol has several pitfalls. In this study, we present the utility of several other steroids in PA subtyping, both during AVS, as well as in peripheral serum. We included patients with PA who underwent AVS at University of Michigan between 2012 and 2018. We used mass spectrometry to simultaneously quantify 17 steroids in adrenal veins (AV) and periphery, both at baseline and after cosyntropin administration. PA was classified as unilateral or bilateral based on a lateralization index ≥ or <4, respectively, separately for baseline and post-cosyntropin administration. Of 131 participants, AV catheterizations was deemed failed in 28 (21 %) patients (36 AVs) at baseline. Eight steroids demonstrated higher AV/periphery ratios than cortisol (P<0.01 for all); 11β-hydroxyandrostenedione, 11-deoxycortisol, and corticosterone rescued most failed baseline catheterizations. Lateralization was generally consistent when using these alternative steroids. Based on pre- and post-cosyntropin data, the remaining 103 patients were classified as: U/U, 37; B/B, 32; U/B, 20; B/U, 14. Discriminant analysis of multi-steroid panels from peripheral serum showed distinct profiles across the 4 groups, with highest aldosterone, 18-oxocortisol and 11-deoxycorticosterone in U/U patients. In conclusion, 11β-hydroxyandrostenedione and 11-deoxycortisol are superior to cortisol for AVS data interpretation. Single assay multi-steroid panels measured in peripheral serum are helpful in stratified PA subtyping and have the potential to circumvent AVS in a subset of patients with PA. **(*Hypertension*. 2020;75:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.13866.)** • **Online Data Supplement**

Key Words: adrenal gland ■ aldosterone ■ hypertension ■ renin

Primary aldosteronism (PA) is traditionally subtyped into unilateral forms, most commonly aldosterone-producing adenoma (APA), or bilateral hyperaldosteronism (BHA).[1] Accurate PA subtyping is essential for guiding clinical management. Unilateral PA can be cured or improved by unilateral adrenalectomy, while BHA requires life-long medical therapy.[1] Adrenal vein sampling (AVS) is recommended by expert guidelines for PA subtyping.[1,2] AVS protocols and criteria for data interpretation have varied between referral centers, leading to heterogeneity in selecting PA surgical candidates.[3,4]

Cortisol is used in all steps of AVS results interpretation. Disadvantages of using cortisol include longer half-life relative to aldosterone and fluctuations during the procedure, particularly important in the absence of cosyntropin stimulation. Furthermore, mild autonomous cortisol excess is relatively common in patients with PA,[5,6] which can lead to cortisol suppression in the contralateral adrenal gland and alter AVS results. Recent studies have proposed alternative biomarkers for AVS data interpretation, including metanephrines, androstenedione (A4), dehydroepiandrosterone, 17α-hydroxyprogesterone (17OHP), and 11-deoxycortisol (11dF).[7–11] A4, dehydroepiandrosterone and 17OHP, however, are also produced by the gonads, and the latter has cyclical variations in reproductive age women. In contrast, 11β-hydroxyandrostenedione (11OHA4) is produced primarily and abundantly in the adrenal glands,[12,13] and we, therefore, hypothesized that 11OHA4 could be a valuable biomarker for adrenal vein catheterization.

Beyond the variability in protocols and data interpretation among expert centers, additional AVS drawbacks, including its high cost, scarce availability and technical challenges, have recently driven efforts to develop noninvasive PA subtyping methods, such as steroid biomarkers measured in peripheral serum.[8,14] Peripheral 18-oxocortisol (18oxoF) and 18-hydroxycortisol (18OHF) have been shown to perform well in identifying APAs in Asian patients, who have a high prevalence of *KCNJ5* mutations.[14] The utility of these hybrid steroids was, however, poor when used alone in Europeans,[8] who display a variety of somatic aldosterone-driver mutations.[15] In such populations, multi-steroid panels hold more promise in PA subtyping based on peripheral blood tests.[8] Herein, we present

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CLINICAL RESEARCH ARTICLE

Subtyping of Primary Aldosteronism in the AVIS-2 Study: Assessment of Selectivity and Lateralization

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Context: Adrenal venous sampling (AVS) is the key test for subtyping primary aldosteronism (PA), but its interpretation varies widely across referral centers and this can adversely affect the management of PA patients.

Objectives: To investigate in a real-life study the rate of bilateral success and identification of unilateral aldosteronism and their impact on blood pressure outcomes in PA subtyped by AVS.

Design and settings: In a retrospective analysis of the largest international registry of individual AVS data (AVIS-2 study), we investigated how different cut-off values of the selectivity index

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Abbreviations: APA, aldosterone-producing adenoma; AV, adrenal vein; AVIS, Adrenal Vein sampling International Study; AVS, adrenal venous sampling; IVC, inferior vena cava; LI, lateralization index; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PASO, primary aldosteronism surgery outcome; PCC, plasma cortisol concentration; RASI, relative aldosterone secretion index; SI, selectivity index.

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(SI) and lateralization index (LI) affected rate of bilateral success, identification of unilateral aldosteronism, and blood pressure outcomes.

Results: AVIS-2 recruited 1625 individual AVS studies performed between 2000 and 2015 in 19 tertiary referral centers. Under unstimulated conditions, the rate of biochemically confirmed bilateral AVS success progressively decreased with increasing SI cut-offs; furthermore, with currently used LI cut-offs, the rate of identified unilateral PA leading to adrenalectomy was as low as <25%. A within-patient pairwise comparison of 402 AVS performed both under unstimulated and cosyntropin-stimulated conditions showed that cosyntropin increased the confirmed rate of bilateral selectivity for SI cut-offs ≥ 2.0, but reduced lateralization rates ($P < 0.001$). Post-adrenalectomy outcomes were not improved by use of cosyntropin or more restrictive diagnostic criteria.

Conclusion: Commonly used SI and LI cut-offs are associated with disappointingly low rates of biochemically defined AVS success and identified unilateral PA. Evidence-based protocols entailing less restrictive interpretative cut-offs might optimize the clinical use of this costly and invasive test. **(*J Clin Endocrinol Metab* 105: 2042–2052, 2020)**

Key Words: aldosterone, aldosteronism, diagnosis, adrenal vein sampling, registry

Primary aldosteronism (PA) is incorrectly regarded as a rare condition, despite evidence showing that it is the most common cause of endocrine hypertension (1–4). Failure to identify and subtype PA at an early stage leaves a multitude of patients exposed to life-long hyperaldosteronism, and thus to a high risk of cardiovascular events, particularly atrial fibrillation, as shown in both retrospective and prospective studies (5–8).

In the work-up of PA patients, the subtyping is a fundamental step, because patients with a unilateral form, mostly aldosterone-producing adenoma (APA) and unilateral adrenal hyperplasia (9, 10), benefit from laparoscopic adrenalectomy to obtain definitive correction of the hyperaldosteronism and often cure of arterial hypertension. Conversely, patients with bilateral PA, predominantly bilateral adrenal hyperplasia (also known as idiopathic hyperaldosteronism), require life-long medical treatment with a mineralocorticoid receptor antagonist (MRA), often in combination with multiple other antihypertensive agents.

To distinguish between unilateral and bilateral PA, all current guidelines advocate use of adrenal vein sampling (AVS) (11, 12), a technically demanding test where success is defined as bilateral selectivity, ie, adequate sampling of both adrenal veins. Confirmation of selectivity also serves to minimize the impact of two potential confounders when ascertaining lateralization of aldosterone excess: the degree of proximity of the catheter's tip to the adrenal cortex, and dilution effect from blood in accessory veins or inferior vena cava.

The criteria to define selectivity and lateralization remain variable, even at major tertiary centers where AVS is performed on a regular basis, as shown by data from a large international survey (AVIS-1) (13) and expert consensus reports (14, 15). This heterogeneity in interpretation can have a profound effect on the clinical decision-making, and thus on the usefulness of AVS.

The Adrenal Vein sampling International Study (AVIS)-2 was planned after completion of AVIS-1(13) with the aim of creating a large international registry of individual AVS data. The results of this study regarding patient outcomes, ie, correction of aldosteronism and rate of cured/improvement of arterial hypertension are reported elsewhere (16): not only did they provide a snapshot of what occurs in real-life and highlight the general outcome benefit of AVS-guided surgical decision-making but also demonstrated the inconsistencies in AVS use and their profound clinical implications (16). Based on those findings, in this study we explored the potential impact and usefulness of more standardized AVS interpretation criteria on management of PA patients. Hence, we herein report on: (i) the potential rate of selective (confirmed successful) AVS studies, (ii) the potential rate of unilateral PA suitable for adrenalectomy; (iii) the post adrenalectomy blood pressure outcomes as a function of the AVS protocol and of commonly advocated diagnostic cut-offs for the indexes defining selectivity (SI) and lateralization (LI).

Methods

The study rationale, design, center recruitment, inclusion/exclusion criteria, population characteristics, and outcome analysis of AVIS-2 were reported in a separate paper (16) and are recapitulated in the Supplementary Methods; all supplementary material and figures are located in a digital research material repository (17). All procedures were carried out according to the Helsinki Declaration. The protocol of the study was approved by the Ethics Committee of both the coordinating center and the participating centers.

In brief, de-identified biochemical data from individual AVS studies were entered in a dedicated web-based platform

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ORIGINAL SCIENTIFIC REPORT

Outcomes After Surgery for Unilateral Dominant Primary Aldosteronism in Sweden

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Abstract

Background Primary aldosteronism (PA) is the most common cause of secondary hypertension. Surgery is the mainstay of treatment for unilateral dominant PA, but reported cure rates varies. The aim of the present study was to investigate contemporary follow-up practices and cure rates after surgery for PA in Sweden.

Methods Patients operated for PA and registered in the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) 2009–2015 were identified. Patient data were extracted, and follow-up data (1–24 months) was recorded. Doses of antihypertensive medication and potassium supplementation were calculated using defined daily doses (DDD), and the Primary Aldosteronism Surgical Outcome (PASO) criteria were used to evaluate outcomes.

Results Of 190 registered patients, 171 (47% female, mean age 53 years, median follow-up 3.7 months) were available for analysis. In 75 patients (44%), missing data precluded evaluation of biochemical cure according to the PASO criteria. Minimal invasive approach was used in 168/171 patients (98%). Complication rate (Clavien-Dindo >3a) was 3%. No mortality was registered. Pre/postoperatively 98/66% used antihypertensives (mean DDD 3.7/1.5). 89/2% had potassium supplementation (mean DDD 2.0/0) before/after surgery. Complete/partial biochemical and clinical success according to the PASO criteria were achieved in 92/7% and 34/60%, respectively.

Conclusion In this study, reflecting contemporary clinical practice in Sweden complete/partial biochemical and clinical success after surgery for PA was 92/7% and 34/60%. Evaluation of biochemical cure was hampered by lack of uniform reporting of relevant outcome measures. We suggest mandatory reporting of surgical outcomes using the PASO criteria for all units performing surgery for PA.

This paper was presented as an oral presentation at the IAES meeting/48th World Congress of Surgery August 11–15, 2019 in Kraków, Poland.

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Clinical Investigation

Stereotactic Body Radiation Therapy of Adrenal Metastases: A Pooled Meta-Analysis and Systematic Review of 39 Studies with 1006 Patients

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Summary

A systematic review and pooled meta-analysis of studies reporting outcomes of stereotactic body radiation therapy for adrenal metastases was performed. Stereotactic body radiation therapy provided good 1-year local control with an excellent safety profile, and dose escalation was found to correlate with improved local control.

Purpose: To perform a systematic review and pooled meta-analysis of adrenal metastasis stereotactic body radiation therapy (SBRT) outcomes, treatment characteristics, and toxicity to define the efficacy and propose guidelines for intervention.

Methods and Materials: We performed a comprehensive literature search of the Embase and PubMed databases of studies reporting outcome or toxicity data for photon-based SBRT of adrenal metastases in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We then conducted a meta-analysis to estimate pooled overall response, local control (LC), and overall survival and analyzed these outcomes in the context of dosimetric parameters and toxicity using metaregression.

Results: Thirty-nine studies published between 2009 and 2019 reporting outcomes on 1006 patients were included. The median follow-up was 12 months, and the median biological equivalent dose (BED10, alpha/beta = 10) was 67 Gy. The pooled overall response was 54.6% (95% confidence interval [CI], 46.5%-62.5%). The pooled 1- and 2-year rates of LC were 82% (95% CI, 74%-88%) and 63% (95% CI, 50%-74%), respectively, and the pooled 1- and 2-year overall survival rates were 66% (95% CI, 57%-74%) and 42% (95% CI, 31%-53%), respectively. There was a strong positive association between SBRT dose

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Steve Braunstein and David Raleigh made equal contributions to this study.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Disclosures: none.

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and 1- and 2-year LC ($P < .0001$, $P = .0002$) and an association with 2-year OS ($P = .03$). Based on a metaregression of dose and LC, BED10 of 60 Gy, 80 Gy, and 100 Gy predicted 1-year LC of 70.5%, 84.8%, and 92.9% and 2-year LC of 47.8%, 70.1%, and 85.6%, respectively. The overall rate of grade 3 or higher toxicity was 1.8%.

Conclusions: SBRT of adrenal metastases provides good 1-year LC with an excellent safety profile, and dose escalation may be associated with improved LC. Prospective studies are needed to validate these findings and determine whether there are subsets of patients for whom adrenal metastasis–directed SBRT may confer a survival advantage. Published by Elsevier Inc.

Introduction

In recent years, there has been growing interest in oligometastasis-directed local therapy based on the hypothesis that cytoreductive and ablative treatments may improve the outcomes of patients with a limited burden of systemic disease.[1-4] The adrenal glands are a common site of metastasis from lung cancer, renal cell carcinoma, and melanoma, and previous studies have reported good outcomes after surgical adrenalectomy or other invasive approaches such as radiofrequency ablation for the treatment of adrenal metastases.[5,6]

Stereotactic body radiation therapy (SBRT) has emerged as an important treatment modality that allows conformal delivery of ablative doses of radiation therapy in a limited number of fractions. In the last decade, a growing number of small retrospective series have been published on SBRT treatment of adrenal metastases.[7-44] However, because cases of adrenal metastasis that are amenable to SBRT and in an appropriate clinical setting are relatively uncommon, these retrospective reports have been limited in sample size, which has hindered robust estimates of treatment efficacy and identification of optimal dosimetric parameters. In light of these limited data, there are also concerns regarding the safety of SBRT for adrenal metastases, particularly with regard to renal toxicity, adrenal insufficiency,[45] and damage to regional gastrointestinal viscera.[46] To our knowledge, no comprehensive meta-analysis has been performed on this topic. A prior qualitative systematic review including 10 studies was published in 2015[47]; however, a significant number of additional studies have been published since then, but no quantitative pooled meta-analysis has been performed to date. Thus, the aim of this study was to identify and pool the collective experience in the English-language literature, with a focus on response rate, local control (LC), overall survival (OS), dosimetry, SBRT technique, and toxicity, to define the efficacy and propose guidelines for adrenal metastasis–directed SBRT.

Methods and Materials

Literature search and inclusion and exclusion criteria

A comprehensive search of the English-language literature was conducted in September 2019 using the Embase and PubMed electronic databases with the following query: (sbrt OR stereotactic OR radiosurgery OR sabr OR knife) AND (adrenal/exp OR adrenal) AND (metastasis/exp OR metastasis OR metastases/exp OR metastases OR metastatic). Studies from any period were included. Duplicate and non-English results were removed, and the subsequent list of studies was systematically screened for relevance first by title and then by assessment of the abstract and full text. Studies were excluded from the meta-analysis if (1) there were no outcome or toxicity data specific to stereotactic radiation therapy of adrenal metastases; (2) the study contained technical or dosimetric data only and no patient outcome or toxicity data; (3) the study was a review, editorial, or commentary; (4) the study reported redundant data already reported in another study; (5) the study reported results of proton therapy; or (6) there were fewer than 5 patients in the study. Thus, studies reporting clinical outcome or toxicity data for photon-based stereotactic radiation therapy of adrenal metastases in 5 or more patients were included in this meta-analysis and systematic review.

SBRT was defined as the delivery of higher fractional doses of radiation than conventional fractionation (>1.8-2.5 Gy) in a relatively small number of fractions, using external beam radiation therapy to a well-defined target and using image guidance or motion management to deliver greater conformality because of sensitive organs at risk. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.[48]

Data extraction

The literature search and study screening were performed by a single investigator (W.C.C.). Studies meeting all inclusion and exclusion criteria were then divided, and data extraction was performed by 4 investigators (W.C.C., J.P., J.D.B., and U.B.). A single investigator (W.C.C.) subsequently re-reviewed extracted data from all included studies and discussed discrepancies with other investors to achieve a consensus. No attempt was made to contact study authors for additional data.

Clinical and dosimetric characteristics were extracted from each study. If median or mean biological equivalent dose using alpha/beta of 10 (BED10) to the target was reported, this was extracted. Otherwise, the study's representative BED10 was calculated from the reported mean/median prescribed dose and fractionation by applying the standard linear quadratic formula, $\mathrm{BED10} = nd \times (1 + d/[a/b])$, where $a/b = 10$ and n and d represent the number of

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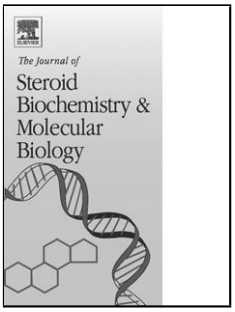

Effect of androgen excess and glucocorticoid exposure on metabolic risk profiles in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Effect of androgen excess and glucocorticoid exposure on metabolic risk profiles in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Highlights

- Metabolic health in patients with congenital adrenal hyperplasia (CAH) is good
- CAH men are prone to increased relative body fat mass
- Hydrocortisone use is superior in terms of body composition in comparison to synthetic glucocorticoids
- Arterial hypertension is rare, but 54 % of patients have an impaired systolic drop at night
- Impaired dipping is independently mediated by higher sodium levels
- Insulin resistance is more common in CAH women and in those with poor androgen control

Abstract

Data on cardiovascular morbidity in adults with congenital adrenal hyperplasia (CAH) is sparse. We therefore aimed to determine the role of androgen control and glucocorticoid therapy on metabolic health. For that purpose, we included 90 patients (N = 39 men, N = 51 women) with classic CAH due to 21-hydroxylase deficiency (N = 61 salt wasting, N = 29 simple virilizing) and an equal number of controls matched for age, sex, BMI and smoking-habits. We could show that there was no difference in intima-media-thickness between patients and controls and only one patient fulfilled all criteria of the metabolic syndrome. CAH men presented with an increased relative body fat mass in comparison to controls (25.6% vs. 22.1%; p = 0.011) while this was not true for CAH women. Body fat was lower in those taking hydrocortisone instead of synthetic glucocorticoids (B = -3.27; p = 0.048). While arterial hypertension was rare, 54 % of patients had an impaired systolic drop at night or were classified as non-dippers (17%). Impaired dipping was not associated with evening glucocorticoid and fludrocortisone intake but mediated by sodium levels. Insulin resistance was more common in CAH women (B = 1.689; p = 0.036) and in those with poor androgen control (B = 0.823; p = 0.046). In summary, we could show that good cardiovascular health outcome in adult CAH patients can be achieved. Hydrocortisone is superior in terms of body composition. It is yet unclear how non-dipping will translate into cardiovascular morbidity in the long-term.

Keywords

Congenital adrenal hyperplasia, 21-hydroxylase deficiency, blood pressure, metabolism, intima media thickness, body composition

Abbreviations

17-OHP	17-hydroxyprogesterone
ACTH	adrenocorticotrophic hormone
CAH	congenital adrenal hyperplasia
DHEAS	dehydroepiandrosterone sulfate
GC	glucocorticoid(s)
HC	hydrocortisone
HOMA-IR	homeostasis model assessment of insulin resistance
IMT	intima media thickness
MS	metabolic syndrome
SHBG	sex hormone binding globuline
SV	simply virilizing
SW	salt-wasting
WHR	waist-to-hip-ratio

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WILEY

ORIGINAL ARTICLE

Efficacy and safety of prenatal dexamethasone treatment in offspring at risk for congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A systematic review and meta-analysis

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Abstract

Objective: To assess the efficacy and safety of prenatal dexamethasone treatment in offspring at risk for congenital adrenal hyperplasia.

Methods: MEDLINE, EMBASE, the Cochrane Library, the clinicaltrials.gov website databases were systematically searched from inception through March 2019. WMD and SMD with 95%CIs were calculated using random or fixed effects models.

Results: There was a significant reduction in virilization in the DEX-treated group (WMD: −2.39, 95%CI: −3.31,-1.47). No significant differences were found in newborn physical outcomes for birth weight (WMD: 0.09, 95%CI: −0.09, 0.27) and birth length (WMD = 0.27, 95%CI: −0.68, 1.21). Concerning cognitive functions, no significant differences in the domains of psychometric intelligence (SMD: 0.05, 95%CI: −0.74, 0.83), verbal memory (SMD: −0.17, 95%CI: −0.58, 0.23), visual memory (SMD: 0.10, 95%CI: −0.14, 0.34), learning (SMD: −0.02, 95%CI: −0.27, 0.22) and verbal processing (SMD: −0.38, 95%CI: −0.93, 0.17). Regarding behavioural problems, no significant differences in the domains of internalizing problems (SMD: 0.16, 95%CI: −0.49, 0.81), externalizing problems (SMD: 0.07, 95%CI: −0.30, 0.43) and total problems (SMD: 0.14, 95%CI: −0.23, 0.51). With respect to temperament, no significant differences in the domains of emotionality (SMD: 0.13, 95%CI: −0.79, 1.05), activity (SMD: 0.04, 95%CI: −0.32, 0.39), shyness (SMD: 0.25, 95%CI: −0.70, 1.20) and sociability (SMD: −0.23, 95%CI: −0.90, 0.44).

Conclusions: Prenatal DEX treatment reduced virilization with no significant differences in newborn physical outcomes, cognitive functions, behavioural problems and temperament. The results need to be interpreted cautiously due to the existence of limitations.

KEYWORDS

21-hydroxylase deficiency, cognition, congenital adrenal hyperplasia, dexamethasone, problem behaviour, temperament, virilization

Time to Diagnosis in Cushing's Syndrome: A Meta-Analysis Based on 5367 Patients

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Context: Signs and symptoms of Cushing's syndrome (CS) overlap with common diseases, such as the metabolic syndrome, obesity, osteoporosis, and depression. Therefore, it can take years to finally diagnose CS, although early diagnosis is important for prevention of complications.

Objective: The aim of this study was to assess the time span between first symptoms and diagnosis of CS in different populations to identify factors associated with an early diagnosis.

Data Sources: A systematic literature search via PubMed was performed to identify studies reporting on time to diagnosis in CS. In addition, unpublished data from patients of our tertiary care center and 4 other centers were included.

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Study Selection: Clinical studies reporting on the time to diagnosis of CS were eligible. Corresponding authors were contacted to obtain additional information relevant to the research question.

Data Extraction: Data were extracted from the text of the retrieved articles and from additional information provided by authors contacted successfully. From initially 3326 screened studies 44 were included.

Data Synthesis: Mean time to diagnosis for patients with CS was 34 months (ectopic CS: 14 months; adrenal CS: 30 months; and pituitary CS: 38 months; $P < .001$). No difference was found for gender, age (<18 and ≥18 years), and year of diagnosis (before and after 2000). Patients with pituitary CS had a longer time to diagnosis in Germany than elsewhere.

Conclusions: Time to diagnosis differs for subtypes of CS but not for gender and age. Time to diagnosis remains to be long and requires to be improved. **(*J Clin Endocrinol Metab* 105: e12–e23, 2020)**

Key Words: hypercortisolism, ACTH, cortisol, symptoms, meta-analysis

Outline

Cushing's syndrome (CS) is a rare, potentially life-threatening endocrine disease causing, among others, metabolic, psychiatric, musculoskeletal, and cardiovascular comorbidities (1). If left untreated, it is associated with increased mortality, mainly due to cardiovascular and infectious complications, but even in appropriately treated CS, mortality remains elevated (2). CS is mostly adrenocorticotropin (ACTH) dependent, the consequence of corticotroph pituitary adenoma or ectopic ACTH secretion from neuroendocrine tumors. Approximately 20% of cases are ACTH independent due to autonomous cortisol production from adrenal sources. Chronically elevated glucocorticoid concentrations cause the characteristic phenotype, such as weight gain, moon face, buffalo hump, muscle weakness, bruisability, skin atrophy, striae rubrae, menstrual irregularities, hirsutism, acne, and co-morbidities like diabetes mellitus, hypertension, hypercholesterolemia, and osteoporosis (3). Due to the rareness of CS and because these symptoms overlap with other non-CS conditions, it can take many years to diagnose CS in a given patient (4). The recent obesity "epidemic" causes additional challenges to distinguish the few patients with true CS from those with a metabolic syndrome. As the duration of hypercortisolism appears to be the most relevant determinant for the degree of morbidity and preterm mortality, it is important to establish the diagnosis as early as possible (5). Also, there is increasing evidence that restitution of symptoms and body changes after surgery depends on the duration of CS (6). Duration of CS is an important factor influencing patient's recovery after successful surgery, especially regarding psychiatric morbidity (7), which coincides with changes in brain structure and function sustained during exposure to glucocorticoid excess (8). We hypothesized that the time span from first symptoms to final diagnosis of CS could have changed to the better over time. This could be due to either improved biochemical screening tools for CS or also increasing awareness for rare diseases (9). The aim of this study was to assess the time between first symptoms and diagnosis of CS in different populations and geographic backgrounds and from different decades by performing a systematic literature review and meta-analysis including additional results from the German Cushing's Registry. We wanted to identify factors that are associated with early or late diagnosis.

Methods and Patients

Study selection

We performed a systematic literature search in PubMed database and Cochrane library according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines (10). We used the terms "Cushing's syndrome," "Cushing syndrome," "Cushing's disease," "Cushing disease," and "pituitary ACTH hypersecretion" in the title or abstract to identify published articles reporting on Cushing's syndrome/disease in general. The literature search was performed in the last week of July 2018.

Inclusion and exclusion criteria

Studies were eligible for analysis when data reporting on time to diagnosis were available as mean

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ORIGINAL ARTICLE

Radiologically defined lipid-poor adrenal adenomas: histopathological characteristics

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Abstract

Background Adrenal lipid-poor adenomas (LPA) are defined by high unenhanced density (≥ 10 HU), and absolute and relative contrast medium washout > 60% and > 40%, respectively, at computerized tomography (CT). To date, no thorough histopathological characterization has been performed in those frequent lesions (one-third of adrenal adenomas). Our aim was to analyze the histopathological characteristics of adrenal LPA.

Methods Patients with LPA ($n = 57$) were selected among consecutive subjects referred for an adrenal incidentaloma or ACTH-independent Cushing syndrome. FluoroDeoxyGlucose-Positron Emission Tomography (FDG-PET) was performed in 37 patients. In patients treated by adrenalectomy ($n = 17$), Weiss score and Lin–Weiss–Bisceglia score (in tumors composed entirely or predominantly of oncocytes) were calculated.

Results Radiological parameters did not differ among patients with ACTH-independent Cushing syndrome ($n = 6$) and those with adrenal incidentalomas associated with primary aldosteronism ($n = 2$), autonomous cortisol secretion ($n = 14$), or non-functioning ($n = 35$). Patients treated by adrenalectomy had larger tumors (28.9 ± 11.2 *vs* 17.3 ± 8.4 mm, $P < 0.001$), higher CT unenhanced density (29.1 ± 11.0 *vs* 23.1 ± 9.0 HU, $P = 0.043$), and FDG-PET adrenal uptake (9.0 ± 6.4 *vs* 4.4 ± 2.3 SUV, $P = 0.003$) than non-operated ones. Oncocytic features > 75% of the tumor were detected in 12/17 cases (70.6%). Five of those showed borderline-malignant histopathological characteristics by Lin–Weiss–Bisceglia score. Among remaining non-oncocytic tumors, 1/5 had a Weiss score ≥ 3. Overall, 6/17 tumors (35.3%) had borderline-malignant potential. Radiological parameters were similar between patients with benign and borderline-malignant tumors.

Conclusions Adrenal LPA are a heterogeneous group of tumors, mostly composed of oncocytomas. Up to 1/3 of those tumors may have a borderline-malignant potential at histopathology.

Keywords Lipid-poor adenoma · Adrenal tumor · Adrenal oncocytoma · Borderline-malignant

A. De Leo, C. Mosconi have contributed equally to the work.

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Adrenal Incidentalomas are Tied to Increased Risk of Diabetes: Findings from a Prospective Study

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Context: The frequency of adrenal incidentalomas and their association with comorbid conditions have been assessed mostly in retrospective studies that may be prone to ascertainment bias.

Objective: The objective of this work is to evaluate the frequency of adrenal incidentalomas and their associated comorbid conditions.

Design: A prospective cohort study was conducted.

Setting: This study took place at a radiology department at a public hospital.

Participants: Unselected outpatients who underwent an abdominal computed tomography (CT) from January 2017 to June 2018. Patients with known or suspected adrenal disease or malignancy were excluded.

Exposure: All abdominal CT scans were evaluated by an experienced radiologist. Hormonal workup including a 1-mg dexamethasone suppression test was performed in patients bearing adrenal incidentalomas.

Main Outcome and Measure: Frequency of adrenal incidentalomas in abdominal CT of unselected patients; frequency of comorbid conditions, and hormonal workup in patients bearing adrenal incidentalomas.

Results: We recruited 601 patients, and in 7.3% of them an adrenal tumor was found serendipitously. The patients bearing an adrenal incidentaloma had higher body mass index ($P = .009$) and waist circumference ($P = .004$) and were more frequently diabetic ($P = .0038$). At multivariable regression analysis, diabetes was significantly associated with the presence of adrenal incidentalomas ($P = .003$). Autonomous cortisol secretion was observed in 50% of patients who did not suppress cortisol less than 50 nmol/L after 1 mg dexamethasone.

Conclusions: The frequency of adrenal incidentalomas is higher than previously reported. Moreover, adrenal incidentalomas are tied to increased risk of type 2 diabetes. This finding is free from ascertainment bias because patients with adrenal incidentalomas were drawn from a prospective cohort with the same risk of diabetes as the background population. **(*J Clin Endocrinol Metab* 105: e973–e981, 2020)**

Key words: adrenal tumor, incidentaloma, prevalence, Cushing, diabetes

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[‡]G.B. and M.T. are co-senior authors of this work.
Abbreviations: ACTH, adrenocorticotropin hormone; BMI, body mass index;CT, computed tomography; CV, cardiovascular; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; ESE/ENSAT, European Society of Endocrinology and the European Network for the Study of Adrenal Tumors; HbA_{1c}, glycosylated hemoglobin.

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Correlation Between Size and Function of Unilateral and Bilateral Adrenocortical Nodules: An Observational Study

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Keywords: adrenal incidentalomas, adrenal MRI, adrenocortical nodules, adrenocorticotropic hormone (ACTH) stimulation test, CT scan, dexamethasone suppression test, mass spectrometry, serum cortisol, subclinical hypercortisolism

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OBJECTIVE. Adrenal incidentalomas occur in 5% of adults and can produce autonomous cortisol secretion that increases the risk of metabolic syndrome and cardiovascular disease. The objective of our study was to evaluate the relationship between adrenal nodule size measured on CT and autonomous cortisol secretion.

SUBJECTS AND METHODS. In a prospective study of 73 patients 22–87 years old with incidentalomas, unilateral in 52 patients and bilateral in 21 patients, we measured maximum nodule diameter on CT and serum cortisol levels at 8:00 am, 60 minutes after the adrenocorticotropic hormone stimulation test, and after the dexamethasone suppression test. We also studied 34 age-, sex-, and body mass index–matched control subjects. Statistics used were Spearman correlation coefficients, *t* tests, ANOVA test, and multivariate analysis.

RESULTS. The mean maximum diameter of unilateral nodules measured on CT was larger on the right (2.47 ± 0.98 [SD] cm) than on the left (2.04 ± 0.86 cm) ($p = 0.01$). In the bilateral cases, the mean diameter of the right nodules was 2.69 ± 0.93 cm compared with 2.13 ± 0.89 cm on the left ($p = 0.06$). Mean baseline serum cortisol level was significantly higher in the patients with incidentalomas (bilateral, 13.1 ± 4.5 mcg/dL [$p < 0.001$]; unilateral, 9.7 ± 3.2 mcg/dL [$p = 0.019$]) than in the control subjects (7.5 ± 3.6 mcg/dL). After dexamethasone suppression test, serum cortisol levels were suppressed to less than 1.8 mcg/dL in 100% of control subjects, 33% of patients with bilateral incidentalomas, and 62% of patients with unilateral incidentalomas ($p < 0.001$). There were significant correlations between maximum nodule diameter on CT and serum cortisol levels after the dexamethasone suppression test ($\rho = 0.500$; $p < 0.001$) and at baseline ($\rho = 0.373$; $p = 0.003$).

CONCLUSION. Increasing size of adrenal nodules is associated with more severe hypercortisolism and less dexamethasone suppression; these cases need further evaluation and possibly surgery because of increased risks of metabolic syndrome and cardiovascular mortality.

The widespread use of abdominal imaging procedures led to the increased discovery of incidental adrenal masses. The frequency of adrenal incidentalomas varies between 4% and 8% of the adult population and is as high as 10% in the elderly population; approximately 20% of adrenocortical nodules are bilateral [1–4]. Abdominal imaging is also used to search for metastasis and determine staging of primary nonadrenal neoplasia. Careful screening is necessary to exclude primary carcinoma or metastasis to the adrenal glands and clinically functional endocrine tumors that produce aldosterone [5], cortisol [6], and catecholamines [7].

Although adrenal nodule size of 4 cm or larger is an important predictor of malignancy, a study that compared imaging with histopathology results after adrenalectomy showed that imaging characteristics are better for predicting malignancy than nodule size and that 45% of adrenal malignancies would have been missed if prediction had been based on a nodule size of 4 cm or larger [8].

Specific adrenal protocols use CT and MRI to evaluate the morphology of adrenal masses based on size, shape, texture, and lipid content (density). Most adenomas are small, between 1.5 and 4 cm, well-defined, and homogeneous lesions that usually have a high lipid content (i.e., low density) in comparison with other adrenal lesions [9, 10]; however, adenomas can be larger than 4 cm in diameter and somewhat heterogeneous, and the 30% of adenomas that are lipid-poor need additional radiologic evaluation and management [11].

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Utility of the 10 Hounsfield unit threshold for identifying adrenal adenomas: Can we improve?

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ABSTRACT

Background: Current recommendations using Hounsfield units (HU) $\leq$ 10 to identify adrenal adenomas on unenhanced computed tomography (CT) miss 10–40% of benign adenomas. We sought to determine if changing HU threshold and adding absolute percent contrast washout (APW) criteria would identify adrenal adenomas better than current recommendations.

Methods: Imaging characteristics were compared between patients with adenomas (n = 128) and those with non-adenomas (n = 54) after unilateral adrenalectomy. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated.

Results: Using HU $\leq$ 10 to identify adenomas had a sensitivity of 47.6%, specificity of 93.3% (AUC = 0.71, $p < 0.001$), PPV of 95.3%, and NPV of 58.1% for identifying adrenal adenomas. Applying HU $\leq$ 16 improved sensitivity (65.4%) without reducing specificity (93.3%) (AUC = 0.79, $p < 0.001$), PPV increased to 96.3%, and NPV decreased to 47.6%. Applying HU $\leq$ 16 as the initial criterion followed by APW > 60% for lesions exceeding 16 HU, sensitivity increased to 93.4%, specificity was 93.3% and PPV 96.6%, and NPV improved to 85.7% (AUC = 0.96, $p < 0.001$).

Conclusions: Criteria of initial threshold of HU $\leq$ 16 followed by APW > 60% for lesions exceeding 16 HU yielded improved sensitivity and specificity in identification of adrenal adenomas.

Introduction

Incidental adrenal lesions are detected on approximately 5% of abdominal CT scans in patients with no known endocrine abnormalities or malignancy and have been reported in up to 8.7% of autopsies.[1,2] The most important consideration in the evaluation of adrenal incidentalomas is differentiating benign lesions from malignancy. Correct identification of adrenal masses as adenomas or non-adenomas assists in appropriate surgical resection of malignancies while preventing unnecessary resection of benign lesions.

The majority of adenomas have low attenuation and low Hounsfield units (HU) on unenhanced computed tomography (CT).[3,4] The American Association of Clinical Endocrinologists (AACE) and the American Association of Endocrine Surgeons (AAES) guidelines suggest using HU $\leq$ 10 to identify adrenal adenomas.[5] However, between 10 and 40% of adenomas are lipid-poor, and will thus attenuate to HU > 10.[6] Indeed, using HU $\leq$ 10 to identify adrenal adenomas has a sensitivity of 71% and a specificity of 98%.[7–9] Previous studies have demonstrated that decreasing HU threshold improved specificity but reduced sensitivity whereas increasing HU threshold improved sensitivity but reduced specificity.[9]

Venous phase post-contrast enhanced CT can identify lipid-poor adenomas because adenomas have absolute percent contrast washout (APW) greater than 60% — the difference between the contrast-enhanced attenuation and the delayed-enhanced attenuation normalized to the unenhanced attenuation.[10–12] To our knowledge, applying HU threshold in conjunction with APW to

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ARTICLE

Carbonic anhydrase 9 immunohistochemistry as a tool to predict or validate germline and somatic *VHL* mutations in pheochromocytoma and paraganglioma—a retrospective and prospective study

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Abstract

The development of pheochromocytomas and paragangliomas is strongly linked to the presence of germline mutations in more than 15 predisposing genes. Among them, germline and somatic *VHL* mutations account for ~10% of all cases. In contrast with SDHA and SDHB immunohistochemistries that are routinely used to validate *SDHx* gene mutations, there is no such tool available for *VHL* mutations. The aim of this study was to evaluate whether CA9 immunostaining could be used as a tool to predict the presence or validate the pathogenicity of *VHL* gene mutations in paraganglioma. Immunohistochemistry for CA9 was performed on 207 tumors. A retrospective series of 100 paragangliomas with known mutation status for paraganglioma susceptibility genes was first investigated. Then, a prospective series of 107 paragangliomas was investigated for CA9 immunostaining followed by germline and/or somatic genetic testing of all paraganglioma susceptibility genes by next-generation sequencing. Cytosolic CA9 protein expression was heterogeneous in the different samples. However, we observed that a membranous CA9 staining was almost exclusively observed in VHL-related cases. Forty two of 48 (88%) *VHL*-mutated samples showed a CA9 membranous immunostaining. Positive cells were either isolated, varying from 1 or 2 cells (5% of cases) to 10–20 cells per tumor block (35% of cases), grouped in areas of focal positivity representing between 1 and 20% of the tissue section (35% of cases), or widely distributed on 80–100% of the tumor sections (25% of samples). In contrast, 142/159 (91%) of non-VHL-mutated tumors presented no membrane CA9 localization. Our results demonstrate that *VHL* gene mutations can be predicted or validated reliably by an easy-to-perform and low-cost immunohistochemical procedure. CA9 immunohistochemistry on paragangliomas will improve the diagnosis of *VHL*-related disease, which is important for the surveillance and therapeutic management of paraganglioma patients, and in case of germline mutation, their family members.

Introduction

Paragangliomas are rare neuroendocrine tumors that arise in the sympathetic or parasympathetic nervous systems, from the head and neck, to the pelvic region. Pheochromocytomas are

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Very high rate of false positive biochemical results when screening for pheochromocytoma in a large, undifferentiated population with variable indications for testing

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ARTICLE INFO

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ABSTRACT

Objective: Pheochromocytoma/Paraganglioma (PPGL) is a rare tumor with non-specific presentations overlapping common entities like anxiety, hypertension, acute illness and episodic "spells." Assessment of urine normetanephrine or metanephrine (UNM-UMN) in real-life, where PPGL is very rare and PPGL mimics extremely common, may show overlap in results with loss of specificity depending on the reference range. We determined the extent to which UNM-UMN are high in people undergoing screening for PPGL.

Design and methods: Retrospective review of all UNM-UMN performed in a central lab serving Southern Alberta over 8 years.

Results: After excluding pediatric ages and patients with CKD, there were 12,572 unique patients with 14,383 measures of UNM-UMN. 85 patients (0.7%) had markedly high UNM-UMN compatible with likely PPGL. Depending on the age category (in decades), 10–22% of all UNM results were above the upper reference limit (URL), particularly between ages of 40–60. Less than 3% had elevations in both UNM and UMN. Of those with high UNM, 99% were less than 3-fold the URL. Based on the population data, a potential new reference range for UNM is suggested, which may be more appropriate to the types of patient who undergo this form of testing.

Conclusions: There is an extraordinarily high prevalence of high UNM seen in real-life use of the test. However, the vast majority of high UNM are unlikely to be PPGL given the disease rarity and the massive number of tests ordered. This suggests the current laboratory URL may be too low (poor specificity) and/or the reference range may not be appropriate to the type of patient being screened for PPGL. Depending on the frequency of use of any screening test in a population, if the disease is rare and the specificity of the test is poor, a high rate of false positive results will be expected.

1. Introduction

Pheochromocytoma/paraganglioma (PPGL) is a very rare disease with an estimated population prevalence of 2–8 per million population [1] and population incidence of 0.8–2 per 100,000 patient years [2,3]. It has been traditionally associated with a classic constellation of symptoms, including paroxysmal hypertension, palpitations, headache and episodic "spells" [4,5]. Owing to the variety of possible clinical presentations and sometimes dramatic complications of acute cardiovascular or cerebrovascular compromise [6,7] with PPGL, there are many types of physicians who might consider PPGL in a differential diagnosis relevant to their specialty. In addition to discrete tumors arising from the adrenal glands, there has been a growing recognition that PPGL also can manifest as extra-adrenal and malignant disease [8] and may be associated with certain germline mutations. Therefore PPGL has become the subject of broader surveillance and screening strategies [9].

One of the great difficulties in PPGL diagnosis relates to the tremendous overlap in clinical presentation with other very common disorders including anxiety [10,11], hypertension [12] and neurological disorders [13,14]; comprehensive clinical reviews list up to 40 different entities that should be considered in any patient presenting with paroxysmal symptoms or "spells" [15]. PPGL screening is recommended and commonly practiced for the investigation of resistant hypertension, a condition that likely affects up to 7–9% of the population [16,17]. Outside of classic paroxysmal "spells", it is recognized

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ARTICLE

Predictors of recurrence of pheochromocytoma and paraganglioma: a multicenter study in Piedmont, Italy

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Abstract

The available data on the natural history of pheochromocytomas and paragangliomas after radical surgery are heterogeneous and discordant. The aim of our retrospective multicenter study was to find predictors of recurrence in patients with pheochromocytomas and sympathetic paragangliomas submitted to radical surgery in Piedmont (a region in northwest Italy). We collected data from 242 patients diagnosed between 1990 and 2016. Forty-two patients (17.4%) had disease recurrence. Multivariate analysis showed that genetic mutation (HR = 3.62; 95% CI 1.44−9.13; $p = 0.006$), younger age (HR = 0.97; 95% CI 0.95−0.99; $p = 0.031$) and larger tumor size (HR = 1.01; 95% CI 1.00−1.02; $p = 0.015$) were independently associated with a higher recurrence risk of pheochromocytoma and paraganglioma; in pheochromocytomas, genetic mutation (HR = 3.4; 95% CI 1.00−11.48; $p = 0.049$), younger age (HR = 0.97; 95% CI 0.94−0.99; $p = 0.02$), higher tumor size (HR = 1.01; 95% CI 1.00−1.03; $p = 0.043$) and PASS value (HR = 1.16; 95% CI 1.03−1.3; $p = 0.011$) were associated with recurrence. Moreover, tumor size was the only predictor of metastatic pheochromocytoma and paraganglioma (HR = 4.6; 95% CI 1.4−15.0; $p = 0.012$); tumor size (HR = 3.93; 95% CI 1.2−16.4; $p = 0.026$) and PASS value (HR = 1.27; 95% CI 1.06−1.53; $p = 0.007$) were predictors of metastatic pheochromocytoma. In conclusion, our findings suggest that the recurrence of pheochromocytoma and sympathetic paraganglioma develops more frequently in younger subjects, patients with a family history of chromaffin tissue neoplasms, mutations in susceptibility genes, larger tumors and higher values of PASS. We recommend genetic testing in all patients with PPGL and strict follow-up at least on an annual basis.

Keywords Endocrine hypertension · Chromaffin system · Pheochromocytoma · Paraganglioma · Genetic testing

Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare tumors arising from adrenomedullary cells and from sympathetic or parasympathetic ganglia, respectively. Approximately 80−85% of chromaffin-cell tumors are PCCs, whereas 15−20% are PGLs. The prevalence of pheochromocytoma and paraganglioma (PPGL) in hypertensive patients varies between 0.2 and 0.6%, while PCC is observed in 5% of patients with adrenal incidentaloma. PCCs and sympathetic PGLs commonly produce catecholamines: epinephrine, norepinephrine and dopamine, while parasympathetic PGLs are often silent [1]. Metanephrines and CT attenuation values are useful parameters to distinguish PPGL from other tumors [2]. It is important to recognize these tumors early to reduce related cardiovascular morbidity/mortality, prevent growth and extension into adjacent tissues, development of metastases and address syndromic forms.

The rule that 10% of chromaffin tumors are paragangliomas, malignant, associated with genetic mutations, affect patients without arterial hypertension, have bilateral adrenal involvement and pediatric onset [3] is no longer

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ORIGINAL ARTICLE

Feasibility of laparoscopic adrenalectomy for metastatic adrenal tumors in selected patients: a retrospective multicenter study of Japanese populations

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Abstract

Background Because of the small numbers of cases in single centers, the indications for and survival benefits of adrenalectomy for adrenal metastasis remain unclear. We evaluated the outcomes of laparoscopic adrenalectomy for patients with adrenal metastasis.

Methods We retrospectively analyzed the records of 67 patients who underwent laparoscopic adrenalectomy for metastatic disease from 2003 to 2017 at 11 hospitals. Associations of clinical, surgical, and pathologic features with overall survival (OS) and positive surgical margins were evaluated using univariate and multivariate Cox regression analyses and univariate logistic regression analysis.

Results Lung cancer (30%) and renal cell carcinoma (30%) were the most common primary tumor types. Intraoperative complications were observed in seven patients (10%) and postoperative complications in seven (10%). The surgical margin was positive in 10 patients (15%). The median OS was 3.8 years. Univariate analysis showed that the tumor size, episodes of extra-adrenal metastasis before adrenalectomy, extra-adrenal metastasis at the time of adrenalectomy, and positive surgical margins were significantly associated with shorter OS ($p=0.022$, $p=0.005$, $p<0.001$, and $p=0.022$, respectively). Multivariate analysis showed that extra-adrenal metastasis at the time of adrenalectomy and positive surgical margins remained statistically significant ($p=0.022$ and $p=0.049$, respectively). In the univariate analysis, the tumor size was significantly associated with positive surgical margins ($p=0.039$).

Conclusions Laparoscopic adrenalectomy for adrenal metastasis can be safely performed in selected patients, and patients with isolated adrenal metastasis and negative surgical margins seem to have more favorable outcomes.

Keywords Neoplasm metastasis · Adrenalectomy · Laparoscopy

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PERSPECTIVE

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Osteoporosis Management in the Era of COVID-19

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ABSTRACT

Osteoporosis is a chronic condition that reflects reduced bone strength and an associated increased risk for fracture. As a chronic condition, osteoporosis generally requires sustained medical intervention(s) to limit the risks for additional bone loss, compromise of skeletal integrity, and fracture occurrence. Further complicating this issue is the fact that the abrupt cessation of some therapies can be associated with an increased risk for harm. It is in this context that the COVID-19 pandemic has brought unprecedented disruption to the provision of health care globally, including near universal requirements for social distancing. In this Perspective, we provide evidence, where available, regarding the general care of patients with osteoporosis in the COVID-19 era and provide clinical recommendations based primarily on expert opinion when data are absent. Particular emphasis is placed on the transition from parenteral osteoporosis therapies. It is hoped that these recommendations can be used to safely guide care for patients with osteoporosis until a return to routine clinical care standards is available.

KEY WORDS: ABALOPARATIDE; BISPHOSPHONAT; COVID-19; DENOSUMAB; FRACTURES; OSTEOPOROSIS; ROMOSOZUMAB; TERIPARATIDE

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially caused clusters of severe respiratory illness in Wuhan, China, in late 2019[1] and has since rapidly spread in Europe and the United States. As of May 5, 2020, a total of 3,517,345 persons were reported to be infected by SARS-CoV-2 and 243,401 persons to have died of coronavirus disease (COVID-19). COVID-19 was characterized as a pandemic by the World Health Organization on March 11, 2020.[2] In response, many countries have implemented a series of unprecedented measures to mitigate the spread of the virus, including large-scale social isolation, travel bans, restriction of public gatherings, and nationwide lockdowns. Although these social distancing strategies have been necessary from a public health standpoint, they have understandably introduced challenges in the management of many chronic medical conditions.[3]

Because osteoporosis is a chronic disease, continued treatment is a prerequisite in many patients in order to sustain therapeutic benefits, as is the case with other chronic conditions. With the exception of bisphosphonates, which have a long biologic half-life, other anti-osteoporosis drugs need to be provided in a regularly scheduled manner. Delaying the administration of certain categories of osteoporosis drugs can have ominous consequences for patients, ranging from loss of bone mass to increases in bone turnover and fracture risk. Hip fractures, the most devastating type of fracture, significantly impair mobility and independence and lead to an approximately 25% 1-year mortality rate.[4] Recognizing the potential detrimental effects of abruptly terminating anti-osteoporosis therapy, the American Society of Bone and Mineral Research (ASBMR) formed a Steering Committee of bone specialists to address this issue.[5] Here we review available evidence and provide clinical guidance for the management of patients with osteoporosis during the COVID-19 pandemic. We acknowledge both that there is a paucity of data to provide evidence-based clinical recommendations and that treatment modalities are likely to vary according to the status of local and national facilities, such as phlebotomy and infusion therapy centers, as well as outpatient clinics. Thus, these recommendations are based primarily on expert opinion and will require reassessment as the worldwide response to COVID-19 evolves.

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Bone mineral density scans

Although bone mineral density (BMD) testing is a helpful tool to assist in the identification and management of patients at high risk of fractures,[6] these scans should be considered as elective. Thus, BMD examinations may need to be postponed when public health guidance recommends the halting of elective imaging procedures. In the absence of BMD testing, fracture risk stratification can still be performed for treatment-naive adults with the use of the Fracture Risk Assessment Tool (FRAX).[7]

Laboratory monitoring

Standard pretreatment laboratory studies, including serum calcium, creatinine, and/or 25-hydroxyvitamin D, are often obtained before the administration of potent antiresorptive agents, such as intravenous (iv) bisphosphonates and denosumab, in order to minimize risk of inducing hypocalcemia. In patients who are initiating new osteoporosis treatment with a potent antiresorptive agent, we recommend obtaining relevant laboratory studies before first administration. However, the absolute risk of inducing clinically significant hypocalcemia after treatment with either zoledronic acid[8] or denosumab[9] is very low in the absence of significant renal insufficiency. Both to facilitate social distancing guidelines and to minimize patient exposure at phlebotomy centers, we suggest that pretreatment laboratory studies before retreatment with iv bisphosphonates and/or denosumab need not be performed if laboratory values obtained within the preceding year were normal and it is the clinical judgment of the medical provider that the patient's health has been stable. However, we do recommend obtaining laboratory studies for patients with fluctuating renal function and for those who are at higher risk of developing hypocalcemia, such as those with malabsorptive disorders, hypoparathyroidism, or advanced renal dysfunction (chronic kidney disease stages 4 or 5) or those maintained on loop diuretics.

Pharmacologic osteoporosis treatment

The initiation of osteoporosis therapy can be done as an outpatient via a non-face-to-face (ie, telephone or video) visit and should not be delayed in patients at high risk for fracture (eg, patients who have recently sustained an osteoporotic fragility fracture or patients taking chronic high-dose glucocorticoids). In particular, oral osteoporosis regimens can be easily initiated during a telemedicine visit; teriparatide and abaloparatide initiation may also be considered but require additional patient training for subcutaneous self-injections that may be more difficult to arrange. Patients who have fractures requiring hospital admission should be considered for osteoporosis medication initiation while hospitalized to minimize the risk of being lost to follow-up in the post-discharge period, which may be further fragmented during the COVID-19 pandemic. Specifically, there is no evidence for impaired fracture healing in patients who receive early initiation of osteoporosis treatment, including bisphosphonates.[10] It should be acknowledged, however, that the administration of iv bisphosphonates may cause a post-infusion inflammatory reaction, particularly in treatment-naive patients. Symptoms of the inflammatory reaction, including fever and myalgias, have the potential to complicate the care of hospitalized patients by triggering a COVID-19 evaluation and may prolong hospitalization.

When possible to do safely, patients who are already treated with osteoporosis medications should continue to receive ongoing therapies including oral and iv bisphosphonates, denosumab, estrogen, raloxifene, teriparatide, abaloparatide, and romosozumab. There is no evidence that any osteoporosis therapy increases the risk or severity of COVID-19 infection or alters the disease course (in either a positive or negative way). However, there are early signals that COVID-19 may be accompanied by an increased risk for hypercoagulable complications,[11,12] in which case caution may be warranted for estrogen and raloxifene use, both of which may modestly increase thrombotic risk.[13,14] It may therefore be prudent to instruct patients to temporarily discontinue these hormonal agents if they develop viral respiratory symptoms. Denosumab also bears particular consideration because it is a monoclonal antibody that inhibits receptor activator of NF-κB ligand (RANKL), and RANKL plays a role in T-cell activation. Studies of denosumab in postmenopausal osteoporosis indicate an increased risk of skin and soft tissue infections.[15] However, no infection safety signals have been found in studies of denosumab in patients receiving concurrent immunomodulatory treatment for rheumatoid arthritis[16–18] and among patients receiving concomitant chemotherapy for solid-organ tumors.[19,20]

Depending on the severity of the local COVID-19 outbreak, we acknowledge that there may be disruptions in the administration of osteoporosis treatments. We thus aim to provide guidance about (i) alternative methods of delivering parenteral osteoporosis treatments that are not self-administered (eg, iv bisphosphonates, denosumab, and romosozumab); and (ii) how to handle temporary disruptions in the pharmacologic management of osteoporosis patients.

Alternative methods of delivering parenteral osteoporosis treatments

- Off-site clinics: The administration of treatments at locations geographically isolated from COVID-19 "hot spots" should be considered whenever possible. However, it should be recognized that this may disadvantage socioeconomically challenged communities if public transportation options are not available.
- Home delivery and administration: This is an option if available but may be logistically difficult to arrange due to reliance on home-visiting medical staff. Self-injection of denosumab (and/or romosozumab) has been proposed and is reportedly available in some locales. However, there are important medico-legal issues to consider surrounding the proper product handling and administration, including the small risk of drug-related hypersensitivity reactions that could occur in the absence of a medical provider, although steps to mitigate such potential risks may be in place in some communities.
- Drive-through administration of denosumab and/or romosozumab: This may also be logistically difficult to arrange. Further, it is recommended that patients be monitored by a medical provider for 15 minutes after injection in the unlikely event of a hypersensitivity reaction.

Temporary disruptions of pharmacologic osteoporosis treatment

In the event that temporary disruption of osteoporosis treatment is necessitated due to COVID-19, we have reviewed evidence about treatment discontinuation effects and have provided

Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS

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Key terms: Osteoporosis, fractures, denosumab, bisphosphonates, teriparatide, bone turnover markers

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ADIS DRUG EVALUATION

Romosozumab: A Review in Postmenopausal Osteoporosis

Julia Paik[1] · **Lesley J. Scott**[1]

Abstract
Romosozumab (Evenity®), a humanized monoclonal antibody, promotes bone formation and inhibits bone resorption by inhibiting sclerostin, a protein involved in the regulation of bone formation. Subcutaneous romosozumab is approved in several countries, including those of the EU for treating severe osteoporosis as well as in the USA for osteoporosis in postmenopausal women at high risk of fracture. In pivotal phase III trials (FRAME and ARCH), 12 months' once-monthly romosozumab 210 mg significantly reduced vertebral and clinical fracture risk versus placebo and oral alendronate in postmenopausal women with osteoporosis. After patients transitioned from romosozumab to 12–24 months of subcutaneous denosumab or oral alendronate, fracture risks were significantly improved versus placebo-to-denosumab and alendronate-only treatment. In these trials and a phase IIIb trial, romosozumab significantly increased bone mineral density (BMD) relative to placebo, alendronate and subcutaneous teriparatide at 12 months, with these benefits maintained 12–24 months after patients transitioned from romosozumab to alendronate or denosumab in pivotal trials. Romosozumab had a generally manageable tolerability profile. While further clinical experience is needed to more definitively establish its efficacy and safety, including its CV safety, romosozumab extends the treatment options in postmenopausal women with osteoporosis who have a high risk of fracture and in those who have failed or are intolerant to other available osteoporosis therapy.

1 Introduction

Bone remodelling is a key component of the structural maintenance of bone and involves balanced coordination between bone resorption and formation [1]. In the context of osteoporosis, the rate of bone resorption surpasses that of bone formation and results in net bone loss. Osteoporosis is therefore characterized by low bone mineral density (BMD) and increased bone porosity. Affected individuals, particularly those with impaired motor function (e.g. the elderly), are more susceptible to fractures, most commonly at the hip, wrist and spine [1].

Romosozumab: clinical considerations in postmenopausal osteoporosis
Promotes bone formation and inhibits bone resorption by binding to and inhibiting sclerostin
Improves vertebral and clinical fracture risk and increases BMD
Provides therapeutic benefits that are maintained after switching to subcutaneous denosumab or oral alendronate therapy
Generally manageable tolerability profile; CV safety profile remains to be fully elucidated

Postmenopausal women are at risk of developing osteoporosis as their levels of estrogen, which is known to limit bone resorption, rapidly decrease [2]. As such, with a phase of rapid menopausal bone loss typically occurring earlier than age-related bone loss, postmenopausal women are likely to experience osteoporotic fractures earlier than men of the same age [2] and have a greater lifetime fracture risk [3].

Estrogens have been shown to inhibit the production of the glycoprotein sclerostin [1], which is produced by mature

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osteocytes and limits bone formation (by inhibiting the Wnt signalling pathway, a key component in bone homeostasis, in osteoblasts [4]). Sclerostin also promotes bone resorption through increased production of receptor activator of nuclear factor kappa-β-ligand osteocytes [5]. Accordingly, individuals with sclerostin deficiency have high BMD and bone growth, as well as a low risk of fractures [6]. Sclerostin has therefore been identified as a therapeutic target in osteoporosis [5]. The current mainstay of treatment for postmenopausal osteoporosis is antiresorptive therapy; however, low BMD in the context of severe osteoporosis is better restored and maintained by preceding antiresorptive therapy with bone-building therapy [7, 8].

Romosozumab (Evenity®) is a sclerostin-targeting humanized monoclonal antibody that is approved in multiple countries for the treatment of postmenopausal osteoporosis in patients with a high risk of fracture. Specific indications may vary between countries; it is approved in the EU [9] for the treatment of severe osteoporosis, and in the USA [10] for the treatment of osteoporosis in postmenopausal women at high risk of fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture) and patients who have failed or are intolerant to other available osteoporosis therapy. This article reviews pharmacological, therapeutic efficacy and tolerability data relevant to the use of romosozumab in these indications; discussions of other indications are beyond the scope of this review.

2 Pharmacodynamic Properties of Romosozumab

The binding and inhibition of sclerostin by romosozumab promotes bone formation through the activation of bone-lining cells and increased bone matrix production and osteoprogenitor cell recruitment [9]; bone resorption is also reduced with sclerostin inhibition, though to a lesser degree [10]. These mechanisms allows rapid bone formation on the trabecular and cortical bone surfaces, thereby increasing bone density and strength [9, 10].

In phase III clinical trials (FRAME [11], ARCH [12] and STRUCTURE [13]) (Sect. 4), the overall effect of romosozumab on bone formation was supported by changes in the concentrations of bone formation and resorption biomarkers (procollagen type 1 N propeptide (P1NP) and C-telopeptide of type 1 collagen (CTX), respectively; CTX was specified as the β-isomer in FRAME [11] and ARCH [12]) in postmenopausal women with osteoporosis treated with once-monthly romosozumab 210 mg. For instance, in a FRAME subgroup analysis ($n = 129$) [11] and in the STRUCTURE study ($n = 436$) [13], romosozumab significantly increased P1NP concentrations and significantly reduced CTX concentrations as early as 14 days following the first dose (data not reported for both studies; $p < 0.001$ vs placebo [11] and $p < 0.0001$ vs baseline levels and teriparatide, a recombinant form of parathyroid hormone) [13]). In FRAME [11] and ARCH subgroup analyses ($n = 266$ in ARCH [12]) and in the STRUCTURE [13] study, P1NP levels peaked in the first month with romosozumab before falling below baseline levels after 6–12 months; at months 1 and 12 (and at month 13 in FRAME [11]), P1NP levels in the romosozumab group were significantly increased compared with baseline levels ($p \leq 0.006$) [11, 13] and with other treatments (alendronate, an antiresorptive agent [12] and teriparatide [13]; $p \leq 0.001$ for both comparisons). CTX levels remained below [11, 12], or close to [13], baseline levels following 12 months' treatment with romosozumab. In FRAME [11], CTX levels were significantly lower than baseline levels at: 14 days; 1 month; 3 months and 14 days; 6 months and 14 days; 9 months; 12 months; and 24 months ($p = 0.04$ for month 24; $p \leq 0.005$ for other timepoints). CTX levels were significantly lower with romosozumab than with teriparatide at: 3 months; 3 months and 14 days; 6 months; 6 months and 14 days; 9 months; and 12 months ($p < 0.0001$) [13]. However, they were significantly higher with romosozumab than with alendronate at months 1, 3, 6, 9 and 12 ($p < 0.001$) [12].

These findings were further supported by bone histomorphometry data in FRAME participants who had bone biopsies [at month 2 (overall evaluable population $n = 34$) and month 12 ($n = 70$)] [14]. For instance, the mineralizing surface to bone surface ratio (MS/BS) and bone formation rate per unit of bone surface (BFR/BS) in the cancellous bone were significantly higher ($p \leq 0.004$) with romosozumab relative to placebo at month 2 (MS/BS 5.6% vs 2.3%; BFR/BS 12.1 $\mu m^3/\mu m^2$/year vs 5.2 $\mu m^3/\mu m^2$/year), but significantly lower ($p \leq 0.014$) at month 12 (MS/BS 0.6% vs 3.0%; BFR/BS 1.6 $\mu m^3/\mu m^2$/year vs 6.8 $\mu m^3/\mu m^2$/year). Parameters relevant to static bone formation showed similar changes over time; for instance, osteoid volume in the cancellous bone was significantly greater at month 2 with romosozumab compared with placebo (median osteoid volume per unit of bone volume 3.0% vs 1.3%, $p = 0.007$) but significantly lower at month 12 (0.8% vs 1.7%, $p = 0.016$) [14].

3 Pharmacokinetic Properties of Romosozumab

Subcutaneous romosozumab displayed nonlinear pharmacokinetics due to sclerostin binding in healthy individuals across doses of 70–210 mg [9, 10], with exposure [area under the concentration–time curve (AUC)] increasing at a greater rate relative to the given dose [10]. Following a 210 mg dose in healthy individuals, the mean maximum serum concentration (C_{max}) and AUC of romosozumab were 22.2 μg/mL and 389 μg·day/mL [10], and the median time

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REVIEW

Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis?

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Abstract

We provide an evidence base and guidance for the use of menopausal hormone therapy (MHT) for the maintenance of skeletal health and prevention of future fractures in recently menopausal women. Despite controversy over associated side effects, which has limited its use in recent decades, the potential role for MHT soon after menopause in the management of postmenopausal osteoporosis is increasingly recognized. We present a narrative review of the benefits versus risks of using MHT in the management of postmenopausal osteoporosis. Current literature suggests robust anti-fracture efficacy of MHT in patients unselected for low BMD, regardless of concomitant use with progestogens, but with limited evidence of persisting skeletal benefits following cessation of therapy. Side effects include cardiovascular events, thromboembolic disease, stroke and breast cancer, but the benefit-risk profile differs according to the use of opposed versus unopposed oestrogens, type of oestrogen/progestogen, dose and route of delivery and, for cardiovascular events, timing of MHT use. Overall, the benefit-risk profile supports MHT treatment in women who have recently (< 10 years) become menopausal, who have menopausal symptoms and who are less than 60 years old, with a low baseline risk for adverse events. MHT should be considered as an option for the maintenance of skeletal health in women, specifically as an additional benefit in the context of treatment of menopausal symptoms, when commenced at the menopause, or shortly thereafter, in the context of a personalized benefit-risk evaluation.

Key messages • Overall the benefit-risk balance for MHT use is more favourable at the age of menopause or in the years thereafter, for example before the age of 60 years and/or within 10 years after menopause, and for unopposed oestrogen (used in hysterectomized women) compared with combined oestrogen plus progestogen in women with an intact uterus.
• There is some evidence that the risk of cardiovascular outcomes depends upon age/time from menopause, such that, particularly for oestrogen only therapy, the risk of such outcomes may be lower when hormone therapy is commenced early postmenopause compared with in older age. This temporal relationship is less well-defined for combined oestrogen-progestogen therapy.
• Transdermal preparations are associated with lower risk of thromboembolic outcomes and are as effective as oral preparations for maintenance of BMD, but their effect on fracture risk reduction is unproven.
• Overall, MHT may be considered as an option for the maintenance of bone health in menopausal women, as an additional benefit in the context of treatment of menopausal symptoms, amongst women who are at low risk of breast cancer and of cardiovascular, cerebrovascular and venous thromboembolic events and who do not warrant a specific skeletal therapy such as a bisphosphonate.

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Keywords Cardiovascular · Epidemiology · Hormone therapy · Menopause · Osteoporosis · Safety

Introduction

Over the last three decades, osteoporosis has progressed from being viewed as an inevitable consequence of ageing to being understood as a major non-communicable chronic disease, with an associated diagnostic definition and effective methods of detection, risk stratification and treatment [1, 2]. We are fortunate now to have a wide range of therapeutic strategies for managing osteoporosis, targeted at improving or maintaining bone mineral density [3, 4]. Across the various pharmaceutical interventions available, it is possible to view particular therapies as most appropriately targeted to particular stages of the risk spectrum. For example, oral bisphosphonate therapy may be appropriate where there is established osteoporosis and high risk of fracture [3]. In a recent position paper from the European Society for the Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF), we described how this appreciation of stratification according to efficacy, costs and side effects, in relation to low, high and very high fracture risk, might be implemented in clinical practice [5]. A key consideration in this work was the approach to women who were currently at low risk but who might well become at high risk in older age and whether interventions based on the high lifetime risk of fracture, rather than the immediate low risk of fracture, might be advised. One class of medication that is highly relevant here is menopausal hormone therapy (MHT), given the clear evidence for its antifracture efficacy, regardless of baseline bone mineral density, and also for the relevant ameliorative effects on menopausal symptoms [6].

MHT was widely used in the 1980s and 1990s for the prevention of symptoms associated with the menopause, such as hot flushes, night sweats and sleep disturbance, with the widely prevailing view that prevention of cardiovascular disease and osteoporosis were additional benefits [7, 8]. The rationale for such an approach was an evidence-base consisting principally of observational studies, in which the use of hormone replacement therapy (as it was known at that time) was associated with generally improved health outcomes, particularly in relation to cardiovascular disease. This whole thesis was challenged by results from the large US Women's Health Initiative (WHI) Hormone Therapy trials, the first of which compared a fixed composition of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) to placebo and was published in 2002 [7, 9]. This trial reported that, whilst this hormone therapy regimen did indeed lead to a decreased risk of fractures, it was associated with increased risks of cardiovascular and cerebrovascular events, as well as with increased risks of breast cancer and other adverse health outcomes [10]. Subsequently, the limitations of inadequately analysed, confounded observational studies and the potential for converse findings from well conducted randomized controlled trials have found a key exemplum in the MHT story [11]. Interestingly, when the original observational studies were re-analysed using state-of-the-art pharmacoepidemiology techniques, which much more effectively control problems such as confounding by indication, then findings more in line with the results from randomized trials were observed [11]. However, these remain analyses of observational studies and therefore should be viewed as less robust evidence than those derived from randomized trials. Subsequent re-analyses of the WHI trials, together with evidence from other trials, have suggested that the benefit-risk profiles of MHT differ according to the timing of use in relation to the menopause and chronological age and by MHT regimen (addition or not of progestogen, type of oestrogen and progestogen, dose of oestrogen and route of administration) [7–9].

There is clearly a complex evidential landscape in which to assess the role of MHT in the prevention/treatment of osteoporosis. In this position paper, based on a narrative literature review, we will use randomized controlled trial evidence and meta-analyses thereof, in order to use the best quality data. Additionally, we focus on the scenario of normal menopause, rather than premature ovarian insufficiency, for which MHT, to replace the hormone deficit, is generally appropriate [12]. We firstly describe the natural history of the menopause in terms of hormonal changes and consequent health outcomes; subsequently, we set out the evidence that MHT is effective in reducing the risk of incident fracture, the independence of this effect from baseline BMD and age. Thereafter, we aim to examine the overall benefit-risk profile of MHT, particularly with regard to cardiovascular outcomes, and to investigate the potential effects of timing in relation to menopausal transition, dose and route of administration as approaches to mitigate adverse effects. We conclude by assessing the potential health economic aspects of the use of MHT for fracture prevention and outline a potential clinical approach.

Natural history of hormonal changes at the menopause and associated health outcomes

Menopausal physiology

The menopause is defined as the permanent cessation of menstruation that results from loss of ovarian follicular activity. Clinically, in women in their 40s or 50s, it is recognized to

REVIEW

Hypophosphatasia in adolescents and adults: overview of diagnosis and treatment

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Abstract
This article provides an overview of the current knowledge on hypophosphatasia—a rare genetic disease of very variable presentation and severity—with a special focus on adolescents and adults. It summarizes the available information on the many known mutations of tissue-nonspecific alkaline phosphatase (TNSALP), the epidemiology and clinical presentation of the disease in adolescents and adults, and the essential diagnostic clues. The last section reviews the therapeutic approaches, including recent reports on enzyme replacement therapy (EnzRT).

Keywords Alkaline phosphatase · Bone · Fractures · Hypomineralization · Hypophosphatasia · Teeth

Introduction

Hypophosphatasia (HPP) was first described in 1948 by Rathbun [1], who reported a novel skeletal pathology characterized by unusual clinical findings, including extremely low levels of alkaline phosphatase (ALP) and seizures.

HPP is now recognized as a rare and heterogeneous inherited disorder of bone and mineral metabolism, caused by a number of loss-of-function mutations in the *ALPL* gene, encoding the tissue-nonspecific isoenzyme of ALP (TNSALP), with generalized reduction of ALP activity (see https://www.ncbi.nlm.nih.gov/gene/249). The clinical expression is highly variable, depending on the type of mutation and the inheritance mechanism, and there are several forms of the disease ranging from lethal to mild. The most severe forms are those affecting infants and young children, with manifestations already appearing in utero [2–5].

The main clinical signs are related to defective bone and tooth mineralization (rickets, osteomalacia, fractures, tooth loss), but other systemic manifestations (seizures, respiratory and kidney problems, chronic pain, weakness, etc.) may be present in the most severe forms. Such systemic manifestations might be connected to the role of TNSALP in purinergic signaling (via dephosphorylation of ATP), which is extremely relevant in the CNS, bone, and other organs [6, 7].

The leading diagnostic clues are low serum ALP and TNSALP activity (hypophosphatasaemia) and increased levels of ALP substrates, i.e., inorganic pyrophosphate (PPi), pyridoxal-5′-phosphate (PLP, the active metabolite of vitamin B6), and phosphoethanolamine (PEA) [2, 3, 8–11].

The aim of this article, written by a group of experts on behalf of the ECTS, is to provide a state-of-the-art review of HPP in adolescents and adults, essentially addressed to bone specialists.

Still now, physicians and even bone specialists, not specifically dealing with rare bone diseases, only pay attention to the presence of high levels of serum ALP, and not to low levels, so that a diagnosis of HPP is often missed or delayed. This article is written to increase the clinicians' awareness of HPP in

CLINICAL TRIAL

JBMR

Burosumab for the Treatment of Tumor-Induced Osteomalacia

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ABSTRACT

Tumor-induced osteomalacia (TIO) is caused by phosphaturic mesenchymal tumors producing fibroblast growth factor 23 (FGF23) and is characterized by impaired phosphate metabolism, skeletal health, and quality of life. UX023T-CL201 is an ongoing, open-label, phase 2 study investigating the safety and efficacy of burosumab, a fully human monoclonal antibody that inhibits FGF23, in adults with TIO or cutaneous skeletal hypophosphatemia syndrome (CSHS). Key endpoints were changes in serum phosphorus and osteomalacia assessed by transiliac bone biopsies at week 48. This report focuses on 14 patients with TIO, excluding two diagnosed with X-linked hypophosphatemia post-enrollment and one with CSHS. Serum phosphorus increased from baseline (0.52 mmol/L) and was maintained after dose titration from week 22 (0.91 mmol/L) to week 144 (0.82 mmol/L, $p < 0.0001$). Most measures of osteomalacia were improved at week 48: osteoid volume/bone, osteoid thickness, and mineralization lag time decreased; osteoid surface/bone surface showed no change. Of 249 fractures/pseudofractures detected across 14 patients at baseline, 33% were fully healed and 13% were partially healed at week 144. Patients reported a reduction in pain and fatigue and an increase in physical health. Two patients discontinued: one to treat an adverse event (AE) of neoplasm progression and one failed to meet dosing criteria (receiving minimal burosumab). Sixteen serious AEs occurred in seven patients, and there was one death; all serious AEs were considered unrelated to treatment. Nine patients had 16 treatment-related AEs; all were mild to moderate in severity. In adults with TIO, burosumab exhibited an acceptable safety profile and was associated with improvements in phosphate metabolism and osteomalacia. © 2020 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research..

KEY WORDS: BONE HISTOMORPHOMETRY; TUMOR-INDUCED BONE DISEASE; CLINICAL TRIALS; OSTEOMALACIA AND RICKETS; PTH/VIT D/FGF23

Introduction

Tumor-induced osteomalacia (TIO) is an ultrarare disease caused by tumors secreting fibroblast growth factor 23 (FGF23).[1] Most patients have phosphaturic mesenchymal tumors, which are often small and occur in soft tissue or bone, making localization difficult and delaying diagnosis. The excess levels of FGF23 in TIO lead to impaired renal phosphate reabsorption, reduced active vitamin D synthesis, and chronic hypophosphatemia. Clinical manifestations include osteomalacia, fractures, musculoskeletal pain, fatigue, severe myopathy, and reduced health-related quality of life, which typically result in rapid clinical deterioration of the patient.

Complete surgical resection of the causative tumor is curative and the established treatment for TIO.[1] Incomplete resection often results in tumor recurrence with symptoms. Roughly 35% to 40% of tumors cannot be localized.[2,3] When the tumor cannot be localized and completely resected, supplementation with multiple daily doses of oral phosphate and active vitamin D analogues is required. However, efficacy of

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GUIDELINES, POSITION STATEMENTS, CONSENSUS STATEMENTS

Management of parathyroid disorders: recommendations of the working group of the Bone Section of the Hellenic Endocrine Society

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Abstract
The Bone Section of the Hellenic Endocrine Society has issued the recommendations herein presented with the aim of providing guidance on optimal management of patients with parathyroid disorders in everyday clinical practice within the Greek health care setting. Although the methodology followed to formulate these recommendations was not strictly based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principles, they were drawn up after an extensive review of the literature and of the currently available guidelines for the management of parathyroid disorders worldwide. Specifically for primary hyperparathyroidism (PHPT), the 2011 guidelines of the Greek National Organization of Medicines were updated accordingly. In particular, definitions, etiologies, and recommended and optional laboratory and imaging examinations are provided both for PHPT and chronic hypoparathyroidism (HypoPT). Finally, treatment algorithms are provided for the management of both PHPT and HypoPT. Specifically for HypoPT, the treatment algorithm describes the recommended steps that should be followed to achieve optimal management of chronic hypocalcemia and the complications of HypoPT through the conventional treatment available in Greece and the use of recombinant human PTH(1-84).

Keywords Hyperparathyroidism · Hypoparathyroidism · Calcium · Phosphate · Parathyroid hormone (PTH) · Recommendations · Greece

Introduction

On the decision of the Bone Section of the Hellenic Endocrine Society, the recommendations herein presented were drawn up with the aim of issuing guidance on optimal management of patients with parathyroid disorders applicable to all diagnostic and therapeutic medical procedures of parathyroid disorders in Greece. The working group, consisting of six endocrinologists specialized in bone metabolism, met to discuss and construct the initial draft. Although these recommendations were not methodologically based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principles, they were formulated after an extensive literature review as well as a review of the current global guidelines for the management of parathyroid disorders. Specifically for primary hyperparathyroidism (PHPT), the 2011 guidelines of the Greek National Organization of Medicines were updated accordingly.

Following review and approval by the Board of Trustees of the Hellenic Endocrine Society, the expert panel endorsed the

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revised guidelines, and the English version of the final manuscript is herein presented.

Overall, these recommendations aim to define the optimal management of patients with parathyroid disorders in everyday clinical practice within the Greek health care setting according to the existing scientific evidence and based on the personal experiences of the authors.

Primary hyperparathyroidism

Definitions

PHPT is a primary disorder of the parathyroid glands characterized by hypercalcemia with increased or inappropriately normal/high-normal parathyroid hormone (PTH) levels [1–4]. In contrast, secondary hyperparathyroidism (SHPT) is defined as the compensatory increase of PTH, mainly in response to hypocalcemia. Finally, tertiary hyperparathyroidism (THPT) is defined as the autonomous secretion of PTH following long-term SHPT, most frequently in the setting of chronic kidney disease (CKD), as well as in other conditions causing hypocalcemia, and in hypophosphatemic disorders.

Recommended and optional laboratory testing for the differential diagnosis of hyperparathyroidism

Recommended testing includes serum measurements of calcium (Ca), albumin (Alb), phosphate (P), PTH, and creatinine (Cr) and 24-h urinary Ca and Cr excretion [1–4]. Total calcium concentration (mg/dl) should be corrected for albumin concentration (gr/dl) using the formula: $Ca_{corrected} = Ca_{measured} + 0.8 \times (4 - \text{albumin})$. This correction should be used for albumin concentrations both lower and higher than 4 g/dl.

Optional testing includes estimation of glomerular filtration rate (eGFR) and measurement of serum 25(OH)D levels. eGFR (ml/min) can be estimated using the formulas:

$$\text{eGFR (males)} = [140 - \text{age (years)}] \times \text{weight (kg)}/[72 \times \text{serum creatinine (mg/dl)}].$$

$$\text{eGFR (females)} = 0.85 \times [140 - \text{age (years)}] \times \text{weight (kg)}/[72 \times \text{serum creatinine (mg/dl)}].$$

Common biochemical patterns in the different types of hyperparathyroidism

When investigating excessive PTH secretion, the following biochemical patterns may be expected, which lead to the diagnosis of the different types of hyperparathyroidism.

Primary hyperparathyroidism: Elevated or high-normal serum Ca levels, decreased serum P levels or within the low-normal range, normal or elevated 24-h urinary Ca, and normal serum Cr levels [2].

Secondary hyperparathyroidism: Decreased or normal serum Ca, variable serum P levels depending on the underling etiology, normal or decreased 24-h urinary Ca, and normal or elevated serum Cr.

Tertiary hyperparathyroidism (end-stage CKD): Elevated serum Ca and P levels and frankly elevated serum Cr levels.

Etiology of PHPT

Autonomous PTH production in PHPT is attributed to the following pathological conditions of the parathyroid glands, listed below according to their incidence [4–6]:

- 75–85%: Single or multiple parathyroid adenomas
- 15–20%: Diffuse parathyroid hyperplasia
- < 0.5%: Parathyroid carcinoma

Symptoms and signs of PHPT

The clinical presentation of PHPT has evolved over the past few decades in the Western world, from a severe symptomatic skeletal disease with renal complications and moderate or severe hypercalcemia to a usually asymptomatic condition detected during routine laboratory testing [3–5, 7]. However, as symptomatic PHPT has clear treatment indications, recognition of the PHPT-induced symptoms and signs is of critical importance for the overall management of the disease. Symptoms and signs of the most frequently involved systems are:

Cardiovascular system: arterial hypertension, left ventricular hypertrophy, cardiac valve calcifications, and shortening of QT interval

Musculoskeletal system: osteopenia-osteoporosis, musculoskeletal pains, arthralgias, low-trauma fractures, "brown tumors," osteitis fibrosa cystica, proximal muscle weakness, hyperactive tendon reflexes, and muscle atrophy

Digestive system: nausea, vomiting, constipation, peptic ulcer, and pancreatitis

Central nervous system: fatigue, weakness, mood and sleep disturbances, depression, difficulty in concentration, changes in cognition, and memory loss

Kidneys: nephrolithiasis, renal colic, nephrocalcinosis, metabolic acidosis, chronic kidney disease, renal insufficiency, and nephrogenic diabetes insipidus

In the absence of symptoms and/or signs that could definitely be attributed to hypercalcemia or to high PTH, PHPT is defined as asymptomatic [1, 7]. Normocalcemic PHPT is diagnosed in the presence of consistently elevated PTH levels with normal, albumin-corrected, and ionized calcium levels, together with preserved renal function (eGFR > 60 ml/min),

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ENDORAMA – Thyroid, January 2021
Maria Papaleontiou, MD
University of Michigan

HYPOTHYROIDISM

- Jonklaas J, Bianco AC, Cappola A, Celi FS, Fliers E, Heuer H, McAninch EA, Moeller LC, Nygaard B, Sawka AM, Watt T, Dayan C 2020 Evidence Based Use of LT4/LT3 Combinations in Treating Hypothyroidism: A Consensus Document. Thyroid doi: 10.1089/thy.2020.0720. Online ahead of print.

- Brito JP, Ross JS, Sangaralingham L, Dutcher SK, Graham DJ, Wang Z, Wu Y, Yao X, Smallridge RC, Bernet V, Shah ND, Lipska KJ 2020 Comparative effectiveness of generic vs brand-name levothyroxine in achieving normal thyrotropin levels. JAMA Netw Open 3(9):e2017645. PMID: 32997127.

- Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM 2020 Association of subclinical hypothyroidism and cardiovascular disease with mortality. JAMA Netw Open 3(2):e1920745. PMID: 32031647.

- Jabbar A, Ingoe L, Junejo S, Carey P, Addison C, Thomas H, Parikh JD, Austin D, Hollingsworth KG, Stocken DD, Pearce SHS, Greenwood JP, Zaman A, Razvi S 2020 Effect of levothyroxine on left ventricular ejection fraction in patients with subclinical hypothyroidism and acute myocardial infarction: a randomized clinical trial. JAMA 324:249–258. PMID: 32692386.

- Gencer B, Moutzouri E, Blum MR, Feller M, Collet TH, Delgiovane C, da Costa BR, Buffle E, Monney P, Gabus V, Müller H, Sykiotis GP, Kearney P, Gussekloo J, Westendorp R, Stott DJ, Bauer DC, Rodondi N 2020 The impact of levothyroxine on cardiac function in older adults with mild subclinical hypothyroidism: A randomized clinical trial. Am J Med 133:848–846.e5. PMID: 32171774.

HYPERTHYROIDISM

- Kitahara CM, Preston DL, Sosa JA, Berrington de Gonzalez A 2020 Association of radioactive iodine, antithyroid drug, and surgical treatments with solid cancer mortality in patients with hyperthyroidism. JAMA Netw Open 3(7):e209660. PMID: 32701159.

- Folkestad L, Brandt F, Lillevag-Johansen M, Brix TH, Hegedüs L 2020 Graves' disease and toxic nodular goiter, aggravated by duration of hyperthyroidism, are associated with Alzheimer's and vascular dementia: A registry-based long-term follow-up of two large cohorts. Thyroid 30:672–680. PMID: 31984866.

- Azizi F, Abdi H, Cheraghi L, Amouzegar A 2020 Treatment of subclinical hyperthyroidism in the elderly: Comparison of radioiodine and long-term methimazole treatment. Thyroid. Epub 2020 Aug 18. PMID: 32811342. Published Online: 23 Sep 2020 https://doi.org/10.1089/thy.2020.0433

- Douglas RS, Kahaly GJ, Patel A, Sile S , Thompson EHZ, Perdok R, Fleming JC, Fowler BT, Marcocci C, Marinò M, Antonelli A, Dailey R, Harris GJ, Eckstein A, Schiffman J, Tang R, Nelson C, Salvi M, Wester S, Sherman JW, Vescio T, Holt RJ, Smith TJ 2020 Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 382:341–352. PMID: 31971679.

THYROID NODULES

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- Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G 2020 Thyrotoxicosis in patients with COVID 19: The THYRCOV Study. Eur J Endocrinol 183(4):381–387. PMID: 32698147.

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Kitahara CM, Preston DL, Sosa JA, Berrington de Gonzalez A 2020 Association of radioactive iodine, antithyroid drug, and surgical treatments with solid cancer mortality in patients with hyperthyroidism. JAMA Netw Open 3(7):e209660. PMID: 32701159.

Abstract

Importance: The long-term health effects of radioactive iodine (RAI) and antithyroid drug (ATD) treatments compared with surgery for hyperthyroidism remain uncertain.

Objective: To compare solid cancer mortality rates associated with RAI and ATD treatments vs surgical management for hyperthyroidism.

Design, setting, and participants: This multicenter cohort study assessed patients treated for hyperthyroidism from January 1, 1946, to December 31, 1964, with follow-up through December 31, 2014. Data analysis was performed from August 1, 2019, to April 23, 2020.

Exposures: Management with RAI, ATDs, surgical intervention, or combinations of these treatments.

Main outcomes and measures: Comparisons of solid cancer mortality rates in each treatment group with expected rates from the general population were assessed using standardized mortality ratios (SMRs), and internal comparisons were assessed using hazard ratios (HRs) adjusted for age, sex, and underlying diagnosis (Graves disease or toxic nodular goiter).

Results: Of 31 363 patients (24 894 [79.4%] female; mean [SD] age, 46.9 [14.8] years) included in the study, 28 523 (90.9%) had Graves disease. The median follow-up time was 26.0 years (interquartile range, 12.3-41.9 years). Important differences in patient characteristics existed across treatment groups at study entry. Notably, the drug-only group (3.6% of the cohort) included a higher proportion of patients with prior cancers (7.3% vs 1.9%-4.0%), contributing to an elevated SMR for solid cancer mortality. After excluding prior cancers, solid cancer SMRs were not elevated in any of the treatment groups (SMR for surgery only, 0.82 [95% CI, 0.66-1.00]; SMR for drugs only, 0.90 [95% CI, 0.74-1.09]; SMR for drugs and surgery, 0.88 [95% CI, 0.84-0.94]; SMR for RAI only, 0.90 [95% CI, 0.84-0.96]; SMR for surgery and RAI, 0.66 [95% CI, 0.52-0.85]; SMR for drugs and RAI, 0.94 [95% CI, 0.89-1.00]; and SMR for drugs, surgery, and RAI, 0.85 [95% CI, 0.75-0.96]), and no significant HRs for solid cancer death were observed across treatment groups. Among RAI-treated patients, HRs for solid cancer mortality increased significantly across levels of total administered activity (1.08 per 370 MBq; 95% CI, 1.03-1.13 per 370 MBq); this association was stronger among patients treated with only RAI (HR, 1.19 per 370 MBq; 95% CI, 1.09-1.30 per 370 MBq).

Conclusions and relevance: After controlling for known sources of confounding, the study found no significant differences in the risk of solid cancer mortality by treatment group. However, among RAI-treated patients, a modest positive association was observed between total administered activity and solid cancer mortality, providing further evidence in support of a dose-dependent association between RAI and solid cancer mortality.

Azizi F, Abdi H, Cheraghi L, Amouzegar A 2020 Treatment of subclinical hyperthyroidism in the elderly: Comparison of radioiodine and long-term methimazole treatment. Thyroid. Epub 2020 Aug 18. PMID: 32811342. Published Online: 23 Sep 2020
https://doi.org/10.1089/thy.2020.0433

Abstract

Background: This study aimed to compare the effectiveness and safety of radioiodine (RAI) and long-term methimazole (MMI) in the treatment of subclinical hyperthyroidism (SH) in the elderly.

Methods: From 306 patients, aged ≥65 years, with SH, 83 patients with thyrotropin <0.1 mU/L entered the study. In this randomized parallel-group trial, 41 and 42 patients were randomized to either RAI or long-term MMI treatment, respectively.

Results: In the RAI and MMI groups, 3 and 4 patients were excluded due to side effects, choosing other modes of treatment, and not returning for follow-up; 35 and 36 patients completed 60 months of follow-up, respectively. In the RAI group, 23 (66%) became hypothyroid, and 12 (34%) remained euthyroid 60 months after a fixed dose of 15 mCi RAI. In the MMI group, the starting dose was 10 mg daily and decreased to 4.9 ± 1.0, 4.3 ± 1.0, 4.4 ± 1.4, 4.3 ± 1.8, and 3.7 ± 1.3 mg after 1, 2, 3, 4, and 5 years of continuous MMI treatment, employing titration method. By the end of study, 34 (94%) patients were euthyroid and 2 patients with diffuse goiter developed spontaneous hypothyroidism with MMI treatment. Minor adverse events occurred in both groups in the first four months of treatment. No death or serious side effects were observed during 60 months of follow-up.

Conclusions: Both RAI and long-term low-dose MMI therapies are effective and safe for treatment of SH in the elderly.

Folkestad L, Brandt F, Lillevag-Johansen M, Brix TH, Hegedüs L 2020 Graves' disease and toxic nodular goiter, aggravated by duration of hyperthyroidism, are associated with Alzheimer's and vascular dementia: A registry-based long-term follow-up of two large cohorts. Thyroid 30:672–680. PMID: 31984866.

Abstract

Background: Dementia is an increasing burden to the health care system. It is currently debated whether hyperthyroidism is associated with a risk of dementia. Our aim was to determine the risk of dementia in hyperthyroid individuals and whether this was associated with duration of hyperthyroidism.

Methods: Risk of dementia in hyperthyroid individuals was evaluated in two cohorts and matched reference populations. The Danish National Patient Registry (DNPR) cohort is a registry-based Danish nationwide cohort followed for a median of 7.2 years (from 1995 to 2013), whereas the OPENTHYRO registry cohort comprises 235,547 individuals who had at least one serum thyrotropin (TSH) measurement in the period from 1995 to 2011 and was followed for a median of 7.3 years. Each hyperthyroid case was matched with four controls according to age and sex using density sampling. Hyperthyroidism was defined as either an International Classification of Diseases Version 10 (ICD-10) diagnosis of toxic nodular goiter (TNG) or Graves' disease (GD), or two measurements of a TSH below 0.3 mU/L in the DNPR and OPENTHYRO registry cohort, respectively. The primary outcome was all-cause dementia, defined as either an ICD-10 code of dementia or prescription of medicine for dementia, with subgroup analyses of vascular dementia and Alzheimer's disease.

Results: The DNPR cohort had 56,128 patients with hyperthyroidism, 2689 of whom were registered with dementia. The reference population had 224,512 individuals, of whom 10,199 had dementia (hazard ratio 1.17; 95% confidence interval [CI]: 1.12-1.23). Risk of dementia, whether Alzheimer's or vascular, was higher in both GD and TNG. The OPENTHYRO registry cohort constituted 2688 hyperthyroid individuals and 10,752 euthyroid control individuals of whom 190 and 473 individuals, respectively, were subsequently diagnosed with dementia (HR 1.06; 95% CI: 0.89-1.26). For each 6 months of decreased TSH, the risk of all-cause dementia was significantly higher (HR 1.16; 95% CI: 1.12-1.22).

Conclusions*:* Using large-scale registry-based data, we found increased risk of dementia in hyperthyroid individuals. Every 6 months of decreased TSH was associated with increased risk of dementia by 16%, compared with individuals with normal TSH. Our data support early diagnosis and intervention in patients with hyperthyroidism.

Douglas RS, Kahaly GJ, Patel A, Sile S , Thompson EHZ, Perdok R, Fleming JC, Fowler BT, Marcocci C, Marinò M, Antonelli A, Dailey R, Harris GJ, Eckstein A, Schiffman J, Tang R, Nelson C, Salvi M, Wester S, Sherman JW, Vescio T, Holt RJ, Smith TJ 2020 Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 382:341–352. PMID: 31971679.

Abstract

Background: Thyroid eye disease is a debilitating, disfiguring, and potentially blinding periocular condition for which no Food and Drug Administration-approved medical therapy is available. Strong evidence has implicated the insulin-like growth factor I receptor (IGF-IR) in the pathogenesis of this disease.

Methods: In a randomized, double-masked, placebo-controlled, phase 3 multicenter trial, we assigned patients with active thyroid eye disease in a 1:1 ratio to receive intravenous infusions of the IGF-IR inhibitor teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks; the last trial visit for this analysis was at week 24. The primary outcome was a proptosis response (a reduction in proptosis of ≥2 mm) at week 24. Prespecified secondary outcomes at week 24 were an overall response (a reduction of ≥2 points in the Clinical Activity Score plus a reduction in proptosis of ≥2 mm), a Clinical Activity Score of 0 or 1 (indicating no or minimal inflammation), the mean change in proptosis across trial visits (from baseline through week 24), a diplopia response (a reduction in diplopia of ≥1 grade), and the mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire across trial visits (from baseline through week 24; a mean change of ≥6 points is considered clinically meaningful).

Results: A total of 41 patients were assigned to the teprotumumab group and 42 to the placebo group. At week 24, the percentage of patients with a proptosis response was higher with teprotumumab than with placebo (83% [34 patients] vs. 10% [4 patients], P<0.001), with a number needed to treat of 1.36. All secondary outcomes were significantly better with teprotumumab than with placebo, including overall response (78% of patients [32] vs. 7% [3]), Clinical Activity Score of 0 or 1 (59% [24] vs. 21% [9]), the mean change in proptosis (-2.82 mm vs. -0.54 mm), diplopia response (68% [19 of 28] vs. 29% [8 of 28]), and the mean change in GO-QOL overall score (13.79 points vs. 4.43 points) (P≤0.001 for all). Reductions in extraocular muscle, orbital fat volume, or both were observed in 6 patients in the teprotumumab group who underwent orbital imaging. Most adverse events were mild or moderate in severity; two serious events occurred in the teprotumumab group, of which one (an infusion reaction) led to treatment discontinuation.

Conclusions: Among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon. (Funded by Horizon Therapeutics; OPTIC ClinicalTrials.gov number, NCT03298867, and EudraCT number, 2017-002763-18.).

Jonklaas J, Bianco AC, Cappola A, Celi FS, Fliers E, Heuer H, McAninch EA, Moeller LC, Nygaard B, Sawka AM, Watt T, Dayan C 2020 Evidence Based Use of LT4/LT3 Combinations in Treating Hypothyroidism: A Consensus Document. Thyroid doi: 10.1089/thy.2020.0720. Online ahead of print.

Abstract

Background: Fourteen clinical trials have not shown a consistent benefit of combination therapy with levothyroxine (LT4) and liothyronine (LT3). Despite the publication of these trials, combination therapy is widely used and patients reporting benefit continue to generate patient and physician interest in this area. Recent scientific developments may provide insight into this inconsistency and guide future studies.

Methods: The ATA, BTA and ETA held a joint conference on November 3rd 2019 (live-streamed between Chicago and London) to review new basic science and clinical evidence regarding combination therapy with presentations and input from twelve content experts. Following the presentations, the material was synthesized and used to develop Summary Statements of the current state of knowledge. After review and revision of the material and Summary Statements, there was agreement that there was equipoise for a new clinical trial of combination therapy. Consensus Statements encapsulating the implications of the material discussed with respect to the design of future clinical trials of LT4/LT3 combination therapy were generated. Authors voted upon the Consensus Statements. Iterative changes were made in several rounds of voting and following comments from ATA/BTA/ETA members.

Results: Of 34 Consensus Statements available for voting 28 received at least 75% agreement, with 13 receiving 100% agreement. Those with 100% agreement included studies being powered to study the effect of deiodinase and thyroid hormone transporter polymorphisms on study outcomes, inclusion of patients dissatisfied with their current therapy and requiring at least 1.2 mcg/kg of levothyroxine daily, use of twice daily liothyronine or preferably a slow-release preparation if available, use of patient-reported outcomes as a primary outcome (measured by a tool with both relevant content validity and responsiveness) and patient preference as a secondary outcome, and utilization of a randomized, placebo-controlled, adequately powered double-blinded parallel design. The remaining statements are presented as potential additional considerations.

Discussion: This manuscript summarizes the areas discussed and presents Consensus Statements to guide development of future clinical trials of LT4/LT3 combination therapy. The results of such redesigned trials are expected to be of benefit to patients and of value to inform future thyroid hormone replacement clinical practice guidelines treatment recommendations.

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OP PHARMA

Brito JP, Ross JS, Sangaralingham L, Dutcher SK, Graham DJ, Wang Z, Wu Y, Yao X, Smallridge RC, Bernet V, Shah ND, Lipska KJ 2020 Comparative effectiveness of generic vs brand-name levothyroxine in achieving normal thyrotropin levels. JAMA Netw Open 3(9):e2017645. PMID: 32997127.

Abstract

Importance: Whether the use of generic vs brand levothyroxine affects thyrotropin levels remains unclear.

Objective: To compare the effectiveness of generic vs brand levothyroxine in achieving and maintaining normal thyrotropin levels among new users.

Design, setting, and participants: This retrospective, 1:1 propensity score-matched longitudinal cohort study used the OptumLabs Data Warehouse administrative claims database linked to laboratory results from commercially insured and Medicare Advantage enrollees throughout the United States. Eligible patients were adults (aged ≥18 years) with thyrotropin levels ranging from 4.5 to 19.9 mIU/L who initiated use of generic or brand-name levothyroxine from January 1, 2008, to October 1, 2017. Data were analyzed from August 13, 2018, to October 25, 2019.

Exposure: Patients received generic or brand-name levothyroxine.

Main outcomes and measures: Proportion of patients with normal vs markedly abnormal thyrotropin levels (<0.1 or >10 mIU/L) within 3 months and with stable thyrotropin levels within 3 months after the thyrotropin value fell into the normal range.

Results: A total of 17 598 patients were included (69.0% female; 74.0% White; mean [SD] age, 55.1 [16.0] years), of whom 15 299 filled generic and 2299 filled brand-name levothyroxine prescriptions during the study period. Among 4570 propensity score-matched patients (mean [SD] age, 50.3 [13.8] years; 3457 [75.6%] female; 3510 [76.8%] White), the proportion with normal thyrotropin levels within 3 months of filling levothyroxine prescriptions was similar for patients who received generic vs brand-name levothyroxine (1722 [75.4%; 95% CI, 71.9%-79.0%] vs 1757 [76.9%; 95% CI, 73.4%-80.6%]; P = .23), as was the proportion with markedly abnormal levels (94 [4.1%; 95% CI, 3.4%-5.0%] vs 88 [3.9%; 95% CI, 3.1%-4.7%]; P = .65). Among 1034 propensity score-matched patients who achieved a normal thyrotropin value within 3 months of initiation of levothyroxine, the proportion maintaining subsequent normal thyrotropin levels during the next 3 months was similar for patients receiving generic vs brand-name levothyroxine (427 [82.6%] vs 433 [83.8%]; P = .62).

Conclusions and relevance: Initiation of generic vs brand-name levothyroxine formulations was associated with similar rates of normal and stable thyrotropin levels. These results suggest that generic levothyroxine as initial therapy for mild thyroid dysfunction is as effective as brand-name levothyroxine.

Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM 2020 Association of subclinical hypothyroidism and cardiovascular disease with mortality. JAMA Netw Open 3(2):e1920745. PMID: **32031647.**

Abstract

Importance: Subclinical hypothyroidism is a common clinical entity among US adults associated in some studies with an increase in the risk of cardiovascular disease (CVD) and mortality. However, the extent to which CVD mediates the association between elevated serum thyrotropin (TSH) and mortality has not yet been well established or sufficiently quantified.

Objective: To elucidate the extent to which subclinical hypothyroidism, elevated serum TSH and normal serum free thyroxine, or high-normal TSH concentrations (ie, upper normative-range TSH concentrations) are associated with mortality through CVD among US adults.

Design, setting, and participants: This cohort study relied on representative samples of US adults enrolled in the National Health and Nutrition Examination Survey in 2001 to 2002, 2007 to 2008, 2009 to 2010, and 2011 to 2012 and their mortality data through 2015. Data were analyzed from January to August 2019.

Main outcomes and measures: Cox proportional hazards regression models were used to investigate associations between the TSH concentration category (subclinical hypothyroidism or tertiles of serum TSH concentrations within the reference range; low-normal TSH, 0.34-1.19 mIU/L; middle-normal TSH, 1.20-1.95 mIU/L; and high-normal TSH, 1.96-5.60 mIU/L) and all-cause mortality. Mediation analysis was used within the counterfactual framework to estimate natural direct associations (not through CVD) and indirect associations (through CVD).

Results: Of 9020 participants, 4658 (51.6%) were men; the mean (SD) age was 49.4 (17.8) years. Throughout follow-up (median [interquartile range], 7.3 [5.4-8.3] years), serum thyroid function test results consistent with subclinical hypothyroidism and high-normal TSH concentrations were both associated with increased all-cause mortality (subclinical hypothyroidism: hazard ratio, 1.90; 95% CI, 1.14-3.19; high-normal TSH: hazard ratio, 1.36; 95% CI, 1.07-1.73) compared with the middle-normal TSH group. Cardiovascular disease mediated 14.3% and 5.9% of the associations of subclinical hypothyroidism and high-normal TSH with all-cause mortality, respectively, with the CVD mediation being most pronounced in women (7.5%-13.7% of the association) and participants aged 60 years and older (6.0%-14.8% of the association).

Conclusions and relevance: In this study, CVD mediated the associations of subclinical hypothyroidism and high-normal TSH concentrations with all-cause mortality in the US general population. Further studies are needed to examine the clinical benefit of thyroid hormone replacement therapy targeted to a middle-normal TSH concentration or active CVD screening for people with elevated TSH concentrations.

Jabbar A, Ingoe L, Junejo S, Carey P, Addison C, Thomas H, Parikh JD, Austin D, Hollingsworth KG, Stocken DD, Pearce SHS, Greenwood JP, Zaman A, Razvi S 2020 Effect of levothyroxine on left ventricular ejection fraction in patients with subclinical hypothyroidism and acute myocardial infarction: a randomized clinical trial. JAMA 324:249–258. PMID: 32692386.

Abstract

Importance: Thyroid hormones play a key role in modulating myocardial contractility. Subclinical hypothyroidism in patients with acute myocardial infarction is associated with poor prognosis.

Objective: To evaluate the effect of levothyroxine treatment on left ventricular function in patients with acute myocardial infarction and subclinical hypothyroidism.

Design, setting, and participants: A double-blind, randomized clinical trial conducted in 6 hospitals in the United Kingdom. Patients with acute myocardial infarction including ST-segment elevation and non-ST-segment elevation were recruited between February 2015 and December 2016, with the last participant being followed up in December 2017.

Interventions: Levothyroxine treatment (n = 46) commencing at 25 μg titrated to aim for serum thyrotropin levels between 0.4 and 2.5 mU/L or identical placebo (n = 49), both provided in capsule form, once daily for 52 weeks.

Main outcomes and measures: The primary outcome measure was left ventricular ejection fraction at 52 weeks, assessed by magnetic resonance imaging, adjusted for age, sex, type of acute myocardial infarction, affected coronary artery territory, and baseline left ventricular ejection fraction. Secondary measures were left ventricular volumes, infarct size (assessed in a subgroup [n = 60]), adverse events, and patient-reported outcome measures of health status, health-related quality of life, and depression.

Results: Among the 95 participants randomized, the mean (SD) age was 63.5 (9.5) years, 72 (76.6%) were men, and 65 (69.1%) had ST-segment elevation myocardial infarction. The median serum thyrotropin level was 5.7 mU/L (interquartile range, 4.8-7.3 mU/L) and the mean (SD) free thyroxine level was 1.14 (0.16) ng/dL. The primary outcome measurements at 52 weeks were available in 85 patients (89.5%). The mean left ventricular ejection fraction at baseline and at 52 weeks was 51.3% and 53.8%, respectively, in the levothyroxine group compared with 54.0% and 56.1%, respectively, in the placebo group (adjusted difference in groups, 0.76% [95% CI, -0.93% to 2.46%]; P = .37). None of the 6 secondary outcomes showed a significant difference between the levothyroxine and placebo treatment groups. There were 15 (33.3%) and 18 (36.7%) cardiovascular adverse events in the levothyroxine and placebo groups, respectively.

Conclusions and relevance: In this preliminary study involving patients with subclinical hypothyroidism and acute myocardial infarction, treatment with levothyroxine, compared with placebo, did not significantly improve left ventricular ejection fraction after 52 weeks. These findings do not support treatment of subclinical hypothyroidism in patients with acute myocardial infarction.

Trial registration: isrctn.org Identifier: http://www.isrctn.com/ISRCTN52505169.

Gencer B, Moutzouri E, Blum MR, Feller M, Collet TH, Delgiovane C, da Costa BR, Buffle E, Monney P, Gabus V, Müller H, Sykiotis GP, Kearney P, Gussekloo J, Westendorp R, Stott DJ, Bauer DC, Rodondi N 2020 The impact of levothyroxine on cardiac function in older adults with mild subclinical hypothyroidism: A randomized clinical trial. Am J Med 133:848–846.e5. PMID: 32171774.

Abstract

Background: Subclinical hypothyroidism has been associated with heart failure, but only small trials assessed whether treatment with levothyroxine has an impact on cardiac function.

Methods: In a randomized, double-blind, placebo-controlled, trial nested within the TRUST trial, Swiss participants ages ≥65 years with subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 4.60-19.99 mIU/L; free thyroxine level within reference range) were randomized to levothyroxine (starting dose of 50 μg daily) to achieve TSH normalization or placebo. The primary outcomes were the left ventricular ejection fraction for systolic function and the ratio between mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e' ratio) for diastolic function. Secondary outcomes included e' lateral/septal, left atrial volume index, and systolic pulmonary artery pressure.

Results: A total of 185 participants (mean age 74.1 years, 47% women) underwent echocardiography at the end of the trial. After a median treatment duration of 18.4 months, the mean TSH decreased from 6.35 mIU/L to 3.55 mIU/L with levothyroxine (n = 96), and it remained elevated at 5.29 mIU/L with placebo (n = 89). The adjusted between-group difference was not significant for the mean left ventricular ejection fraction (62.7% vs 62.5%, difference = 0.4%, 95% confidence interval -1.8% to 2.5%, P = 0.72) and the E/e' ratio (10.6 vs 10.1, difference 0.4, 95% confidence interval -0.7 to 1.4, P = 0.47). No differences were found for the secondary diastolic function parameters or for interaction according to sex, baseline TSH, preexisting heart failure, and treatment duration (P value >0.05).

Conclusion: Systolic and diastolic heart function did not differ after treatment with levothyroxine compared with placebo in older adults with mild subclinical hypothyroidism.

Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, Law CY, Leung EKH, To KKW, Tan KCB, Woo YC, Lam CW, Hung IFN, Lam KSL 2020 Thyroid dysfunction in relation to immune profile, disease status and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab 2020 Nov 3;dgaa813. doi: 10.1210/clinem/dgaa813. Online ahead of print.

Abstract

Objective: SARS-CoV-2-related thyroiditis is increasingly recognized. The role of thyroid autoimmunity and SARS-CoV-2 viral load in SARS-CoV-2-related thyroid dysfunction is unclear. We evaluated the thyroid function of a cohort of COVID-19 patients, in relation to their clinical features, biochemical, immunological and inflammatory markers.

Methods: Consecutive adult patients, without known thyroid disorders, admitted to Queen Mary Hospital for COVID-19 from 21 July to 21 August, 2020 were included. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine, free triiodothyronine (fT3) and anti-thyroid antibodies were measured on admission.

Results: Among 191 patients with COVID-19 (mean age 53.5 ± 17.2 years; 51.8% male), 84.3% were mild, 12.6% were moderate, and 3.1% were severe. 13.1% had abnormal thyroid function. Ten patients had isolated low TSH, suggestive of subclinical thyrotoxicosis due to thyroiditis, although the contribution of autoimmunity was likely in two of them. Autoimmune thyroiditis probably also contributed to subclinical hypothyroidism in another patient. Ten patients had isolated low fT3, likely representing non-thyroidal illness syndrome. Lower SARS-Cov-2 PCR cycle threshold values and elevated C-reactive protein were independently associated with occurrence of low TSH (p=0.030) and low fT3 (p=0.007) respectively. A decreasing trend of fT3 with increasing COVID-19 severity (p=0.032) was found. Patients with low fT3 had more adverse COVID-19-related outcomes.

Conclusion: Around 15% of patients with mild to moderate COVID-19 had thyroid dysfunction. There may be a direct effect of SARS-CoV-2 on thyroid function, potentially leading to exacerbation of pre-existing autoimmune thyroid disease. Low fT3, associated with systemic inflammation, may have a prognostic significance.

Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G 2020 Thyrotoxicosis in patients with COVID 19: The THYRCOV Study. Eur J Endocrinol 183(4):381–387. PMID: 32698147.

Abstract

Objective: This study assessed thyroid function in patients affected by the coronavirus disease-19 (COVID-19), based on the hypothesis that the cytokine storm associated with COVID-19 may influence thyroid function and/or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may directly act on thyroid cells, such as previously demonstrated for SARS-CoV-1 infection.

Design and methods: This single-center study was retrospective and consisted in evaluating thyroid function tests and serum interleukin-6 (IL-6) values in 287 consecutive patients (193 males, median age: 66 years, range: 27-92) hospitalized for COVID-19 in non-intensive care units.

Results: Fifty-eight patients (20.2%) were found with thyrotoxicosis (overt in 31 cases), 15 (5.2%) with hypothyroidism (overt in only 2 cases), and 214 (74.6%) with normal thyroid function. Serum thyrotropin (TSH) values were inversely correlated with age of patients (rho -0.27; $P < 0.001$) and IL-6 (rho -0.41; $P < 0.001$). In the multivariate analysis, thyrotoxicosis resulted to be significantly associated with higher IL-6 (odds ratio: 3.25, 95% confidence interval: 1.97-5.36; $P < 0.001$), whereas the association with age of patients was lost ($P = 0.09$).

Conclusions: This study provides first evidence that COVID-19 may be associated with high risk of thyrotoxicosis in relationship with systemic immune activation induced by the SARS-CoV-2 infection.

Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, Ferrante E, Orsi E, Resi V, Longari V, Cuzzocrea M, Bandera A, Lazzaroni E, Dolci A, Ceriotti F, Re TE, Gori A, Arosio M, Salvi M 2020 SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 8(9):739–741. PMID: 32738929.

No abstract available.

Rahman S, Pandeya N, Neale RE, McLeod DSA, Bain C, Baade PD, Youl P, Allison R, Leonard S, Jordan SJ 2020 Obesity is associated with BRAFV600E-mutated thyroid cancer. Thyroid 30:1518–1527. PMID: 32228152.

Abstract

Background: Thyroid cancer incidence has increased in many parts of the world since the 1980s, as has the prevalence of obesity. Evidence suggests that people with greater body size have higher thyroid cancer risk. However, it is unclear whether this association is causal or is driven by over-diagnosis of indolent cancers, because overweight/obese people use health services more frequently than those of normal weight, thus conferring greater opportunity for incidental diagnosis. Assessing whether obesity is associated with higher-risk thyroid cancers might help clarify this issue.

Methods: We recruited 1013 people diagnosed with thyroid cancer between 2013 and 2016 and 1057 population controls, frequency matched by sex and age group. We used logistic regression to assess the association between body mass index (BMI) and overall thyroid cancer risk as well as by tumor BRAF mutational status as a marker of potentially higher-risk cancer.

Results: Overall, obesity was associated with greater risk of thyroid cancer (odds ratio [OR] = 1.72; 95% confidence interval [CI 1.37-2.16] for obese vs. normal BMI). The association with obesity was significantly stronger for BRAF-mutation positive than BRAF-negative papillary thyroid cancers (PTCs; OR = 1.71 [CI 1.17-2.50] for BRAF-positive vs. BRAF-negative cancers). The increased risks associated with overweight/obesity did not vary by histological subtypes or presence/absence of adverse tumor histologic features.

Conclusions: Greater risk of *BRAF*-mutated PTCs among those with high BMI suggests that the association may not merely reflect greater health care service use and indicates an independent relationship between obesity and clinically important thyroid cancer.

Jensen CB, Saucke MC, Francis DO, Voils CI, Pitt SC 2020 From overdiagnosis to overtreatment of low-risk thyroid cancer: A thematic analysis of attitudes and beliefs of endocrinologists, surgeons, and patients. Thyroid 30:696–703. PMID: 31910092.

Abstract

Introduction: The optimal management for patients with small, low-risk thyroid cancer is often debated. We aimed to characterize the attitudes and beliefs of providers and patients about management of small, low-risk thyroid cancer and how they relate to overtreatment.

Methods: We conducted 34 semi-structured interviews with surgeons (n = 12), endocrinologists (n = 12), and patients with <1.5 cm papillary thyroid cancer (n = 10). Interviews probed about diagnosis and treatment decision-making, including nonoperative options. We used thematic analysis to identify themes related to overtreatment and created concept diagrams to map observed relationships between themes.

Results: When providers discussed management of small, low-risk thyroid cancer, most felt that overtreatment was a problem, and some brought it up without prompting. Providers often believed that overtreatment results from overdiagnosis and relayed how the process commonly starts with incidental discovery of a thyroid nodule on imaging. Providers viewed biopsy of the nodule as a reflexive or habitual action. They ascribed inappropriate biopsy to lack of adherence to or knowledge of guidelines, radiologist recommendations, and the desire of patients and physicians to minimize diagnostic uncertainty. Providers described subsequent cancer diagnosis as an event that "opens Pandora's box" and often provokes a strong instinctive, culturally rooted need to proceed with surgery-specifically total thyroidectomy. Consequently, most providers felt that it is easier to prevent overdiagnosis than overtreatment and recommended strategies such as improving guideline adherence, resetting patients' expectations, and engaging the media. In contrast, patients did not bring up or openly discuss overtreatment or overdiagnosis. Some patients described the seemingly automatic process from an incidental finding to surgery. Their statements confirmed that the "need to know" was a major motivation for biopsying their nodule. Patients felt that once they had a cancer diagnosis, surgery was a foregone conclusion. Patients admitted their knowledge about thyroid nodules and cancer was low, leaving room for education about the need for biopsy and less extensive treatment options.

Conclusions: Surgeons' and endocrinologists' attitudes and beliefs about overtreatment focus on the automaticity of overdiagnosis. Both patients and providers are cognizant of the cascade of clinical events that propel patients from incidental discovery of a thyroid nodule to surgery.

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Papaleontiou M, Evron JM, Esfandiari NH, Reyes-Gastelum D, Ward KC, Hamilton AS, Worden F, Haymart MR 2020 Patient report of recurrent and persistent thyroid cancer. Thyroid. 2020 Sep;30(9):1297-1305. PMID: 32183609.

Abstract

Background: Despite the excellent survival of most patients with differentiated thyroid cancer (DTC), recurrent and persistent disease remain major concerns for physicians and patients. However, studies on patient report of recurrent and persistent disease are lacking.

Methods: Between February 1, 2017, and October 31, 2018, we surveyed eligible patients who were diagnosed with DTC between 2014 and 2015 from the Georgia and Los Angeles Surveillance, Epidemiology, and End Results cancer registries (N = 2632; response rate, 63%). Patients who reported current disease status were included in this study (n = 2454). Patient-reported data were linked to registry data. A multivariable, multinomial logistic regression analysis was conducted to determine patient and tumor characteristics associated with recurrent and persistent thyroid cancer. Quality of life was evaluated using the Patient-Reported Outcomes Measurement Information System-Global Health v1.2 questionnaire. Meaningful change in global health was defined as a minimal difference of a half standard deviation or 5 points compared with the mean (T score = 50) of a sample population matching the United States 2000 General Census.

Results: Of the 2454 patients completing the survey, 95 (4.1%) reported recurrent disease and 137 (5.8%) reported persistent disease. In multinomial analyses, T3/T4 classification and cervical lymph node involvement (N1) were associated with both report of recurrent (adjusted relative risk ratio [RRR] 1.99, 95% confidence interval [CI 1.16-3.42]; adjusted RRR 2.03 [CI 1.29-3.21], respectively) and persistent disease (adjusted RRR 3.48 [CI 1.96-6.20]; adjusted RRR 3.56 [CI 2.41-5.24], respectively). Additionally, Hispanic ethnicity was associated with report of recurrent disease (adjusted RRR 1.99 [CI 1.23-3.24]). Regarding quality of life, the median scores in patients with persistent disease met criteria for meaningful change in global physical health (T-score = 44.9) and global mental health (T-score = 43.5) when compared with the general population norms. Median scores in patients with cured or recurrent disease did not meet criteria for meaningful change.

Conclusions: Patient report is a reasonable method of assessing recurrent and persistent disease. Impact on quality of life is more marked for patients with reported persistent disease. Our findings will help personalize treatment and long-term follow-up in these patients.

Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, Godbert Y, Barlesi F, Morris JC, Owonikoko TK, Tan DSW, Gautschi O, Weiss J, de la Fouchardière C, Burkard ME, Laskin J, Taylor MH, Kroiss M, Medioni J, Goldman JW, Bauer TM, Levy B, Zhu VW, Lakhani N, Moreno V, Ebata K, Nguyen M, Heirich D, Zhu EY, Huang X, Yang L, Kherani J, Rothenberg SM, Drilon A, Subbiah V, Shah MH, Cabanillas ME 2020 Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 383(9):825-835. PMID: 32846061.

Abstract

Background: *RET* mutations occur in 70% of medullary thyroid cancers, and *RET* fusions occur rarely in other thyroid cancers. In patients with *RET*-altered thyroid cancers, the efficacy and safety of selective RET inhibition are unknown.

Methods: We enrolled patients with *RET*-mutant medullary thyroid cancer with or without previous vandetanib or cabozantinib treatment, as well as those with previously treated *RET* fusion-positive thyroid cancer, in a phase 1-2 trial of selpercatinib. The primary end point was an objective response (a complete or partial response), as determined by an independent review committee. Secondary end points included the duration of response, progression-free survival, and safety.

Results: In the first 55 consecutively enrolled patients with *RET*-mutant medullary thyroid cancer who had previously received vandetanib, cabozantinib, or both, the percentage who had a response was 69% (95% confidence interval [CI], 55 to 81), and 1-year progression-free survival was 82% (95% CI, 69 to 90). In 88 patients with *RET*-mutant medullary thyroid cancer who had not previously received vandetanib or cabozantinib, the percentage who had a response was 73% (95% CI, 62 to 82), and 1-year progression-free survival was 92% (95% CI, 82 to 97). In 19 patients with previously treated *RET* fusion-positive thyroid cancer, the percentage who had a response was 79% (95% CI, 54 to 94), and 1-year progression-free survival was 64% (95% CI, 37 to 82). The most common adverse events of grade 3 or higher were hypertension (in 21% of the patients), increased alanine aminotransferase level (in 11%), increased aspartate aminotransferase level (in 9%), hyponatremia (in 8%), and diarrhea (in 6%). Of all 531 patients treated, 12 (2%) discontinued selpercatinib owing to drug-related adverse events.

Conclusions: In this phase 1-2 trial, selpercatinib showed durable efficacy with mainly low-grade toxic effects in patients with medullary thyroid cancer with and without previous vandetanib or cabozantinib treatment. (Funded by Loxo Oncology and others; LIBRETTO-001 ClinicalTrials.gov number, NCT03157128.).

Maniakas A, Dadu R, Busaidy NL, Wang JR, Ferrarotto R, Lu C, Williams MD, Gunn GB, Hofmann M-C, Cote G, Sperling J, Gross ND, Sturgis EM, Goepfert RP, Lai SY, Cabanillas ME, Zafereo M 2020 Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000-2019. JAMA Oncol Aug 6;e203362. PMID: 32761153.

Abstract

Importance: Anaplastic thyroid carcinoma (ATC) historically has a 4-month median overall survival (OS) from time of diagnosis, with disease-specific mortality approaching 100%. The association between recent major advancements in treatment and OS has yet to be evaluated.

Objective: To evaluate rates of OS in patients with ATC over the last 2 decades.

Design, setting, and participants: Retrospective cohort study in a single tertiary care institution. Patients with histopathological confirmation of ATC from January 2000 to October 2019 were included and divided into 3 groups according to date of presentation: 2000-2013, 2014-2016, and 2017-2019.

Main outcomes and measures: Overall survival compared among different treatment eras and differing therapies, including targeted therapy, immunotherapy, and surgery.

Results: Of 479 patients (246 men [51%]; median age, 65.0 [range, 21.1-92.6] years) with ATC evaluated, 52 (11%) were stage IVA, 172 (36%) stage IVB, and 255 (53%) stage IVC at presentation. The median OS of the entire cohort was 0.79 years (9.5 months), ranging from 0.01 to 16.63. The OS at 1 and 2 years was 35% (95% CI, 29%-42%) and 18% (95% CI, 13%-23%) in the 2000-2013 group (n = 227), 47% (95% CI, 36%-56%) and 25% (95% CI, 17%-34%) in the 2014-2016 group (n = 100), and 59% (95% CI, 49%-67%) and 42% (95% CI, 30%-53%) in the 2017-2019 group (n = 152), respectively (P < .001). The hazard ratio was 0.50 (95% CI, 0.38-0.67) for the 2017-2019 group compared with the 2000-2013 patients (P < .001). Factors associated with improved OS included targeted therapy (hazard ratio, 0.49; 95% CI, 0.39-0.63; P < .001), the addition of immunotherapy to targeted therapy (hazard ratio, 0.58; 95% CI, 0.36-0.94; P = .03), and surgery following neoadjuvant BRAF-directed therapy (hazard ratio, 0.29; 95% CI, 0.10-0.78; P = .02). Patients undergoing surgery following neoadjuvant BRAF-directed therapy (n = 20) had a 94% 1-year survival with a median follow-up of 1.21 years.

Conclusion and relevance: In this large single-institution cohort study spanning nearly 20 years, changes in patient management appear to be associated with significant increase in survival. The era of untreatable ATC is progressively being replaced by molecular-based personalized therapies, with integration of multidisciplinary therapies including surgery and radiation therapy.

Zhang B, Tian J, Pei S, Chen Y, He X, Dong Y, Lu Z, Mo X, Huang W, Cong S, Zhang S 2019 Machine learning–assisted system for thyroid nodule diagnosis. Thyroid 29:858–867. PMID: 30929637.

Abstract

Background: Ultrasound (US) examination is helpful in the differential diagnosis of thyroid nodules (malignant vs. benign), but its accuracy relies heavily on examiner experience. Therefore, the aim of this study was to develop a less subjective diagnostic model aided by machine learning.

Methods: A total of 2064 thyroid nodules (2032 patients, 695 male; M_{age} = 45.25 ± 13.49 years) met all of the following inclusion criteria: (i) hemi- or total thyroidectomy, (ii) maximum nodule diameter 2.5 cm, (iii) examination by conventional US and real-time elastography within one month before surgery, and (iv) no previous thyroid surgery or percutaneous thermotherapy. Models were developed using 60% of randomly selected samples based on nine commonly used algorithms, and validated using the remaining 40% of cases. All models function with a validation data set that has a pretest probability of malignancy of 10%. The models were refined with machine learning that consisted of 1000 repetitions of derivatization and validation, and compared to diagnosis by an experienced radiologist. Sensitivity, specificity, accuracy, and area under the curve (AUC) were calculated.

Results: A random forest algorithm led to the best diagnostic model, which performed better than radiologist diagnosis based on conventional US only (AUC = 0.924 [confidence interval (CI) 0.895-0.953] vs. 0.834 [CI 0.815-0.853]) and based on both conventional US and real-time elastography (AUC = 0.938 [CI 0.914-0.961] vs. 0.843 [CI 0.829-0.857]).

Conclusions: Machine-learning algorithms based on US examinations, particularly the random forest classifier, may diagnose malignant thyroid nodules better than radiologists.

Thomas J, Haertling T 2020 AIBx, Artificial intelligence model to risk stratify thyroid nodules. Thyroid 30:878–884. PMID: 32013775.

Abstract

Background: Current classification systems for thyroid nodules are very subjective. Artificial intelligence (AI) algorithms have been used to decrease subjectivity in medical image interpretation. One out of 2 women over the age of 50 years may have a thyroid nodule and at present the only way to exclude malignancy is through invasive procedures for those that are suspicious on ultrasonography. Hence, there exists a need for noninvasive objective classification of thyroid nodules. Some cancers have benign appearance on ultrasonogram. Hence, we decided to create an image similarity algorithm rather than image classification algorithm.

Materials and Methods: Ultrasound images of thyroid nodules from patients who underwent either biopsy or thyroid surgery from February 2012 to February 2017 in our institution were used to create AI models. Nodules were excluded if there was no definitive diagnosis of it being benign or malignant. A total of 482 nodules met the inclusion criteria and all available images from these nodules were used to create the AI models. Later, these AI models were used to test 103 thyroid nodules that underwent biopsy or surgery from March 2017 to July 2018.

Results: Negative predictive value (NPV) of the image similarity model was 93.2%. Sensitivity, specificity, positive predictive value (PPV), and accuracy of the model were 87.8%, 78.5%, 65.9%, and 81.5%, respectively.

Conclusions: When compared with published results of ultrasound thyroid cancer risk stratification systems, our image similarity model had comparable NPV with better sensitivity, specificity, and PPV. By using image similarity AI models, we can decrease subjectivity and decrease the number of unnecessary biopsies. Using image similarity AI model, we were able to create an explainable AI model that increases physician's confidence in the predictions.

Cesareo R, Pacella CM, Pasqualini V, Campagna G, Iozzino M, Gallo A, Lauria Pantano A, Cianni R, Pedone C, Pozzilli P, Taffon C, Crescenzi A, Manfrini S, Palermo A 2020 Laser ablation versus radiofrequency ablation for benign non-functioning thyroid nodules: Six-month results of a randomized, parallel, open-label, trial (LARA trial). Thyroid 30:847–856. PMID: 32056501.

Abstract

Background: No direct prospective studies comparing laser ablation (LA) and radiofrequency ablation (RFA) for debulking benign non-functioning thyroid nodules (BNTNs) exist. We aimed at comparing the efficacy and safety of both techniques in patients with solid or predominantly solid BNTN.

Methods: This six-month, single-use, randomized, open-label, parallel trial compared the following primary endpoints between the RFA and LA groups six months after treatment: (i) nodule volume reduction expressed as a percentage of nodule volume at baseline; (ii) proportion of nodules with more than 50% reduction (successful rate). We enrolled subjects with a solitary BNTN or dominant nodule characterized by pressure symptoms/cosmetic problems or patients without symptoms who experienced a volume increase >20% in one year. Nodules underwent core needle biopsy for diagnosis. Patients were randomly assigned (1:1) to receive LA or RFA. Safety was assessed in all randomly assigned participants.

Results: Sixty patients were randomly assigned to receive either RFA or LA (1:1) between January 2016 and November 2018. Both groups were similar in basal nodule volume, thyroid function, histology, symptoms/cosmetic score, and procedure time. At six months, the nodule volume reduction was 64.3% (95% confidence interval, CI 57.5-71.2) in the RFA group and 53.2% ([CI 47.2-95.2]; p = 0.02) in the LA group. This effect was also confirmed in the linear regression model adjusted for age, baseline volume, and proportion of cellular component (LA vs. RFA percent change Delta = -12.8, p = 0.02). No significant difference was observed in success rate six months after treatment (RFA vs. LA: 86.7% vs. 66.7%, p = 0.13) or in thyrotropin level between the groups. Although improved, no significant difference was observed between RFA and LA for compressive symptoms (RFA: 2.13 vs. 3.9, p < 0 · 001; LA: 2.4 vs. 3.87, p < 0.001) and cosmetic score (RFA: 1.65 vs. 2.2, p < 0.001; LA: 1.85 vs. 2.2, p < 0.001). The adverse event rates (local pain, dysphonia, thyrotoxicosis, fever, hematoma) were 37% (n = 11) and 43% (n = 13) for RFA and LA, respectively, with no requirement for hospitalization.

Conclusion: Although the success rate was similar in the RFA and LA groups, RFA achieved a significantly larger nodule volume reduction at six months.

Zafereo M, McIver B, Vargas-Salas S, Domínguez JM, Steward DL, Holsinger FC, Kandil E, Williams M, Cruz F, Loyola S, Solar A, Roa JC, León A, Droppelman N, Lobos M, Arias T, Kong CS, Busaidy N, Grubbs EG, Graham P, Stewart J, Tang A, Wang J, Orloff L, Henríquez M, Lagos M, Osorio M, Schachter D, Franco C, Medina F, Wohllk N, Diaz RE, Veliz J, Horvath E, Tala H, Pineda P, Arroyo P, Vasquez F, Traipe E, Marín L, Miranda G, Bruce E, Bracamonte M, Mena N, González HE 2020 A Thyroid Genetic Classifier correctly predicts benign nodules with indeterminate cytology: Two independent, multicenter, prospective validation trials. Thyroid;30(5):704-712.

Abstract

Background: Although most thyroid nodules with indeterminate cytology are benign, in most of the world, surgery remains as the most frequent diagnostic approach. We have previously reported a 10-gene thyroid genetic classifier, which accurately predicts benign thyroid nodules. The assay is a prototype diagnostic kit suitable for reference laboratory testing and could potentially avoid unnecessary diagnostic surgery in patients with indeterminate thyroid cytology.

Methods: Classifier performance was tested in two independent, ethnically diverse, prospective multicenter trials (TGCT-1/Chile and TGCT-2/USA). A total of 4061 fine-needle aspirations were collected from 15 institutions, of which 897 (22%) were called indeterminate. The clinical site was blind to the classifier score and the clinical laboratory blind to the pathology report. A matched surgical pathology and valid classifier score was available for 270 samples.

Results: Cohorts showed significant differences, including (i) clinical site patient source (academic, 43% and 97% for TGCT-1 and -2, respectively); (ii) ethnic diversity, with a greater proportion of the Hispanic population (40% vs. 3%) for TGCT-1 and a greater proportion of African American (11% vs. 0%) and Asian (10% vs. 1%) populations for TGCT-2; and (iii) tumor size (mean of 1.7 and 2.5 cm for TGCT-1 and -2, respectively). Overall, there were no differences in the histopathological profile between cohorts. Forty-one of 155 and 45 of 115 nodules were malignant (cancer prevalence of 26% and 39% for TGCT-1 and -2, respectively). The classifier predicted 37 of 41 and 41 of 45 malignant nodules, yielding a sensitivity of 90% [95% confidence interval; CI 77-97] and 91% [95% CI 79-98] for TGCT-1 and -2, respectively. One hundred one of 114 and 61 of 70 nodules were correctly predicted as benign, yielding a specificity of 89% [95% CI 82-94] and 87% [95% CI 77-94], respectively. The negative predictive values for TGCT-1 and TGCT-2 were 96% and 94%, respectively, whereas the positive predictive values were 74% and 82%, respectively. The overall accuracy for both cohorts was 89%.

Conclusions: Clinical validation of the classifier demonstrates equivalent performance in two independent and ethnically diverse cohorts, accurately predicting benign thyroid nodules that can undergo surveillance as an alternative to diagnostic surgery.

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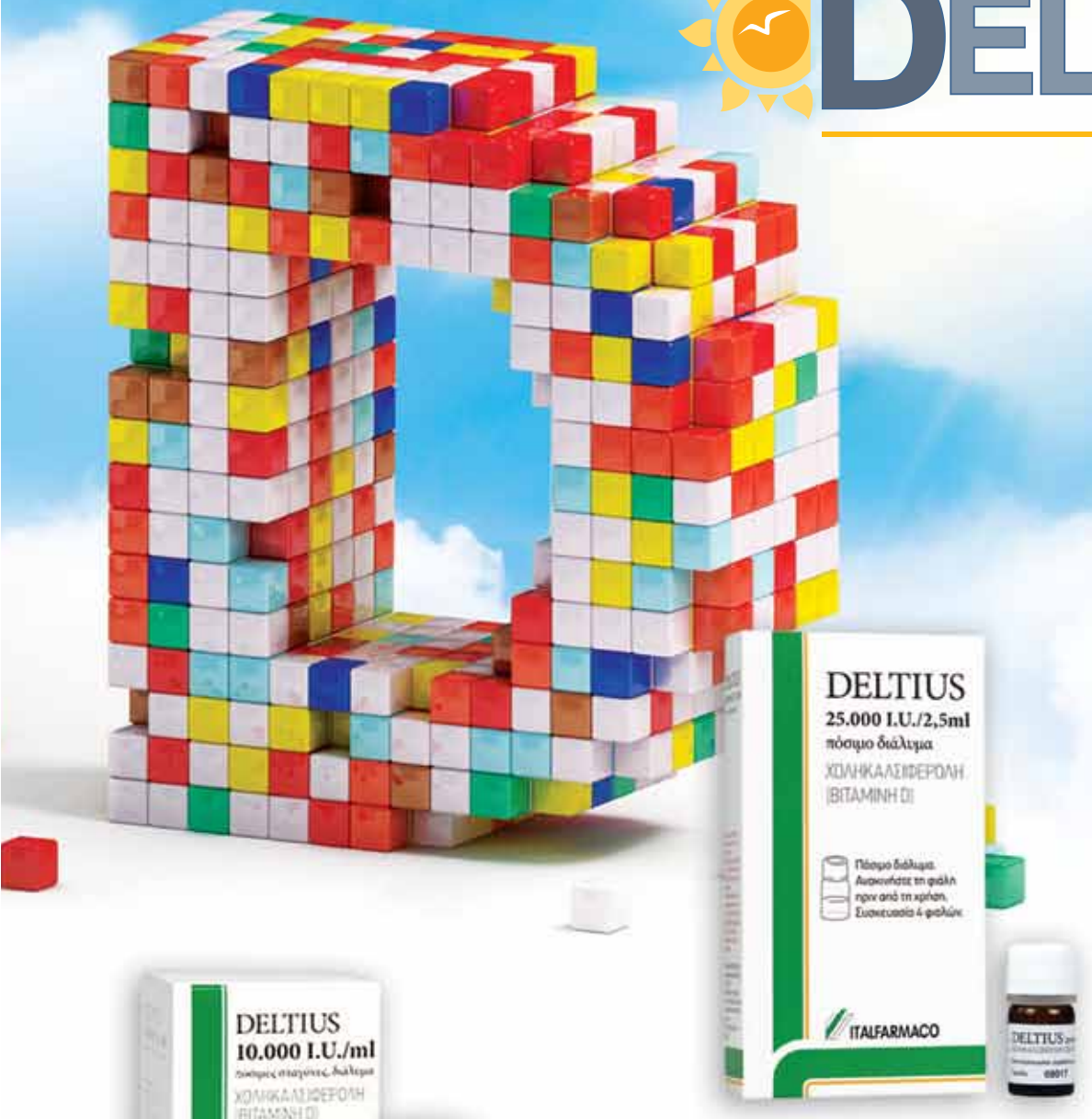

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Η ενδοκρινολογία στην εποχή του Covid-19

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Endocrine and metabolic aspects of the COVID-19 pandemic

Mónica Marazuela[1] · Andrea Giustina[2] · Manuel Puig-Domingo[3]

Abstract
COVID-19 infection has tremendously impacted our daily clinical practice as well as our social living organization. Virtually all organs and biological systems suffer from this new coronavirus infection, either because the virus targets directly specific tissues or because of indirect effects. Endocrine diseases are not an exception and some of endocrine organs are at risk of direct or indirect lesion by COVID-19. Although there is still no evidence of higher predisposition to contract the infection in patients with diabetes and/or obesity, the coexistence of these conditions contributes to a worse prognosis because both conditions confer an impaired immunologic system. Cytokines storm can be amplified by these two latter conditions thereby leading to multisystemic failure and death. Glycaemic control has been demonstrated to be crucial to avoiding long hospital stays, ICU requirement and also prevention of excessive mortality. Endocrine treatment modifications as a consequence of COVID-19 infection are required in a proactive manner, in order to avoid decompensation and eventual hospital admission. This is the case of diabetes and adrenal insufficiency in which prompt increase of insulin dosage and substitutive adrenal steroids through adoption of the sick day's rules should be warranted, as well as easy contact with the health care provider through telematic different modalities. New possible endocrinological targets of COVID-19 have been recently described and warrant a full study in the next future.

Keywords Covid-19 · Diabetes mellitus · Obesity · Malnourishment · Pituitary · Thyroid · Calcium · Vitamin D · Hypoadrenalism

Abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
BMI	Body mass index
COVID-19	Coronavirus disease 2019
DPP4	Human dipeptidyl peptidase 4
H1N1	Influenza A
ICUs	Intensive care units
MERS	Middle East respiratory syndrome
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane protease serine 2

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1 Introduction

Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak requires that endocrinologists move forward, even more, to the first line of care of our patients, in collaboration with other physicians such as those in internal medicine and emergency units. This will preserve the health condition and prevent the adverse COVID-19-related outcomes in people affected by different endocrine diseases. People with diabetes in particular, are among those in high-risk categories for developing serious illness modality of COVID-19 infection if they get the virus, but other endocrine diseases such as obesity, malnutrition and adrenal insufficiency may also be strongly impacted by COVID-19 [1, 2] (Fig. 1).

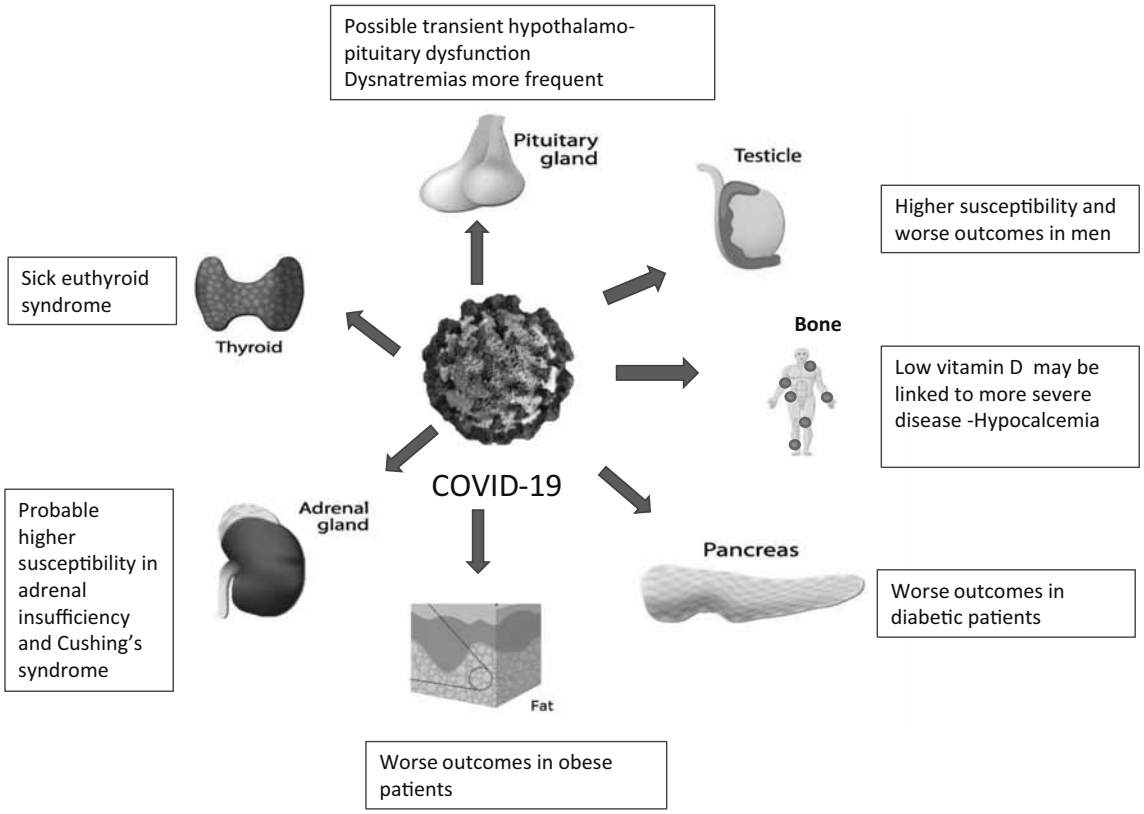

Fig. 1 Different endocrine glands/organs that can be affected by COVID-19: 1) Pituitary: possible hypothalamic-pituitary disfunction and alterations in antidiuretic hormone metabolism. 2) Thyroid: sick euthyroid syndrome; 3) Adrenal: probable higher susceptibility to COVID-19 in adrenal insufficiency and Cushing's syndrome; 4) Bone. Low vitamin D may be linked to more severe disease Increased risk of hypocalcemia. 5) Testicle: Higher susceptibility and worse outcomes have been reported in men; 6) Diabetes. Worse outcomes in diabetic patients; 7) Obesity. Worse prognosis in obese patients

2 COVID-19 infection and diabetes mellitus

Individuals with diabetes may be at increased risk of infections, especially influenza and pneumonia. This is why all people with diabetes are recommended pneumococcal and annual influenza vaccinations [3]. In general, it is assumed that this risk can be reduced, though not completely eliminated, through good glycemic control. Data about the incidence of COVID-19 in patients with diabetes are limited at present, but are increasing steadily every week; early reports have identified diabetes and obesity as predictors of higher incidence [4–7]. However, as population testing is still limited, and only in a few countries massive COVID-19 screening has been performed, whether or not diabetes is associated to a higher risk to contract COVID-19 is still unknown. The data currently available come mostly from hospital consultation cohorts (Fig. 2).

In this setting, the series by Petrilli et al. [8], in which 4103 patients were attended and 1999 were admitted to hospital, 15% of the overall cohort was found to have diabetes, which is not far from the prevalence of diabetes in the general population in their age range in the US. Thus, confirming what was found with Influenza A (H1N1) pandemic, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreaks, the present coronavirus epidemics does not seem to account for a much higher capacity to infect people with diabetes [9].

2.1 Increased risk of morbidity and mortality in patients with diabetes regarding COVID-19 infection

Virtually all reports coincide that morbidity and mortality due to COVID-19 infection are increased by the presence of diabetes. In the series published by New York city hospitals, diabetes was more prevalent in those patients requiring admission (31.8%) than in those not requiring admission (5.4%) [8] (Fig. 2). Indeed, diabetes was also reported as an important risk factor for worse disease modality and excessive mortality while the occurrence of the Influenza A (H1N1) pandemic, SARS-CoV and MERSCoV outbreaks [4]. Influenza A (H1N1) pandemic, tripled the risk of hospitalization and quadrupled the risk of intensive care unit (ICU) admission when diabetes was present [3]. Consistent with that, data from China found that diabetes accounted for 8%–16% of hospitalized patients [10, 11], being diabetes prevalence across China around 5% [12].

A large report of the Centers for Disease Control and Prevention of the United States showed that 78% of COVID-

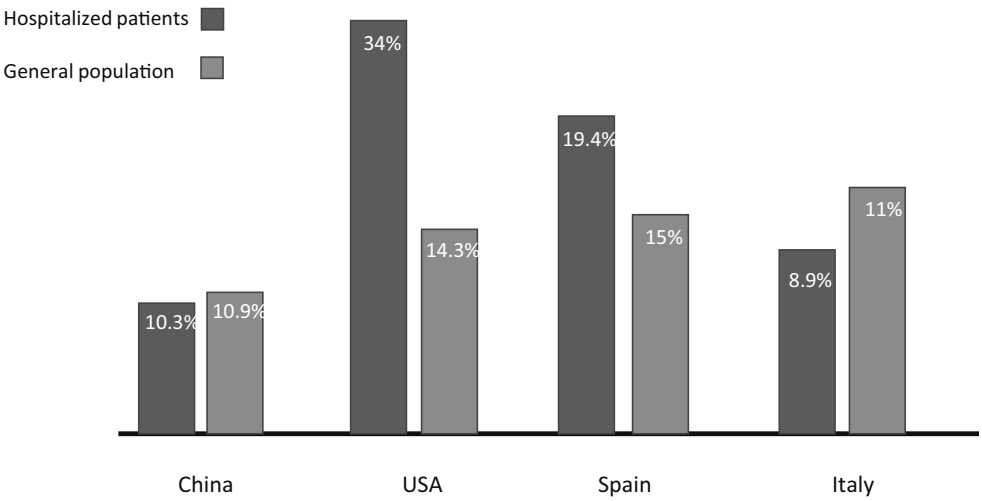

Fig. 2 Prevalence of diabetes mellitus in hospitalized COVID 19+ versus general population in different countries The prevalence of diabetes is higher in hospitalized patients in USA and Spain, but not in China or Italy

19 patients in ICUs had diabetes, cardiovascular diseases including hypertension or chronic lung disease [13]. A study performed by the Chinese Centre for Disease Control and Prevention including 72,314 cases (hospital admitted and ambulatory controlled) reported an overall mortality of 2.3% (1023 deaths among 44,672 confirmed cases) and in those having diabetes it reached 7.3% [1]. An additional report from China including 1590 hospitalized cases analyzed a composite endpoint including admission to ICU, intensive ventilation, or death, and after adjusting for smoking status and age. It was found that diabetes significantly increased the risk of severity according to the composite endpoint (hazard ratio 1.59, 95% CI 1.03–2.45); in this series, 34.6% of severe cases had diabetes compared to 14.3% in non-severe cases [14].

General mortality rates are difficult to evaluate due to the lack of data on non-symptomatic cases, as in most countries universal microbiological screening for COVID-19 has not been implemented, thus leading to an overestimation of the prevalence of case fatality. As indicated, in China the overall fatality rate was 2.3% and in people with diabetes it was 7.3% [1]. Data published in Italy, indicate that more than 70% of patients who died due to COVID-19 had either diabetes, cardiovascular disease or cancer as comorbidities [7].

In summary, according to current accumulated data, persons with diabetes are at increased risk for COVID-19 infection medical complications including death. Accordingly, an increased vigilance and testing of people with diabetes in specialized outpatient and general medicine clinics for COVID-19 is required, as well as a proactive hospitalization policy [15].

2.2 Importance of glycemic control in those with coexistence of COVID-19 infection and diabetes

To date, only a limited number of studies have addressed the role of hyperglycemia in the pathogenesis and prognosis of viral respiratory diseases [1, 16]. However, it has been shown that elevated blood glucose levels can directly rise glucose concentrations in airway secretion [17]. In vitro glucose exposure of pulmonary epithelial cells significantly increases influenza virus infection and replication. In addition, elevated glucose levels impair the antiviral immune response. As a consequence, patients with diabetes use to have a higher viral charge as well as a much severe disease when infected with respiratory viruses. These findings are consistent with the reports of patients infected with the highly pathogenic avian influenza, in which hyperglycemia was associated with increased fatal outcome. Hyperglycemia may also affect pulmonary function, and therefore, respiratory dysfunction induced by influenza virus is exacerbated in patients with diabetes [18, 19]. In viral disease animal models, diabetes is associated with numerous lung structural changes, including augmented permeability of the alveolo-capillary membrane and a collapsed alveolar epithelium [20]. It is anticipated that glycemic control can have beneficial effects in patients with coexistent diabetes and viral respiratory diseases such as COVID-19. However, in the clinical setting, optimal metabolic control has been difficult to achieve mostly because of practical limitations encountered during the treatment of this patients' group [21]. Interleukin 6 and D-dimer levels are more elevated in hyperglycemic patients compared to normoglycemic ones. Both, patients with hyperglycemia not previously known as having diabetes and patients with known diabetes had a higher risk of severe disease than those without diabetes [22]. This emphasizes the importance of early detection of hyperglycemia at the hospital setting and the necessity of its prompt and effective treatment with insulin [23–25].

2.3 Treatment for people with diabetes infected by COVID-19

People with diabetes who are infected with COVID-19 may probably experience a deterioration of glycemic control, like

in any other infectious episode. Proactive basal insulin dosage increase and correctional bolus may be required to maintain normoglycemia and prevent deterioration of metabolic control in those under insulin treatment [15].

Diabetic ketoacidosis coexisting with COVID-19 is particularly hazardous to treat, because of the risk of pulmonary fluid accumulation [26]. A report from a Chinese cohort consisting of 658 patients suggests that COVID-19 infection can cause ketosis per se in non-diabetic persons and may increase the risk of ketoacidosis in those with diabetes [27, 28].

In general, mild COVID-19 illness in people with type 2 diabetes on oral agents may be allowed to keep their usual treatment, provided that the patient stays under well control, but treatment modification must be indicated immediately upon clinical judgement, if development of severe COVID-19-related symptoms appear, especially high fever and potential dehydration. Oral agents, particularly metformin and sodium glucose cotransporter-2 inhibitors need to be stopped also, if serious illness condition develops [26]. Insulin is the preferred agent to control hyperglycemia in hospitalized patients, as it the most efficacious for any intercurrent situation, including infections [4]. Although sodium glucose cotransporter-2 inhibitors may predispose to ketoacidosis, a controversial clinical trial with dapaglifozin has been approved in COVID-19 patients with moderate illness including respiratory failure, the DARE-19 study (NCT04350593), aiming to evaluate the reduction of disease progression and death.

2.4 Role of DPP-4 in COVID-19 as virus target

Remarkably, human dipeptidyl peptidase 4 (DPP-4) has also been identified as a functional receptor of the S-protein of MERS-Co-V [29]. MERS-CoV binds to the DPP-4 receptor-binding domain and interacts with T cells and nuclear factors, such as nuclear factor kappa b (NF-kB), a key factor in the pathogenesis of inflammatory disorders. DPP-4 plays an important role in the regulation of the immune system by activating T cell repertoire and upregulating nuclear factor kappa b pathway [30]. Transgenic mouse models expressing human DPP-4 exposed to MERS-CoV had impaired inflammatory monocyte/macrophage phenotype, CD4+ T cells and lower expression of tumor necrosis factor alpha, interleukin 6 and Arg1 [31]. Remarkably, it has been recently demonstrated that human DPP-4/CD26 may interact with the S1 domain of the viral spike glycoprotein of SARS-CoV-2, thus allowing an additional way for the virus to enter the cell, beside the main one, which is angiotensin-converting enzyme (ACE)2 [32].

Thus, the question is whether DPP-4 inhibitors used currently for treatment of type 2 diabetes play a role not just regarding metabolic control, but also contributing to modify COVID-19 attack in these patients, either inducing protection or progression of infection (Fig. 3). It is tempting to postulate that inhibition of DDP-4 with the current antidiabetic drugs such as sitagliptin, vildagliptin or linagliptin may impair the virus/DPP-4 interaction, thereby protecting the cell from virus entrance. However, the binding of SARS-CoV-2 and MERS-CoV takes place at residues not located nearby the DPP-4i binding pocket of current gliptin drugs, thus requiring more studies in order to clarify this question [33].

It is known that DDP-4 inhibition modulates inflammation and has anti-fibrotic effects; depending on the potency of these properties, DPP-4 inhibitors may eventually have some protective effects in case of severe COVID-19 infection. The potential decrease of the magnitude COVID-19 cytokines storm under DPP-4 inhibitors action sounds attractive but, so far, no data are available to provide a consistent answer.

3 COVID-19 and obesity

3.1 Increased risk of morbidity and mortality in patients with obesity regarding COVID-19 infection

Until recently, there were no specific data in the literature reporting that subjects with obesity have a higher risk of developing severe forms of COVID-19, as first studies from China [1] and Italy [34] did not provide data on body weight and height. However, last reports have found a strong link between obesity and admission to critical care as well as the use of invasive mechanical ventilation [35]. In a study from Shenzhen (China), obesity was associated with a 142% higher risk of developing severe pneumonia [36]. The Intensive Care National Audit & Research Centre in United Kingdom observed that 72.1% of patients with confirmed COVID-19 were overweight or obese and that among patients with body mass index (BMI) >30 who had undergone intensive care, 60.9% of them died [37]. Among 4103 patients in New York City, BMI >40 kg/m2 was the second strongest independent predictor of hospitalization, after old age [8]. In a retrospective single French center evaluating 124 consecutive patients, obesity (BMI >30 kg/m2) and severe obesity (BMI >35 kg/m2) were present in 47.6% and 28.2% of cases admitted to intensive care unit. The need for invasive mechanical ventilation was associated with a BMI ≥35 kg/m2 [38]. Several reports from around the world have previously identified obesity and severe obesity as risk factors for hospitalization and mechanical ventilation in the H1N1 influenza virus [39]. Together, these data raise the question of whether there is a mechanistic link between obesity and COVID-19 and whether obesity might independently contribute to COVID-19 risk or at least to more severe forms of the disease.

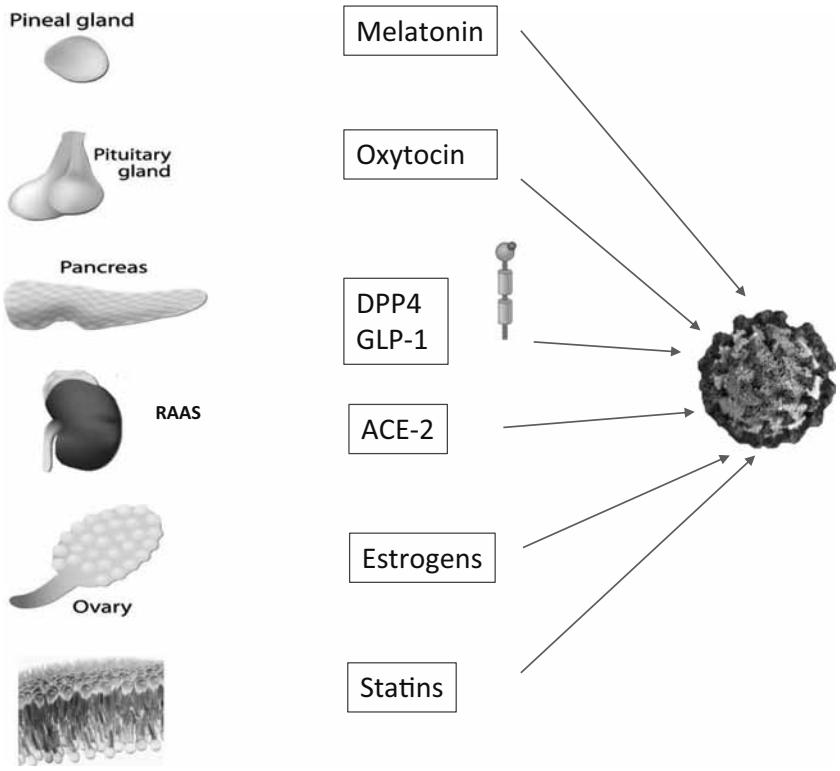

Fig. 3 Possible endocrine and metabolic targets that have been considered for COVID-19 therapy. Different hormones and drugs have been included as possible targets for COVI-19 including melatonin, oxytocin, DPP-4 (human dipeptidyl peptidase 4), ACE-2 (angiotensin converting enzyme-2), estrogens and statins

3.2 How can obesity impact COVID-19 infection?

The high impact of H1N1 Influenza and now COVID-19 in patients with obesity and severe obesity is probably related to the deleterious effects of obesity on pulmonary function (Fig. 4). Obesity is associated with decreased expiratory reserve volume, functional capacity and respiratory system compliance. Severe obesity causes sleep apnea syndrome and in those with increased abdominal obesity, pulmonary function is further impaired by decreased diaphragmatic excursion.

In addition, obesity contributes to increase the risk of different comorbidities including diabetes, cardiovascular risk and thrombosis, which may have a great impact in COVID-19 infected patients outcomes, thus confirming that obesity rises the severity of COVID-19 infection [10, 40].

In addition, obesity could increase per se, the risk of different comorbidities including diabetes, cardiovascular risk and thrombosis in COVID-19, which can intensify the severity of COVID infection.

When it comes to the immune response, there is a clear association between obesity and chronic inflammation that can modify innate and adaptive immune responses, making the immune system more vulnerable to infections [41]. Obesity is related to low-grade inflammation that is associated to adipocyte hypoxia and dysfunction. This results in an exuberant secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), interleukin (IL) 1β and interleukin 6 and adipokines that lead to the recruitment of immune cells macrophage, T cell and B-cells, creating an auto-regenerating inflammation loop [42]. In this scenario, inflammatory macrophage and innate lymphoid subsets replace tissue regulatory M2 phenotypic cells. In addition, there are alterations of lymphocyte phenotype with a decrease in T regulatory and Th2 cells and an increase in Th1 an Th17. Viral infection may amplify the already primed organ cytokine response in adipose tissue [42]. In parallel, one of the most important mechanisms underlying the severity of lung disease in COVID-19 is represented by the so called "cytokine storm", which can lead to acute respiratory distress syndrome or even multiple organ failure in the worst case. The cytokine storm identified in multiple respiratory viral infections including COVID-19 exhibits an overproduction of interferon, tumor necrosis factor α, interleukins, and different chemokines. Thus, considering that subjects with obesity have also a pre-set proinflammatory milieu, it is expected that COVID-19 could further exacerbate inflammation exposing them to higher levels of circulating inflammatory molecules compared to lean human subjects. This seems a feasible mechanistic explanation of the increased risk of severe complications of COVID-19 in subjects with obesity [43].

Obese individuals may exhibit greater viral shedding suggesting potential for enhanced viral exposure, especially if several family members are overweight. This may be aggravated in overcrowded multigenerational households, which are more common in the socioeconomically deprived communities in which obesity is prevalent [44]. In addition, in influenza infection obesity not only increases the severity but also enhances viral diversity. The altered microenvironment associated with obesity supports the emergence of more virulent

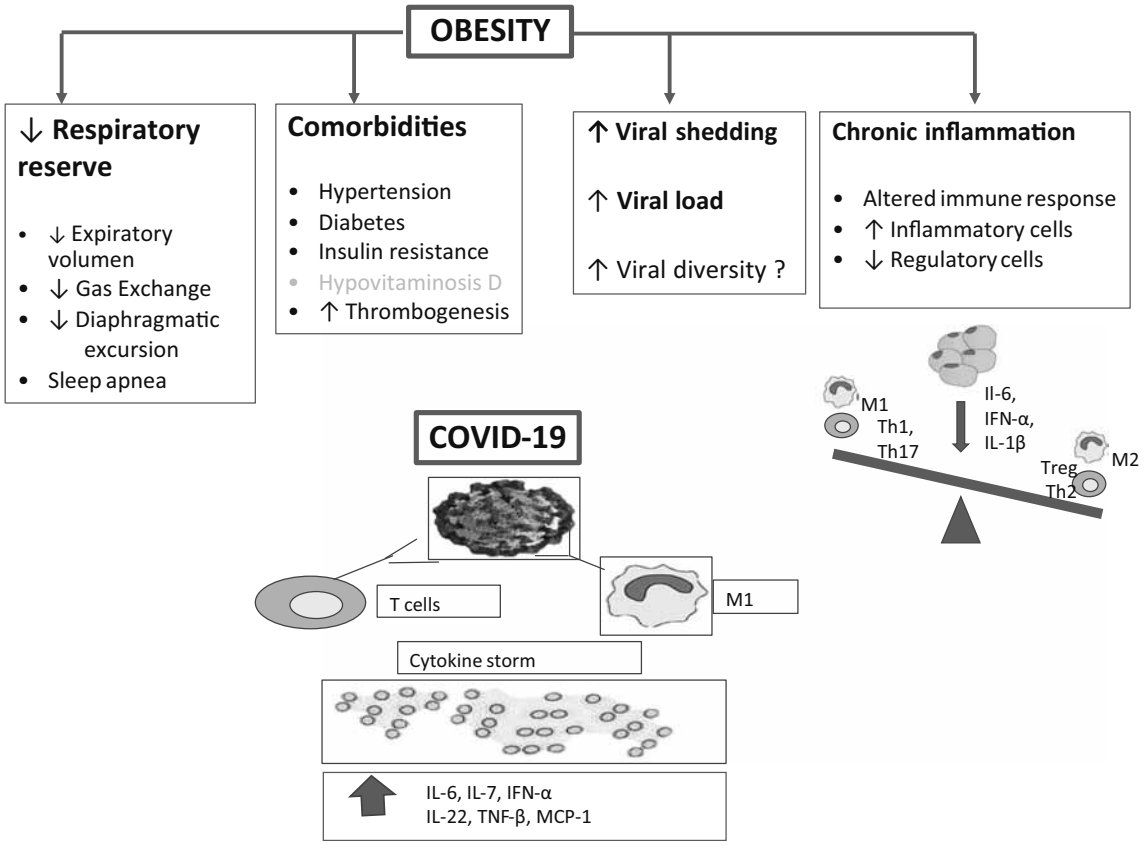

Fig. 4 Potential mechanisms that link obesity to worse outcomes in COVID-19. Obese patients have 1) a impaired respiratory function; 2) associated cardiovascular, metabolic and thrombotic comorbidities which reduce the capability to cope with COVID-19. In addition, obese patients have 3) increased viral shedding and viral load and 4) an amplified immune response due to altered balance between inflammatory and regulatory cells. During COVID-19 infection there is also an altered immune response that is amplified by the dysregulated immune system of the obese patients

influenza virus population capable of inducing greater disease severity. This could be related to an impaired interferon response, which is seen in experimental models, both in obese mice and obesity-derived human bronchial epithelial cells [45]. The same could happen in COVID-19 infection.

Finally, subjects with obesity have also mechanical issues related to excessive weight that make difficult an early diagnosis with pulmonary ultrasound and other imaging techniques, thus leading to a diagnosis of COVID-19 in the advanced stage which is most associated to highest mortality. The lack of medical or intensive care units not designed to accommodate optimally patients with severe obesity, the difficulty of intubation and insertion of catheters related to excess of weight may lead to a slowdown in therapeutic steps, worsening prognosis in patients with obesity and COVID-19 [46].

3.3 Recommendations for people with obesity regarding COVID-19 infection

There is a need for increased vigilance, priority on detection and testing, as well as a proactive therapy policy for patients with obesity and COVID-19 infections. The assessment of metabolic phenotype is crucial. This includes body mass index, waist and hip circumferences and levels of glucose. Such measurements might not be forgotten to be done, both, in the primary care setting as well as in the hospital setting to accurately assess the risk of these persons.

It is critical that patients with body mass index greater than 40, which has been reported as a critical cut-off for mortality risk [8], take all the possible precautions to avoid infection. Losing weight, lowering blood pressure and controlling blood sugar have always been important to prevent severe health consequences, but the risk of severe COVID-19 infection might now be another important reason to focus on these issues.

Persons with obesity who become COVID-19 ill and require treatment in intensive care units present very important challenges in their therapeutic management, as it is more difficult to intubate them. It can also be more difficult to obtain diagnostic imaging (as there are weight limits on imaging machines) and patients are more difficult to position and transport by nursing staff. Also, the decision to extubate those patients is more challenging when it comes to these patients. Healthcare systems in general are not yet well set up enough to manage an increasing number of patients with obesity in ICUs

and the current crisis could probably highlight their limitations even more.

4 Nutrition & vitamin D and COVID-19

Regarding undernourished subjects, COVID-19 infection is associated to a high risk of malnutrition development, mostly related to augmenting requirements and the presence of a severe acute inflammatory status. These patients show also a hyporexic state, thus contributing to an acute negative nutritional balance. Estimated nutritional requirements for these patients are 25–30 kcal/kg of weight and 1.5 g protein/kg/day [47]. A nutrient dense diet is recommended in hospitalized cases including high protein supplements, administered in 2–3 intakes per day and containing at least 18 g of protein per intake. If nutritional requirements are not met during hospital stay, complementary or complete enteral feeding may be required and, in case that enteral feeding may not be possible due to inadequate gastrointestinal tolerance, the patient should be put on parenteral nutrition. COVID-19 patients' outcome is expected to improve with an adequate nutritional support.

Vitamin D deficiency is widespread in Southern Europe where vitamin D fortified food is not widely used [48]. Vitamin D insufficiency has been reported to increase predisposition to systemic infections and to impair immune response or even to enhance the development of autoimmune diseases [49]. Moreover, it has been shown that vitamin D supplementation can prevent respiratory infections [50] and poor vitamin D status may aggravate the health outcome of ICU patients while its correction could decrease morbidity and mortality in this clinical setting [51]. Therefore, besides the hypothesis that hypovitaminosis D may be a predisposing factor to COVID-19 infection and aggressiveness in some European countries [52], we strongly recommend to maintain vitamin D treatment in those already diagnosed with hypovitaminosis D [53] and suggest considering the supplementation with vitamin D of elderly comorbid persons at home confinement if they are no yet under supplementation [54, 55]. Studies on levels of 25 OH Vitamin D and their prognostic role in COVID-19 as well as on potential benefits of vitamin D intervention in this clinical setting are underway [56].

5 Lipids and COVID-19

Hypertrygliceridemia has been described as a side effect during COVID-19 infection, with four cases reported up to date. In two of them hypertrygliceridemia was related with lopinavir/ritonavir treatment [57] and in two others, patients were receiving a combination of this therapy with tocilizumab [58]. Lopinavir/ritonavir has been previously associated with lipid abnormalities, including elevations of total cholesterol and triglycerides [59]. Chronic use of tocilizumab in rheumatoid arthritis has also been shown to increase lipid parameters, in particular triglycerides [60].

Statins have been postulated as a possible add-on treatment for COVID-19 patients, based on their known immunomodulatory properties [61]. Statins exert pleiotropic effects on inflammation and oxidative stress and modulate the immune response at different levels, including immune cell adhesion and migration, antigen presentation, and cytokine production [62]. Observational studies have reported the effectiveness of statin treatment in some viral infections including reducing influenza-related hospitalizations and deaths [63]. As statins are low-cost, extensively tested, well-tolerated drugs in a health crisis such as the current COVID-19 pandemic, they could be an option when treatment with more expensive drugs may not be implemented. Continuation of preexisting statin therapy must be recommended.

6 The pituitary and COVID-19

Evidence of altered pituitary function in SARS was first reported by Leow et al. [64]. Sixty-one survivors of the SARS outbreak were evaluated after recovery: 40% had evidence of central mild hypocortisolism and 5% also had central hypothyroidism [64]. Edema and neuronal degeneration along with SARS-CoV genome have been identified in the hypothalamus on autopsy studies [64]. In the case of COVID-19 both the hypothalamic and pituitary tissues express ACE2 and could also be viral targets [65]. Currently, we do not have any such data in COVID-19; however, considering the high frequency of neurological symptoms, one can assume that SARS-CoV-2 may affect the hypothalamus–pituitary as well, directly or via immune-mediated hypophysitis [66].

6.1 Recommendations for people with pituitary disorders regarding COVID-19 infection

Management of pituitary tumors without mass effects and without hormonal hypersecretion can be deferred for several months and if possible, all patients should receive medical therapy [67]. In the case of pituitary tumors (except prolactinomas) with severe visual deterioration, surgery is the treatment of choice, with previous assessment of COVID-19 status [68].

Patients with pre-existing endocrine conditions may be vulnerable to perturbations in plasma sodium in more severe cases of COVID-19. None of the published reports so far have reported a higher prevalence of dysnatremia in COVID-19 [69]. Regarding management of diabetes insipidus, since patients have limited accessibility to blood testing, the priority should be to avoid hyponatremia [70]. This can be performed delaying desmopressin to allow regular periods of free water

clearance to prevent dilutional hyponatremia. It is also useful to measure body weight daily. In addition, patients with diabetes insipidus who develop respiratory complications of COVID-19 are at significantly increased risk of dysnatremia and should have a close monitorization [70].

7 The thyroid and COVID-19

Data on thyroid involvement by coronavirus are most scarce. A study conducted during the SARS outbreak in 2003 had reported that serum Triiodothyronine and thyroxine levels were lower in patients with SARS as compared to controls, both during the acute and convalescent phases. This could simply imply an underlying euthyroid sick syndrome. However, a study of the autopsy in five patients with SARS has shown marked destruction of the follicular and parafollicular thyroid cells [71] and not a reduction in thyroid follicular size associated with euthyroid sick syndrome [72]. Destruction of follicular cells may also be identified as a low triiodothyronine and thyroxine profile. Data on thyroid function or thyroid pathology are yet not available in COVID-19 [65].

Regarding Graves' disease, COVID-19 can be a precipitating factor for initiation or relapse of the disease (M. Marazuela, personal experience). Several medical societies have recommended to take special care to patients with hyperthyroidism receiving antithyroid drugs, because symptoms of the rare side effect of agranulocytosis can overlap with COVID-19. In this scenario, if symptoms of COVID-19, agranulocytosis should be ruled out immediately with a full blood count.

Diagnostic work-up of thyroid nodules as well as thyroid surgery for either benign or malignant thyroid nodules for differentiated thyroid cancers have been generally postponed during COVID-19 pandemic [73] -although individualized choices based on accurate risk profile analysis were recommended. Interestingly, 1 out of 12 patients who received radioiodine for differentiated thyroid carcinoma also showed interstitial pneumonia on single photon emission computed tomography [74].

8 The adrenal and COVID-19

8.1 Adrenal insufficiency

Life-long replacement treatment aiming to mimic physiologic plasma cortisol concentrations is not easy to be achieved in adrenal insufficiency patients. Many circumstances, either organic and/or psychological, might unbalance the physiologic cortisol requirements. COVID-19 pandemic may be a new reason for patient and physician concern.

Adrenal insufficiency may confer a potentially increased risk of acquiring COVID-19 infection, as this condition is associated to an impaired natural immunity function, with a defective action of neutrophils and natural killer-cells [75]. This may explain, in part, the slightly increased rate of infectious diseases in these patients, as well as an overall higher mortality. Although patients with adrenal insufficiency may have a greater risk of complications due to the potential for an adrenal crisis to be triggered by the infection, there is still no evidence that those patients have a more severe course of COVID-19 [76].

Regarding cortisol dynamics, autopsy studies performed on patients who died from SARS-CoV showed degeneration and necrosis of the adrenal cortical cells, pointing to a direct cytopathic effect of the virus. Hence, it is likely that cortisol dynamics may be altered in patients with SARS (and also with SARS-CoV-2) [65]. In addition, there is an interesting hypothesis that certain amino acid sequences in the SARS-CoV are molecular mimics of the host adrenocorticotropic hormone (ACTH). This could blunt the stress-induced cortisol rise, as antibodies produced against the viral particles will inadvertently destroy the circulating ACTH [77]. However, it is not yet known whether SARS-CoV-2 might be employing this same strategy.

The increase in morbidity and mortality in adrenal insufficiency could also be accounted by an insufficient compensatory self-adjusted rise of the hydrocortisone dosage at the time of the beginning of an episode of the infection. In this regard, in the case of suspicion of COVID-19, the "sick days" rule should be established as soon as minor symptoms appear [78]. Additionally, patients are also recommended to have sufficient stock at home of steroid pills and hydrocortisone injections if social confinement is required during the COVID-19 outbreak. In addition, until there is enough information, patients with AI should observe stringent social distancing.

8.2 Cushing's syndrome

Patients with Cushing's disease, but particularly those under supraphysiologic doses of steroids [79] may be also at a higher risk of COVID-19 infection because of the steroids potential immunosuppressive action. This issue is important, as around 5% of the world's population is taking chronic corticosteroids and there is a high prevalence of AI among these patients [80]. In these cases, under empiric principles, it might be recommendable to follow the same rules as patients with adrenal insufficiency.

Regarding diagnosis and therapy of patients with endogenous Cushing's when extensive differential diagnostic testing is not feasible, it should be deferred. Salivary cortisol/cortisone tests should be avoided due to the potential of viral contamination and infection of laboratory staff. Treatment of potential co-morbidities (such as hypertension and diabetes)

should be optimized and medical treatment must be initiated. Any form of treatment can be considered to switch to a block and replace regime (metyrapone or ketoconazole plus glucocorticoid) in order to ease the monitoring [81].

9 Calcium & Hypoparathyroidism and COVID-19

Several studies showed a key role of calcium in viral fusion for many enveloped viruses such as SARS-CoV, MERS-CoV and Ebolavirus. Moreover, calcium promoted their replication directly interacting with fusion peptides of these viruses [82–84]. Hypocalcemia had already shown to be common in patients with SARS (60% of patients at hospital admission), although generally mild [85], and in patients with Ebola virus disease (62%) [86]. A case of COVID-19 infection has been recently reported as possible precipitating cause of subclinical postsurgical hypoparathyroidism presenting with severe hypocalcemia [87]. This case suggested that hypocalcemia may occur also in COVID-19 infection. In fact, very recently we found in a retrospective single Institution study including 531 patients with COVID-19 a high prevalence of hypocalcemia (in about 80% of cases) on initial hospital evaluation. Hypocalcemic patients were more frequently elderly males with linear correlation between calcium levels and LDH and PCR levels. In multivariate analyses, hypocalcemia was an independent risk factor associated with hospitalization whereas it predicted ICU admission and mortality only in univariate analysis. [88].Therefore, all patients with postsurgical hypoparathyroidism should continue their treatment to avoid severe acute hypocalcemia, which can be life-threatening, and eventually should be adequately treated [89]. Moreover, mild hypoparathyroid patients not requiring chronic treatment should undergo careful surveillance in areas hit by outbreak of COVID-19 outbreaks, particularly if overweight/obese [90]. Finally, since hypocalcemia may have negative impact on cardiac outcomes [87], calcium evaluation, monitoring and adequate supplementation if needed in all hospitalized patients with COVID-19 infection is recommended.

10 Androgens and COVID-19

Evaluation of the gender-related distribution has revealed that men had a higher susceptibility to the virus infection and worse clinical outcomes and COVID-19 deaths compared with women. These gender differences were observed among all age groups of adult patients [10, 91].

A possible mechanism that may drive clinical outcomes is a compromised antiviral immune response to SARS-CoV-2 in men. Generally, androgens have an immune suppressive effect and women are disproportionately affected with inflammatory disease. Regarding SARS-CoV infected mice in males, gonadectomy or treatment with an antiandrogen compound did not affect the morbidity and mortality; conversely, estrogen depletion by ovariectomy or treatment with an estrogen receptor antagonist dramatically increased both morbidity and mortality suggesting a protective effect for the estrogen receptor signaling pathway [92]. In addition, in animal experiments, estrogen treatment upregulated estrogen receptor signaling, silenced the cytokine storm and lead to an improved survival rate.

SARS-CoV-2 viral entry requires two host proteins [93]: the angiotensin converting enzyme-2 (ACE2) and the transmembrane protease, serine 2 (TMPRSS2) Androgen receptor activity has been considered a requirement for the transcription of TMPRSS2 gene [94] and TMPRSS2 is the most frequently altered gene in primary prostate cancer [95]. The modulation of TMPRSS2 expression by testosterone has been postulated to contribute to male predominance of COVID-19 infection [96]. Since TMPRSS2 is expressed also at pulmonary level, the use of TMPRSS2 inhibitors, currently being used for prostate cancer, represents an appealing target for prevention or treatment for COVID-19 pneumonia [93].

Adverse outcomes of COVID-19 in men could also be associated to a higher prevalence of comorbidities, including hypertension, cardiovascular disease, and lung disease.

11 Ongoing COVID-19 research involving endocrine targets

11.1 Role of ACE2 and inhibitors of the renin-angiotensin system

The SARS-CoV binds to the zinc peptidase ACE2, a surface molecule that is localized in the endothelial cells of arteries and veins, arterial smooth muscle, respiratory tract epithelium, epithelia of the small intestine, and immune cells, to enter the host cell [97]. With SARS-CoV, it was shown that ACE2 overexpression facilitated viral entry and replication in cells [98]. SARS-CoV-2 probably targets the same spectrum of cells targeted by SARS-CoV, which in the lungs are primarily localized in pneumocytes and macrophages [93]. Acute respiratory distress syndrome (ARDS), which is the most serious complication of both SARS and COVID-19, is likely explained by this lung tropism. Moreover, extrapulmonary manifestations of COVID-19 may also be related to the systemic distribution of ACE2 in the gastrointestinal tract and the heart [15, 99]. There is evidence that ACE2 expression increases on the cell membrane with the use of ACE inhibitors and angiotensin-receptor blockers [100]. There is a theoretical concern that by increasing ACE2 expression they could facilitate the entry of virus into the host cell and increase the chances of infection or its severity [101].

Unfortunately, data if ACE inhibitors or angiotensin-receptor blockers modify ACE2 levels or activity (or both) are lacking in experimental animal models or in humans [102]. SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently downregulate ACE2 expression in order that the enzyme is unable to exert protective effects in organs and this may be in part responsible for organ injury in Covid-19 [102]. At present, we cannot rule out that long-term intake of ACE inhibitors and/or angiotensin-receptor blockers may facilitate SARS-CoV-2 entry and virus replication. Conversely, it is yet unknown whether intake of ACE inhibitors and/or angiotensin-receptor blockers, when infected, is beneficial with regard to pulmonary outcome. Possibly, we are dealing here with a double-edged sword, depending on the phase of the disease: increased baseline ACE2 expression could potentially rise infectivity and ACE inhibitors/angiotensin-receptor blockers use would be an addressable risk factor. Conversely, once infected, downregulation of ACE2 may be the hallmark of COVID-19 progression. Consequently, upregulation by preferentially using renin-angiotensin system blockade and ACE2 replacement in the acute respiratory syndrome phase may turn out to be beneficial [103, 104]. At present, to our knowledge, there are no peer reviewed experimental or clinical data demonstrating a specific benefit or risk of using ACE inhibitors, angiotensin-receptor blockers, or renin angiotensin aldosterone antagonists in COVID-19 patients. Moreover, abrupt withdrawal of renin angiotensin aldosterone antagonists in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes. In this regard, the European Society of Cardiology, Council on Hypertension; American College of Cardiology, the American Heart Association and the Heart Failure Society of America and the American Society of hypertension have released policy statements strongly recommending that patients should continue treatment with their usual antihypertensive therapy because there is no clinical or empirical scientific evidence to suggest that treatment with ACE inhibitors or angiotensin receptor blockers should be discontinued because of the COVID-19 infection [103, 105].

11.2 Use of oxytocin in COVID [106]

Oxytocin exerts a dual effect by mobilizing the immune defenses, and by suppressing pathogenic responses due to overreactions of the innate immunity. In humans, in the early phases of infectious disease, oxytocin can limit the excessive proinflammatory and oxidative stress reactions, by decreasing interleukins levels [106]. Of particular interest to Covid-19, is the nitric oxide, which is a key signaling molecule acting as a host response modulator in viral infections. In humans, activation of the oxytocin receptor, which is expressed in the pulmonary artery, can produce a vasolidatory effect [107]. Oxytocin has been postulated as a prospective therapeutic agent for Covid-19.

11.3 Use of melatonin in COVID 19

Viruses induce an explosion of inflammatory cytokines and reactive oxygen species, and melatonin, a well-known anti-inflammatory and anti-oxidative molecule, protects against acute respiratory distress syndrome caused by viral and other pathogens. Melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for COVID-19 patients. In addition, melatonin could be an adjuvant to prevent pulmonary fibrosis [108]. Notably, melatonin has a high safety profile [109]. There are no reports on the use of melatonin in COVID-19 to date [108].

Compliance with ethical standards

Conflict of interest The authors have declared that no competing financial interests exist.

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Review

Thieme

Endocrine Conditions and COVID-19

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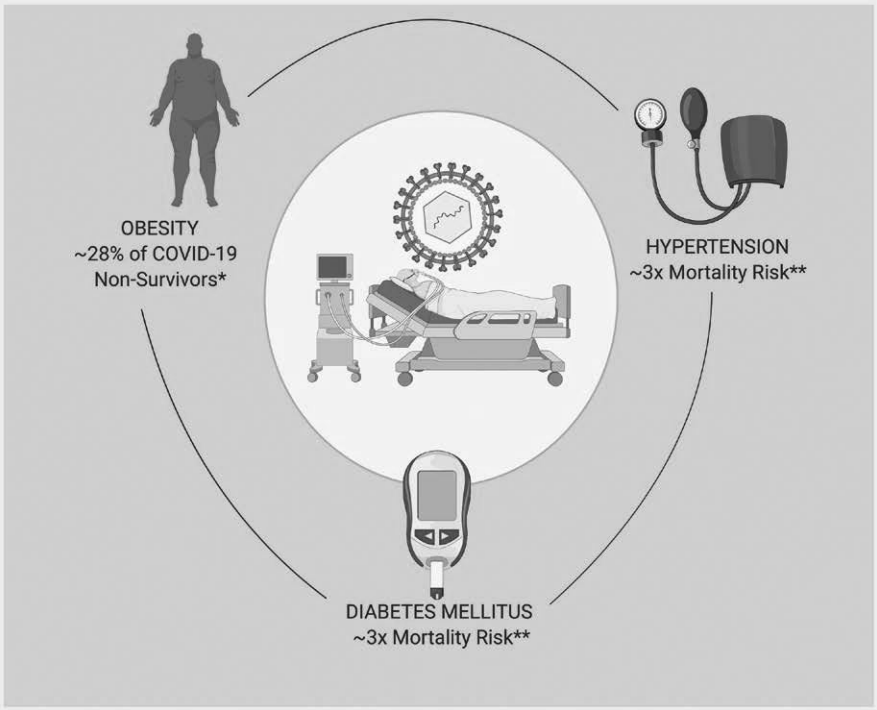
ABSTRACT

COVID-19 was declared a global pandemic by the WHO and has affected millions of patients around the world. COVID-19 disproportionately affects persons with endocrine conditions, thus putting them at an increased risk for severe disease. We discuss the mechanisms that place persons with endocrine conditions at an additional risk for severe COVID-19 and review the evidence. We also suggest precautions and management of endocrine conditions in the setting of global curfews being imposed and offer practical tips for uninterrupted endocrine care.

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 with over 3,059,642 cases and 211,028 deaths being reported from 213 countries and territories at the time of writing this review [1, 2]. There is increasing evidence to suggest that patients with endocrinopathies such as diabetes mellitus (DM), hypertension (HTN), obesity and cardiovascular disease are at higher risk for COVID-19 related complications [3]. Reports from the UK and US have indicated a high prevalence of DM and obesity in COVID-19 non-survivors and severe cases [4, 5]. In the US, the most commonly reported cardiometabolic comorbidities associated with COVID-19 are HTN (49.7 %), obesity (48.3 %), DM (28.3 %), and cardiovascular disease (27.8 %) (▶ **Fig. 1**) [6]. Furthermore, DM is the most common comorbidity in COVID-19 deaths according to one report [4]. Given these data, both the WHO and the US Centers for Disease Control and Prevention (CDC) list DM, HTN and obesity as risk factors for development of more severe COVID-19 outcomes [6–8]. In this review, we summarize common endocrinopathies associated with COVID-19.



▶ **Fig. 1** Clinical impact of endocrine conditions on COVID-19 *Louisiana Department of Health Updates for 3/27/2020. http://ldh.la.gov **ref [3].

Overview of the Novel Coronavirus-Cell Interaction

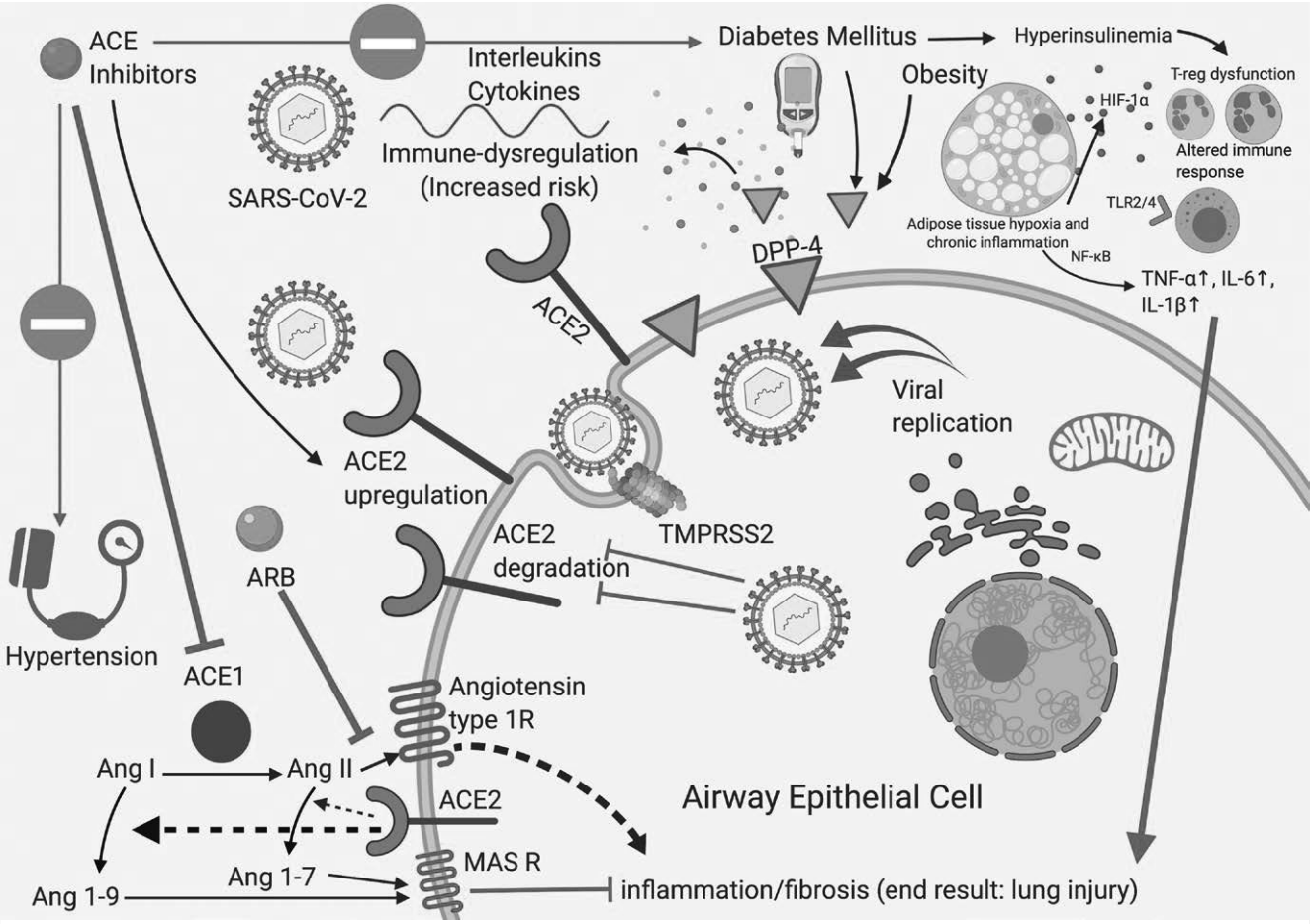
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus that was identified as the causative pathogen of COVID-19 [9]. This virus enters the intracellular environment by binding of the spike protein on its receptor binding domain (RBD) to angiotensin converting enzyme 2 (ACE2) which is present on the epithelial surface of human cells (▶ **Fig. 2**) [9]. Notably, ACE2 is a distinct molecule from the well-known angiotensin converting enzyme 1 (ACE1), which is a therapeutic target. After attachment to ACE2, the SARS-CoV-2 recruits a serine protease TMPRSS2, which facilitates viral protein priming and cytoplasmic entry (▶ **Fig. 2**) [10]. ACE2 is cleaved by a protease ADAMTS17, which in turn reduces its surface expression. After entering the cytoplasm, the virus enters the nucleus via an endosomal pathway and viral replication ensues [10].

Diabetes mellitus

Pathophysiology and risk

There are several reasons why DM may aggravate the risk of severe COVID-19. First, DM may facilitate cell entry of SARS-CoV-2 by augmenting the surface expression of ACE2 through hyperinsulinemia-mediated reduction in ADAMTS17 activity [11–13]. In humans, higher expression of ACE2 protein in the pancreatic islets was associated with hyperglycemia and diabetes caused by SARS-coronavirus (SARS-CoV) another coronavirus that uses ACE2 for cell entry, suggesting that SARS-CoV-2 may act through a similar mechanism [14]. Second, ACE2 modulators such as ACE1 inhibitors (ACEi), angiotensin receptor blockers (ARBs), and thiazolidenediones, which are used frequently in DM may upregulate ACE2 expression [9, 15]. Third, DM is associated with complement defects and reduced antigen stimulated IL-6, IL-8 and TNF-α [16, 17]; and impairment of T-regulator cells (Tregs) and antigen presenting cells (APCs) that may exacerbate the immunodeficiency [18]. Fourth, co-existing HTN and obesity, acting via HIF-1α and toll-like receptors, may contribute to the pre-existing chronic inflammation leading to impaired immune-mediated clearance of SARS-CoV-2 [18, 19]. Lastly, dipeptidyl peptidase-4 (DPP-4), a surface glycoprotein, which degrades glucagon like peptide 1 ('GLP-1', an incretin hormone), is known to be elevated in DM and obesity [20–22], and also functions as a surface receptor for coronaviruses [23, 24]. Although the latter is yet to be shown for SARS-CoV-2, the unique role of DPP-4 in coronavirus infections makes DPP-4 inhibition a possible therapeutic target, which may work both by reducing DPP-4 expression and offsetting the cytokine mediated end organ damage [19, 25]. This assessment is further strengthened by evidence that DPP-4 inhibition showed anti-inflammatory effects in pre-clinical human studies [19, 26, 27]. Taken together, patients with DM may be predisposed to cytokine storms resulting in end organ injury and mortality (▶ **Fig. 2**) [28].

A review of sixteen clinical studies with a total of 9,011 patients with COVID-19 revealed a prevalence of DM between 2.0 % and 56.6 % [median (IQR) %: 13.2 (9.10–23.70)], highlighting the high risk that patients with DM face in the wake of the global COVID-19 pandemic (▶ **Table 1**) [3, 6, 29–43]. Additionally, hyperglycemia has been seen in 35–58 % of inpatients with COVID-19 suggesting the burden of impaired glucose metabolism [29, 34]. Other studies have reported a higher DM prevalence in severe cases of COVID-19 when compared to mild cases (14.3 vs. 5.0 %, p = 0 · 009) [39],



▶ **Fig. 2** Molecular interplay between endocrine conditions, ACE modulation and COVID-19: Illustration of endocrine conditions, mitigating factors and associated risks of COVID-19. Red arrows demonstrate deleterious effects and block arrows reflect inhibition. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; Ang: Angiotensin; DPP-4: Dipeptidyl peptidase-4.

as well as an increased mortality risk and an increased case fatality rate in patients with DM (~3x, ▶ **Fig. 1**) [3], in comparison to persons without DM (7.3 vs. 2.3 %, respectively), indicating the amplified risk to patients with DM [44]. In a different study DM was highlighted as the most common comorbidity occurring in 41 % of all COVID-19 deaths [4]. Additionally, one study noted that COVID-19-affected patients with DM as a sole comorbidity had a 16.5 % mortality rate compared to 0 % in comorbidity free COVID-19 patients, whereas another reported poor outcomes in COVID-19 inpatients with uncontrolled hyperglycemia compared to their euglycemic counterparts [45, 46]. The US CDC included DM as a risk factor for severe COVID-19 in their clinical guidance [8].

Evidence of an increased risk of long term metabolic complications in patients that have recovered from SARS, caused by SARS-CoV, raises concern for a possible increased risk for similar complications in COVID-19. This was demonstrated in a follow-up study of thirty one recovered SARS patients in comparison to healthy volunteers at 12 years that revealed abnormal glucose metabolism in 60 % (vs. 16 %), hyperlipidemia in 68 % (vs. 40 %), and cardiovascular abnormality in 44 % (vs. 0 %) of study participants [47]. It was speculated that the use of pulse dose glucocorticoids may have contributed to these long-term metabolic derangements [47]. Glucocorticoid use in hospitalized COVID-19 patients may also play a role in acute inpatient hyperglycemia. However, glucocorticoid use has fallen out of favor in the routine management of COVID-19 according to CDC and WHO guidelines [48, 49] and evidence points to glucocorticoids attenuating anti-inflammatory angiotensin 1–7 levels and delaying viral clearance (▶ **Fig. 3**), providing a molecular basis for avoiding their universal use [50, 51]. A clinical trial is currently underway to determine the efficacy of systemic glucocorticoid therapy in COVID-19 [52].

Clinical approach

Recently, the American Diabetes Association (ADA) issued patient recommendations regarding preparedness and precautions for COVID-19 (▶ **Table 2**) including keeping updated contact information; ensuring adequate stocks of simple carbohydrates, medications and insulin; and ensuring availability of supplies such as rubbing alcohol, glucagon kits, ketone strips, soap and household items [53]. The American Association of Clinical Endocrinologists also emphasizes adequate emergency preparedness and provided a checklist of emergency plan action items to ensure the uninterrupted care of DM (▶ **Table 2**) [54, 55].

From a clinical practice standpoint patient counseling should include discussing glycemic goals and sick day insulin dosing regimens, as well as adequate hydration and maintaining access to food

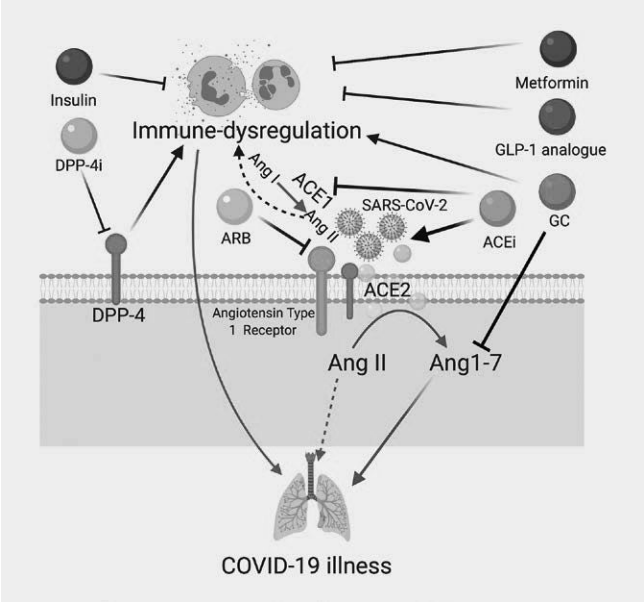
▶ **Table 1** Prevalence of diabetes mellitus (DM) and hypertension (HTN) in patients with COVID-19.

Title	Author	Sample	Diabetes prevalence	Hypertension prevalence	Obesity prevalence
Clinical Course and Outcomes of Critically Ill Patients With SARS-CoV-2 Pneumonia in Wuhan, China: A Single-Centered, Retrospective, Observational Study	Yang et al. [29]	52 critically sick patients	17 %	NR	NR
Clinical Characteristics of Coronavirus Disease 2019 in China	Guan et al. [82]	1099 patients	7.40 %	15 %	NR
Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China	Zhang et al. [31]	140 patients	12.10 %	30 %	NR
Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China	Wang et al. [32]	138 patients	10.10 %	31.20 %	NR
Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series	Xu et al. [33]	62 patients	2 %	8 %	NR
Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	Chen et al. [34]	99 patients	13 %	NR	NR
A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster	Chan et al. [41]	Family of 6 patients	16 %	32 %	NR
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	Zhou et al. [3]	191 patients	19 %	30 %	NR
Analysis of Myocardial Injury and Cardiovascular Diseases in Critical Patients with New Coronavirus Pneumonia	Chen et al. [83]	150 patients	13.3 %	32.6 %	NR
A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19	Cao et al. [36]	199 patients	11.16 %	NR	NR
Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State	Arentz et al. [38]	21 critically sick patients	33.3 %	NR	NR
Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series.	Qian et al. [40]	91 patients	8.79 %	16.48 %	NR
Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan.	Shi et al. [39]	487 patients	6 %	20.3 %	NR
Clinical Characteristics of Covid-19 in New York City	Goyal et al. [42]	393 patients	25.2 %	50.1 %	35.8 %
Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020	Garg et al. [6]	178 patients	28.3 %	49.7 %	48.3 %
Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area	Richardson et al. [43]	5700 patients	56.6 %	33.8 %	41.7 %

NR: Not reported.

(including nonperishable items, glucose and electrolyte tablets). Furthermore, adoption and continuation of a healthy diet and recommended 150 minutes of weekly exercise such as indoor walking and other physical distancing compatible exercises should be encouraged [56]. Recommended vaccinations for influenza, pneumococcal and other infections should be emphasized (based on CDC or equivalent local authority guidelines). The latter is of major importance since viral co-infection has been frequent in COVID-19 [57–59]. Furthermore, patients should be notified of insulin availability without a prescription in many countries as a contingency measure (US, Canada, India, Mexico, etc.) [60–63].

For inpatient hyperglycemia management, the blood glucose target recommended by the *ADA Standards of Medical Care in Diabetes* is 140–180 mg/dL for most critically-ill and non-critically ill patients, with more stringent glycemic goals (blood glucose 110–140 mg/dL) recommended for selected patients if hypoglycemia can be avoided [64]. However, specific glycemic targets for patients with COVID-19 have not been released by the ADA to date. In the aforementioned guidelines, the ADA recommends the consideration of more liberal glycemic goals (blood glucose > 180 mg/dL) for patients that have severe comorbidities, are terminally ill, or where frequent glucose monitoring or close nursing supervision is not possible. In these patients less aggressive insulin regimens with the



▶ **Fig. 3** Effects of commonly used drugs in obesity, diabetes mellitus, and hypertension on immune dyregulation. Red arrows indicate negative clinical consequences, green arrows indicate positive clinical implications, black arrows reflect stimulation and block arrows signify inhibition. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; Ang: Angiotensin; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon like peptide-1; GC: Glucocorticoids.

aim of minimizing glycosuria, dehydration, and electrolyte disturbances may be more appropriate, however clinical judgment combined with continuing assessment of clinical status that includes changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels, should be incorporated into medical decision making. Furthermore, it is reasonable to discontinue sodium-glucose co-transporter-2 inhibitors (SGLT-2i) that have been associated with intravascular volume depletion and increased risk of euglycemic ketosis [56]. Discontinuation of sulfonylureas is also advisable, particularly in critical patients, where drug renal clearance may be compromised [56]. Chloroquine and hydroxochloroquine, which are under investigation for efficacy in the treatment of COVID-19, may cause hypoglycemia [65, 66]. In contrast, antiviral drugs such as ritonavir and lopinavir, which were used for COVID-19 previously, are associated with hyperglycemia [67]. Use of these drugs should also be accompanied by adjustments in diabetes regimens.

Because of the need for flexible management, insulin remains the safest drug for the management of hyperglycemia in DM patients and has an added anti-inflammatory effect in the critical illness setting [68]. Importantly, DPP-4 inhibitors and GLP-1 receptor analogues may not only attenuate the chronic inflammatory state in DM but also have independent lung-protective and immunomodulatory effects (in pre-clinical studies) and may prove beneficial (▶ **Fig. 3**) [19, 69–71].

Panic-buying is a major threat in this crisis. Fortunately, to date, there is no report of a major household or medical supply shortage and clinicians should counsel patients against this practice to ensure adequate availability for others [72–74].

Resources and future directions

The Endocrine Society has established a dedicated COVID-19 webpage with resources for clinicians and researchers with many other societies such as the European Society of Endocrinology and the Society for Endocrinology (▶ **Table 2**) [75].

This pandemic has led to a fast-tracking of telemedicine. Authorities in the US, Canada and France announced wider coverage of telemedicine visits, which is likely to directly benefit patients with DM [76, 77]. However, it is not known whether the telemedicine visits will suffice for insulin pump follow-up, which currently mandate inperson visits.

There are still many areas of uncertainty that warrant further investigation with respect to DM and COVID-19. Some of these include the differences between type 1 and type 2 DM, optimal vs. poor glycemic control, and the effect of age and other co-existing conditions in patients with DM among others.

Hypertension

Pathophysiology and risk

A high prevalence of HTN has been noted among patients with COVID-19, with HTN possibly predisposing to an elevated risk for more severe disease. The risk could stem from a variety of reasons. Foremost, HTN is associated with immune dysregulation, which manifests as higher IL-17 levels, abnormal natural killer cell function and cytotoxic T-cell anomalies partly reversible with mineralocorticoid receptor antagonists [78, 79]. Other contributors include overactive sympathetic drive, dysregulated NFκB and elevations in the pro-inflammatory peptide, angiotensin II (▶ **Fig. 2**) [80, 81].

A review of twelve studies, which included data from 8,635 patients with COVID-19, revealed the prevalence of HTN to be between 8.0 and 50.1 % [median (IQR) %: 30.6 (17.43–33.50)] (▶ **Table 1**) [3, 6, 30–33, 35, 37, 39–43, 82, 83]. A US-based study reported a 50.1 % prevalence of HTN [42]. Moreover, one study [34] of 191 patients found a 3-fold higher risk of mortality in patients with HTN while other studies reveled a 1.57–2.71-fold risk of severe COVID-19 illness [39, 84] (▶ **Fig. 1**). Shi et al. also included HTN as one of three indices in a COVID-19 risk assessment score [39]. This risk may be further enhanced by the co-existence of DM, which is present in 60.2–85.8 % of persons with HTN (depending on the diagnostic threshold used) [85].

However, it should be noted that HTN is highly prevalent among the elderly, and the elderly are over-represented among COVID-19 patients requiring hospital admission and critical care. Thus, the risk attributed to HTN might be the result of reverse causality. The prevalence of HTN or DM may be greater in severe patients, but studies have failed to report if these comorbidities co-exist with others, hence increasing the risk for severity. Moreover, the associated risks currently remain associations. A comprehensive isolation of the exposure of HTN or DM has not been reported. Therefore the causal risk carried by these comorbidities individually, or together, has not been established and remains unclear.

Renin-angiotensin-aldosterone system and COVID-19

SARS-CoV-2 enters the human body through attachment to the ACE2 receptors that are present on the cell surface of type 2 alveolar epithelial cells in the lungs (▶ **Fig. 2**) [9, 86, 87]. These receptors are also present in other tissues, with tissue ACE2 levels not al-

▶ **Table 2** Endocrinology and COVID-19: Resources and Links.

Society	Resource	Web Link
American Association of Clinical Endocrinologists	Diabetes emergency plan (for patients)	http://mydiabetesemergencyplan.com
Endocrine Society	General resources for endocrinologists	https://www.endocrine.org
European Society of Endocrinology	General resources for endocrinologists	https://www.ese-hormones.org
Society for Endocrinology	General resources for endocrinologists	https://www.endocrinology.org/clinical-practice/covid-19-resources-for-managing-endocrine-conditions
Society for Endocrinology	Adrenal insufficiency position statement	https://www.endocrinology.org/news/item/14050/Coronavirus-advice-statement-for-patients-with-adrenal %2fpituitary-insufficiency
American Diabetes Association	Inpatient blood glucose management	https://care.diabetesjournals.org/content/43/Supplement_1/S193
American Thyroid Association	Frequently asked questions	https://www.thyroid.org/covid-19/coronavirus-frequently-asked-questions
National Osteoporosis Foundation	Patients and Providers Fact Sheet	https://cdn.nof.org/wp-content/uploads/NOF-COVID-Factsheet_.pdf
National Center for Transgender Equality	Plan of Action	https://transequality.org/covid19/plan
The National Institute of Diabetes and Digestive and Kidney Diseases	General guidelines	https://www.niddk.nih.gov/health-information/endocrine-diseases/adrenal-insufficiency-addisons-disease
Centers for Disease Control and Prevention	General guidelines	https://www.cdc.gov/coronavirus/2019-ncov/index.html
World Health Organization	General guidelines	https://www.who.int/emergencies/diseases/novel-coronavirus-2019

ways correlating with plasma ACE2 activity [88]. Although ACEi/ARBs do not directly affect ACE2 activity, some studies in experimental animal models have shown that ACEi/ARBs can upregulate the expression and activity of ACE2 in certain tissues including the heart and kidney, but studies regarding their effects on ACE2 expression and activity in the lungs are lacking [89, 90]. One study demonstrated increased intestinal messenger RNA levels of ACE2 in patients previously treated with ACEi but not in those treated with ARBs [91]. Equally, there are reports of higher ACE2 urinary levels in type 1 and 2 DM but the clinical implications of these findings remains unclear in the context of COVID-19 [70, 92, 93]. In light of these findings, it has been proposed that ACEi/ARBs could enhance the risk for severe COVID-19 and re-evaluating their use has been suggested [94–96]. On the contrary, higher plasma ACE2 may bind SARS-CoV-2 and protect against lung and other tissue injury (shown in animal models) and this is proposed as a therapeutic target [97]. Furthermore, angiotensin 1–7 uptitrated by the use of ACEi/ARBs may offer immunoprotection and attenuate the severity of COVID-19 by acting via the Mas receptor pathway (▶ **Fig. 2**) [98–101]. Similarly, ACEi may reduce angiotensin II levels and attenuate immunodysregulation [102]. This position is further supported by other recent reviews that point to the confusing nature of these unproven assertions regarding greater risk to COVID-19 patients taking ACEi/ARBs [98, 103–105]. No direct evidence to support the theoretical risk of ACEi/ARBs use with regards to COVID-19 severity has been published as of April 22, 2020. One clinical study reported milder COVID-19, improved immune function and lower viral loads in patients with HTN who were treated with ACEi/ARBs compared to those who were not [106] and better clinical outcomes in another study [107]. These findings refute the theoretical concerns about these agents and support their continued use (▶ **Table 2**) [106, 107].

Various societies have endorsed the continued use of ACEi/ARBs based on the lack of evidence of harm (▶ **Table 2**). The European Society of Cardiology released a statement strongly recommending "*that patients and physicians continue their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection*" [108]. Many others followed suit (▶ **Table 2**) [108–112]. The American Heart Association recently published a white paper reporting the lack of studies investigating and demonstrating evidence of harm [103]. A clinical trial, 'Recombinant Human Angiotensin Converting Enzyme 2 (rhACE2) as a Treatment for Patients With COVID-19 ' (ClinicalTrials.gov Identifier: NCT04287686), is currently examining the role of ACE2 receptor modulation in COVID-19 and may provide conclusive evidence on this matter [113, 114].

Obesity

Pathophysiology and risk

Obesity is a state of chronic adipose tissue hypoxia leading to a pro-inflammatory state with increased levels of IL-1, IL-6, and TNF-α (▶ **Figs. 2** and ▶ **3**) [18, 115, 116]. The immunological dysfunction in obesity could also stem from T-cell insulin resistance and exhaustion [18]. We speculate that this would presumably lead to an altered immune response, not only to the virus but also to a future vaccine. One review raised the possibility of adipose tissue representing a SARS-CoV-2 target and reservoir, albeit no study reflect-

ing this has been published to date [117]. Another study demonstrated prolonged influenza viral shedding in obese persons [118]. Likewise, the alteration of myeloid and lymphoid responses within the adipose tissue consequently leads to an aberration of adipokine profiles [117, 119]. Similarly, obesity is linearly associated with raised C-reactive protein (CRP) levels, which is proximately triggered by adipocytic derived IL-6 [115, 120]. Not surprisingly, CRP has been correlated with severe disease, providing a pathophysiological link between obesity and poor COVID-19 outcomes [121, 122]. There is also evidence to suggest attenuated Mas receptor signaling (of angiotensin 1–7) within the renin-angiotensin-aldosterone system may further aggravate the pre-existing immune dysregulation [123, 124]. In addition, higher levels of pro-inflammatory DPP-4 levels seen in obesity and the consequent hyperinsulinemia may both independently exacerbate COVID-19 risks (▶ **Figs. 2** and ▶ **3**) [21]. While the benefits of DPP-4 inhibition are unproven, there is a clear anti-inflammatory and lung-protective effect of GLP-1 receptor analogues in obesity that may prove useful in mitigating risks for severe disease [71, 125]. Furthermore, co-existing obesity hypoventilation syndrome and obstructive sleep apnea, both complications of obesity, may compromise respiratory function that could also account for the observed effects. Moreover, obesity is independently linked with a higher thrombosis risk that is especially relevant as COVID-19 has an increased predilection for microangiopathy and venous thrombosis [126–128]. The latter, in conjunction with compromised cardiorespiratory reserve, may acutely impede mechanical ventilation of critically-ill obese persons. Furthermore, it is vital for future investigations to analyze the link between patients' anthropometric characteristics and severe COVID-19 since visceral adiposity is likely to represent a higher risk for COVID-19 illness [129]. On a more chronic basis, obesity poses an additional challenge both from a nursing and a rehabilitation standpoint [130].

Recently, the Louisana Department of Health reported obesity as the third most common comorbidity (after DM and chronic kidney disease) associated with mortality, with a prevalence of 28 % in COVID-19 non-survivors (▶ **Fig. 1**) [4]. Moreover, the CDC reported obesity being present in 48.3 % of all COVID-19 hospitalized patients [6]. A review of three clinical studies, comprising of a total of 6,271 patients showed that obesity was prevalent in 35.8–48.3 % [median (IQR) %: 41.7 (35.80–48.30)] of hospitalized COVID-19 patients (▶ **Table 1**) [6, 42, 43]. Another study noted obesity as an independent risk for COVID-19 hospitalization [131]. The National Health Service in the UK also reported obesity as a risk factor for severe disease and mortality in COVID-19 [5]. In light of these data, the CDC updated their guidance to include a BMI > 40 kg/m^2 as a risk factor for severe COVID-19 [8].

Common 'Bad' actors in metabolic disease related cytokine storm

It is important to consider the cumulative pathophysiology of commonly described endocrinopathies and COVID-19 severity. In this section, we discuss plausible underlying mechanisms for severe COVID-19 in hosts with these conditions.

Betacoronaviruses, including SARS-CoV-2, enter human cells by binding to ACE2 in various tissues. However, betacoronaviruses such as MERS-CoV and SARS-CoV also directly infect immune cells. Specifically, MERS-CoV binds to monocytes and dendritic cells and SARS-CoV affects T-cells through DPP-4 receptors [132]. After being exposed to a betacoronavirus, monocytes, macrophages and dendritic cells release the proinflammatory cytokine IL-6. IL-6 has two major modes of pleiotropic signaling (*cis* and *trans*) [133]. *Cis*-signaling occurs when IL-6 attaches to its membrane bound receptors (mIL-6R) present on immune cells, triggering activation of other immune pathway cells such as T-cells, B-cells and natural killer cells and leading to further IL-6 release and immune activation. Pathological activation of this signaling leads to a cytokine release syndrome (CRS). *Trans*-signaling occurs when IL-6 binds to its soluble receptor (sIL-6R) that is present in vascular endothelium. This triggers the release of vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein-1 (MCP-1). Together with reduction of E-cadherin, the result is increased vascular permeability and leakage causing syndromes such as CRS, acute respiratory distress syndrome (ARDS) and shock [134]. A third pathological signaling mechanism is the *trans*-pathway (distinct from *trans*-signaling), which is mediated by attachment of IL-6 on T-helper 17 cells, which leads to pathological consequences such as ARDS [132].

The 'bad' actors of immune dysregulation are increased in obesity, DM and HTN and may account for the severity of disease. For instance, IL-6 levels are significantly higher in type 1 and 2 DM and directly proportional to BMI in obese persons [115, 120, 135]. IL-6 has a bidirectional relationship with DM as it is implicated in causing insulin resistance and disorders of glucose homeostasis [136]. T-cells in type 1 DM are more sensitive to IL-6 possibly leading to immune dysregulation and CRS [137]. In HTN, IL-6 levels are higher, likely mediated by the increased levels of angiotensin II and aldosterone, which directly trigger IL-6 secretion by the vasculature [138]. This effect is blocked by ARBs and mineralocorticoid receptor antagonists [139]. Elevated CRP, another predictor of COVID-19 severity, is a downstream effect of IL-6, and elevated in obesity, DM and HTN [140]. DPP-4, a known co-receptor of beta-coronaviruses is higher in persons with obesity and DM, and has independent pro-inflammatory effects [20]. Finally, the possibility of the pathological *trans*-pathway signaling of IL-6 in obesity, DM and HTN cannot be excluded given the pre-existing immune-dysregulatory state, and may contribute to CRS and clinical consequences such as ARDS. Taken together, the 'bad actors' of immune dysregulation linked with severe COVID-19 are highly prevalent in obesity, DM and HTN, and may account for the higher severity noted in these states. ▶ **Fig. 3** describes the immune-pharmacology of endocrine conditions and COVID-19.

Other endocrinopathies

Hypothalamic-pituitary-adrenal axis

Glucocorticoids have both immune-stimulatory and -inhibitory effects [141]. During the initial phase of viral infection, glucocorticoids prime the immune response to counteract foreign antigens. However, in the advanced phase of viral infection, blunting of the hypothalamic-pituitary-adrenal axis activation may occur that may lead to glucocorticoid insufficiency in the critical illness setting [141]. Given the widespread use of glucocorticoids and the possible risk to patients with adrenal insufficiency (AI), the Society for

Endocrinology released an advisory statement conveying the lack of evidence to support a higher risk for contracting COVID-19 in patients with AI (▶ **Table 2**). They also reinforced sick-day glucocorticoid dosing and physical distancing rules as these patients may theoretically be at a higher risk for COVID-19 complications and mortality due to adrenal crisis, although this has yet to be described [142]. A recent opinion piece also highlighted the increased risks faced by patients taking physiological and supraphysiological doses of glucorticoids and encouraged identification of these patients and counseling about possible risks and precautions [143]. Patients with AI are at an elevated risk of infection, and patients with primary AI have been shown to have significantly decreased natural killer cell cytotoxicity that may compromise early recognition and elimination of virally infected cells and impair anti-viral immune defenses, although COVID-19 specific infection risk has not been reported to date [144]. Recently, COVID-19 specific guidance for the management of AI was published that advised specific sick-day rules in addition to reinforcing the importance of education and physical distancing [145]. This guidance recommended that adults with AI on physiological glucocorticoids and acute suspected or confirmed COVID-19 should double their morning hydrocortisone dose and then take 20mg hydrocortisone every 6 hours in order to provide evenly spaced glucocorticoid coverage for the persistent acute inflammation and often continuous fever experienced by patients with COVID-19. Those taking prendisonole 5–15 mg daily should take 10mg every twelve hours while those on doses of prednisolone > 15 mg should continue to take their usual daily prednisolone dose but should split this into a morning and afternoon dose of at least 10mg each. Once the patient shows resolution of fever and significant clinical improvement, the hydrocortisone dose can be tapered to double the physiologic replacement dose and then normal routine doses when fully recovered. If the clinical symptoms and signs of COVID-19 worsen, it is recommend that patients contact emergency medical services and administer a subcutaneous or intramuscular injection of hydrocortisone 100 mg (or take 50–100 mg hydrocortisone orally if this injection is not available) [145]. Those with AI who contract COVID-19 and require mechanical ventilation or are severely ill, should be dosed according to acute stress dosing guidelines (▶ **Table 2**) [145]. Additionally, the use of venous thromboembolism prophylaxis with heparin in patients receiving glucocorticoids is recommended, given the increased risk of thrombotic events in COVID-19 [141]. Furthermore, an increased risk to those with posterior pituitary deficits and electrolyte abnormalities has been logically speculated and the need to stock reasonable supplies emphasized [143].

In another piece, addressing the management of Cushing syndrome during the COVID-19 pandemic, deferring biochemical workup for mild Cushing syndrome, appropriate management of comorbidities, risk-benefit assessment of definitive treatment (pharmacotherapy and surgery), and *Pneumocystis jirovec*i prophylaxis were emphasized [146]. According to the authors, for those on maintenance pharmacotherapy, dose titration according to clinical features or on the basis of the most recent biochemical values is reasonable [146]. Authors also advised postponement of imaging and localization studies for suspected (mild) cases. Further, they recommended urgent treatment only in sight- or life-threatening situations and reinforcement of sick-day rules, highlighting the need to re-evaluate the care of these patients once the current pandemic abates or is under control in the local geographical region [146].

Hypothalamic-pituitary-thyroid axis

It is known that ACE2 receptors are expressed in thyroid tissue and play a critical role in physiological processes [147]. An overexpression of ACE2 has also been implicated in thyroid cancer progression [147]. In hyperthyroid animals, cardiac angiotensin 1–7 activity was augmented, suggesting a renin-angiotensin-aldosterone system regulating effect of thyroid hormones [148]. In observational studies, thyroid abnormalities, including sick euthyroid syndrome and thyroiditis, were reported in 3.6 % of patients [108] and other endocrine disorders (excluding DM and HTN) were present in 13 % of COVID-19 patients [34]. Direct damage to thyroid tissue from COVID-19 has also been reported at autopsy [149]. Thyroid disorders were also linked with a higher mortality risk in one report [150]. From a clinical practice standpoint, structural thyroid disease management warrants careful consideration. In particular, we agree with one opinion piece that suggested prioritization of suspected anaplastic and aggressive medullary thyroid cancer (serum calcitonin ≥ 10 pg/ml) while deferring the care of less aggressive differentiated thyroid cancer [151].

Diabetes insipidus

Central and nephrogenic diabetes insipidus (DI) pose a particular challenge due to reduced availability of laboratory (electrolyte) testing. An opinion piece recently highlighted this challenge, encouraging the practice of once a week aquaresis by omitting one dose of vasopressin in individuals with existing DI [152]. This would primarily prevent retention of excess free water and consequently maintain eunatremia. Further, they emphasized that the major risk in these patients is that of hyponatremia, which could be mitigated by daily bodyweight measurements, early self-recognition of clinical features of hyponatremia and counseling patients about drinking to thirst. In the inpatient setting, patients are vulnerable to hyponatremia both due to overtreatment of DI, and excess vasopressin from COVID-19 pneumonia in the context of syndrome of inappropriate antidiuretic hormone secretion [153]. For that reason, 0.9 % saline should be used for volume resuscitation, and in the critical illness setting where frequent shifts in volume distribution occurs. Moreover, frequent clinical and biochemical assessment of sodium status should occur, while hypotonic fluids should be employed in hypernatremic patients [152]. Special caution should be exercised in the care of adipsic DI patients and endocrinology consultants should be involved early in their inpatient care [152].

Bone and mineral metabolism

While there is no evidence of increased risk of COVID-19 to patients with bone-mineral metabolism disorders, the unprecedented global lockdowns have significantly affected their care. Given that most infusion centers, outpatient laboratories and bone scanning centers are temporarily closed, the National Osteoporosis Foundation released a guidance statement (▶ **Table 2**) [154]. It is advisable for those on medications such as Denosumab and Romosozumab to receive timely infusions, however, infusions of bisphospho-

nates such as Zolendronic acid may be deferred due to their long half-life [154].

Hyperlipidemia

Hyperlipidemia was present in 5 % of patients according to a review of 190 patients hospitalized with COVID-19 [31]. The development of metabolic/lipid abnormalities in patients who recover from COVID-19 may also be anticipated based on data from the SARS cohort population [47]. Endocrinologists may be healthcare providers for this group in the future and should be wary of the possible long-term metabolic complications that may exist following COVID-19 infection.

Racial differences in COVID-19 outcomes

Several reports of higher mortality among Black and Hispanic people have emerged [155, 156]. The CDC recently reported that 33 % of COVID-19 inpatients in the US were Black despite only constituting 13 % of the US population [6]. The state of Louisiana reported that Black and Asian patients constituted 59 % and 0.83 % of COVID-19 non-survivors [157]. New York City also reported a disproportionate mortality among Hispanics and Blacks [158]. While ACE2 expression is higher in Asian populations compared to Whites or Blacks, our current knowledge of these differences does not justify the disproportionate mortality [159, 160]. This scourge is likely multifactorial: 1. Higher genetic predisposition to endocrine disorders, such as an increased prevalence of HTN in Black and obesity among Latin/Hispanic patients and 2. Racial disparity in access to healthcare and hospitals that may delay timely care, coupled with suboptimally controlled underlying chronic disease. The CDC surveillance data of the COVID-19–associated hospitalization rate among patients for the 4-week period ending March 28, 2020, was 4.6 per 100 000 population, with the following race/ethnicity data: 261 (45.0 %) were non-Hispanic white (White), 192 (33.1 %) were non-Hispanic Black (Black), 47 (8.1 %) were Hispanic, 32 (5.5 %) were Asian, two (0.3 %) were American Indian/Alaskan Native, and 46 (7.9 %) were of other or unknown race [6]. These social barriers for racial minorities amplify their vulnerability to endocrine disease in general and to COVID-19 as a consequence.

Sex differences in COVID-19 outcomes

In the US, over half of COVID-19 related hospitalizations occurred among men (5.1 vs. 4.1 per 100 000 population). Sex differences for general infections are likely multifactorial, including robustness of the immune responses (both innate and adaptive), sex-dependent production of steroid hormones (including testosterone and estrogens), immune response-related X-linked genes, and presence of disease susceptibility genes. The estrogen receptor signaling pathway has been identified as critical for protection in females infected with coronaviruses [151]. A plausible explanation for higher COVID-19 affection of men may be related to the downstream steps after ACE2 binding of SARS-CoV-2. As described previously, the SARS-CoV-2 viral capsid binds to surface ACE2 and subsequently engages a cellular serine protease TMPRSS2 for protein priming (▶ **Fig. 2**) [10]. From oncological studies, it is known that TMPRSS2 is an androgen responsive gene, which is highly expressed in men [161]. As suggested by one study, the higher TMPRSS2 expression in men could account for their higher vulnerability to COVID-19 [161]. Further studies are required to ascertain the sex differences in COVID-19 related outcomes.

Care of transgender persons

Human immunodeficiency virus (HIV) infection and cancer are more frequent in transgender persons when compared to the general population [162, 163]. These conditions coupled with pre-existing endocrinopathies can compromise the immune function, presumably leading to a higher COVID-19 risk in transgender persons. However, there is currently no published evidence to support this [162]. Transgender persons also frequently face social challenges such as poverty, homelessness and inadequate access to healthcare, which diminishes their ability to observe COVID-19 precautions and seek timely care [164]. It is therefore advisable that clinicians re-inforce and individualize guidance to this population while ensuring sufficient prescription refills. A plan of action is available at https://transequality.org/covid19/plan (▶ **Table 2**) [164]. For elective procedures such as gender confirmation surgery, postponement is appropriate in line with the CDC and WHO guidelines [48, 49].

General COVID-19 precautions for patients with endocrine conditions

- All patients should maintain updated contact information for their healthcare
- Adequate availability of prescription refills should be ensured
- Emergency precautions and sick-day rules should be addressed on all routine clinic visits
- Providers should remain up to date with evolving COVID-19 data and perform a careful critical appraisal of the available and increasing literature to be able to identify high-quality evidence to facilitate informed decisions to individualize care
- Elective endocrine clinic visits should be deferred and alternative communication means such as telehealth visits consistent with social distancing should be encouraged
- Mailing of prescriptions rather than inperson pickup should be adopted wherever feasible
- Patients should be advised to stay updated with recommended vaccinations
- Smoking (including hookah/waterpipe) cessation should be advised [165]
- Panic buying and stockpiling of medical supplies should be strongly discouraged
- Patients should be informed of COVID-19 resources (CDC, WHO websites etc.) to obtain accurate information and follow best practices with respect to COVID-19 (▶ **Table 2**)

Conclusion

In conclusion, endocrinologists routinely care for a high proportion of COVID-19 vulnerable patients who are at increased risk for life-threatening complications. Clinicians should counsel patients on emergency preparedness, contingency plans, maintaining adequate but not excessive supplies, social distancing and accessing reliable information resources. Further, care should only be based on available evidence and caution should be exercised against basing decisions on incomplete or inconclusive evidence. These meas-

ures may mitigate some of the risks faced by our vulnerable patient population in this unprecedented crisis.

Authors' Disclaimer

To the best knowledge of the authors, the studies included in this article report data from distinct patient populations consistent with ethical scientific publication, a matter of concern in recent times [166]. Additionally, due to the ongoing COVID-19 crisis this document is not based on extensive systematic review or meta-analysis, but on expert consensus. The document should be considered as guidance only; it is not intended to determine an absolute standard of medical care. The doctors concerned must make the management plan for an individual patient

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Conflict of Interest

The authors declare that they have no conflict of interest. Dr. Stratakis laboratory holds patents on the function of the PRKAR1A, PDE11A, and GPR101 molecules and has received research funding from Pfizer Inc. for work related to GPR101 and acromegaly/gigantism.

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REVIEW Open Access

A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective

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Abstract

Currently, the world is in the seventh month of the COVID-19 pandemic. Globally, infections with novel SARS-CoV-2 virus are continuously rising with mounting numbers of deaths. International and local public health responses, almost in synchrony, imposed restrictions to minimize spread of the virus, overload of health system capacity, and deficit of personal protective equipment (PPE). Although in most cases the symptoms are mild or absent, SARS-CoV-2 infection can lead to serious acute respiratory disease and multisystem failure. The research community responded to this new disease with a high level of transparency and data sharing; with the aim to better understand the origin, pathophysiology, epidemiology and clinical manifestations. The ultimate goal of this research is to develop vaccines for prevention, mitigation strategies, as well as potential therapeutics.

The aim of this review is to summarize current knowledge regarding the novel SARS CoV-2, including its pathophysiology and epidemiology, as well as, what is known about the potential impact of COVID-19 on reproduction, fertility care, pregnancy and neonatal outcome. This summary also evaluates the effects of this pandemic on reproductive care and research, from Canadian perspective, and discusses future implications.

In summary, reported data on pregnant women is limited, suggesting that COVID-19 symptoms and severity of the disease during pregnancy are similar to those in non-pregnant women, with pregnancy outcomes closely related to severity of maternal disease. Evidence of SARS-CoV-2 effects on gametes is limited. Human reproduction societies have issued guidelines for practice during COVID-19 pandemic that include implementation of mitigation practices and infection control protocols in fertility care units. In Canada, imposed restrictions at the beginning of the pandemic were successful in containing spread of the infection, allowing for eventual resumption of assisted reproductive treatments under new guidelines for practice. Canada dedicated funds to support COVID-19 research including a surveillance study to monitor outcomes of COVID-19 during pregnancy and assisted reproduction. Continuous evaluation of new evidence must be in place to carefully adjust recommendations on patient management during assisted reproductive technologies (ART) and in pregnancy.

Keywords: SARS-CoV-2, COVID-19, ART-assisted reproductive technologies, Pregnancy, Reproduction

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REVIEWS

COVID-19 and diabetes mellitus: from pathophysiology to clinical management

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Abstract | Initial studies found increased severity of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with diabetes mellitus. Furthermore, COVID-19 might also predispose infected individuals to hyperglycaemia. Interacting with other risk factors, hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin–angiotensin–aldosterone system (RAAS), is the main entry receptor for SARS-CoV-2; although dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Preliminary data, however, do not suggest a notable effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 susceptibility. Owing to their pharmacological characteristics, sodium–glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended. Currently, insulin should be the main approach to the control of acute glycaemia. Most available evidence does not distinguish between the major types of diabetes mellitus and is related to type 2 diabetes mellitus owing to its high prevalence. However, some limited evidence is now available on type 1 diabetes mellitus and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, in December 2019 and has spread worldwide. As of 29 October 2020, 44,351,506 globally confirmed cases of COVID-19 have been reported on the World Health Organization COVID-19 dashboard, including 1,171,255 deaths. The fatality rate for COVID-19 has been estimated to be 0.5–1.0%[1–3]. From 1 March to 30 May 2020, 122,300 excess all-cause deaths occurred in the USA, of which 95,235 (79%) were officially attributed to COVID-19 (REF.[4]). Of note, mortality from COVID-19 and seasonal influenza is not equivalent, as deaths associated with these diseases do not reflect frontline clinical conditions in the same way. For example, COVID-19 pandemic-hit areas have been facing critical shortages in terms of access to supplies such as ventilators and intensive care unit (ICU) facilities[5].

SARS-CoV-2 is a positive-stranded RNA virus that is enclosed by a protein-decorated lipid bilayer containing a single-stranded RNA genome; SARS-CoV-2 has 82% homology with human SARS-CoV, which causes severe acute respiratory syndrome (SARS)[6]. In human cells, the main entry receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2)[7], which is highly expressed in lung alveolar cells, cardiac myocytes, vascular endothelium and various other cell types[8]. In humans, the main route of SARS-CoV-2 transmission is through virus-bearing respiratory droplets[9]. Generally, patients with COVID-19 develop symptoms at 5–6 days after infection. Similar to SARS-CoV and the related Middle Eastern respiratory syndrome (MERS)-CoV, SARS-CoV-2 infection induces mild symptoms in the initial stage for 2 weeks on average but has the potential to develop into severe illness, including a systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), multi-organ involvement and shock[10]. Patients at high risk of severe COVID-19 or death have several characteristics, including advanced age and male sex, and have underlying health issues, such as cardiovascular disease (CVD), obesity and/or type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)[11–13]. A few early studies have shown that underlying CVD and diabetes mellitus are common among patients with COVID-19 admitted to ICUs[14,15]. T2DM is typically a disease of advanced age,

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Key points

- Underlying diabetes mellitus and cardiovascular diseases are considered risk factors for increased coronavirus disease 2019 (COVID-19) disease severity and worse outcomes, including higher mortality.
- Potential pathogenetic links between COVID-19 and diabetes mellitus include effects on glucose homeostasis, inflammation, altered immune status and activation of the renin–angiotensin–aldosterone system (RAAS).
- During the COVID-19 pandemic, tight control of glucose levels and prevention of diabetes complications might be crucial in patients with diabetes mellitus to keep susceptibility low and to prevent severe courses of COVID-19.
- Evidence suggests that insulin and dipeptidyl peptidase 4 inhibitors can be used safely in patients with diabetes mellitus and COVID-19; metformin and sodium–glucose cotransporter 2 inhibitors might need to be withdrawn in patients at high risk of severe disease.
- Pharmacological agents under investigation for the treatment of COVID-19 can affect glucose metabolism, particularly in patients with diabetes mellitus; therefore, frequent blood glucose monitoring and personalized adjustment of medications are required.
- As COVID-19 lacks definitive treatment so far, patients with diabetes mellitus should follow general preventive rules strictly and monitor glucose levels more frequently, engage in physical activity, eat healthily and control other risk factors.

Cytokine storm
An uncontrolled excessive production of markers of inflammation, followed by an abnormal inflammatory response, which results from the effects of a combination of pro-inflammatory immunoactive molecules, such as interleukins, interferons, chemokines and tumour necrosis factor.

and, therefore, whether diabetes mellitus is a COVID-19 risk factor over and above advanced age is currently unknown.

The basic and clinical science of the potential inter-relationships between diabetes mellitus and COVID-19 has been reviewed[16]. However, knowledge in this field is emerging rapidly, with numerous publications appearing frequently. This Review summarizes the new advances in diabetes mellitus and COVID-19 and extends the focus towards clinical recommendations for patients with diabetes mellitus at risk of or affected by COVID-19. Most available research does not distinguish between diabetes mellitus type and is mainly focused on T2DM, owing to its high prevalence. However, some limited research is available on COVID-19 and T1DM, which we highlight in this Review.

Potential mechanisms

The presence of diabetes mellitus and the individual degree of hyperglycaemia seem to be independently associated with COVID-19 severity and increased mortality[11,12,17,18]. Furthermore, the presence of typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increases COVID-19 mortality[11,19]. We propose some pathophysiological mechanisms leading to increased cardiovascular and all-cause mortality after infection with SARS-CoV-2 in patients with diabetes mellitus (FIG. 1).

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COVID-19 and glucose metabolism. In human monocytes, elevated glucose levels directly increase SARS-CoV-2 replication, and glycolysis sustains SARS-CoV-2 replication via the production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor 1α[20]. Therefore, hyperglycaemia might support viral proliferation. In accord with this assumption, hyperglycaemia or a history of T1DM and T2DM were found to be independent predictors of morbidity and mortality in patients with SARS[21]. Furthermore, comorbid T2DM in mice infected with MERS-CoV resulted in a dysregulated immune response, leading to severe and extensive lung pathology[22]. Patients with diabetes mellitus typically fall into higher categories of SARS-CoV-2 infection severity than those without[23,24], and poor glycaemic control predicts an increased need for medications and hospitalizations, and increased mortality[18,25] (TABLE 1; Supplementary Table 1).

Of note, glycaemic deterioration is a typical complication of COVID-19 in patients with impaired glucose regulation or diabetes mellitus. For example, in patients requiring insulin, SARS-CoV infection was associated with a rapidly increasing need for high doses of insulin (often approaching or exceeding 100 IU per day)[26]. Changes in insulin needs are seemingly associated with the levels of inflammatory cytokines[26,27]. Although ketoacidosis is typically a problem closely associated with T1DM, in patients with COVID-19, ketoacidosis can also occur in those with T2DM. For example, in a systematic review, 77% of patients with COVID-19 who developed ketoacidosis had T2DM[28].

Inflammation and insulin resistance. The most common post-mortem findings in the lungs of people with fatal COVID-19 are diffuse alveolar damage and inflammatory cell infiltration with prominent hyaline membranes[29]. Other critical findings include myocardial inflammation, lymphocyte infiltration in the liver, macrophage clustering in the brain, axonal injuries, microthrombi in glomeruli and focal pancreatitis[29]. These findings indicate an inflammatory pathology in COVID-19 (FIG. 1). In addition, an integrated analysis showed that patients with severe COVID-19 have a highly impaired interferon type I response with low IFNα activity in the blood, indicating high blood viral load, and an impaired inflammatory response[30]. It has also been reported that the inborn errors of type I interferon immunity related to TLR3 and IRF7 (REF.[31]), or B cell immunity[32], underlie fatal COVID-19 pneumonia in 12.5% of men and 2.6% of women. The aforementioned findings indicate considerable variations in immune phenotypes among patients with COVID-19.

Some patients with severe COVID-19 experience a cytokine storm, which is a dangerous and potentially life-threatening event[33,34]. A retrospective study of 317 patients with laboratory-confirmed COVID-19 showed the presence of active inflammatory responses (IL-6 and lactate dehydrogenase) within 24 h of hospital admission, which were correlated with disease severity[35]. Furthermore, blood levels of IL-6 and lactate dehydrogenase are independent predictors of COVID-19

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Glucocorticoid excess and COVID-19 disease

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Abstract
The pandemic of coronavirus disease (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing high and rapid morbidity and mortality. Immune system response plays a crucial role in controlling and resolving the viral infection. Exogenous or endogenous glucocorticoid excess is characterized by increased susceptibility to infections, due to impairment of the innate and adaptive immune system. In addition, diabetes, hypertension, obesity and thromboembolism are conditions overrepresented in patients with hypercortisolism. Thus patients with chronic glucocorticoid (GC) excess may be at high risk of developing COVID-19 infection with a severe clinical course. Care and control of all comorbidities should be one of the primary goals in patients with hypercortisolism requiring immediate and aggressive treatment. The European Society of Endocrinology (ESE), has recently commissioned an urgent clinical guidance document on management of Cushing's syndrome in a COVID-19 period. In this review, we aim to discuss and expand some clinical points related to GC excess that may have an impact on COVID-19 infection, in terms of both contagion risk and clinical outcome. This document is addressed to all specialists who approach patients with endogenous or exogenous GC excess and COVID-19 infection.

Keywords Cushing's syndrome · SarsCoV2 · Glucocorticoid · Infections · Cortisol · Immune system

1 Introduction

Severe acute respiratory syndrome due to coronavirus SARS-CoV2, or COVID-19, has recently been identified to be a cause of severe pneumonia, with potential evolution to acute respiratory distress syndrome (ARDS), further complicated by cardiovascular and renal injury, particularly in older patients with metabolic comorbidities, such as obesity, hypertension and diabetes, in which higher morbidity and mortality have been observed [1, 2]. Metabolic alterations are common clinical features of Cushing's syndrome (CS), a complex and challenging disease characterized by chronic glucocorticoid (GC) excess [3–5]. CS can be exogenous, resulting from chronic administration of corticosteroids, or endogenous, due to adrenal overproduction of cortisol. In around 80% of cases, endogenous CS is caused by excessive adrenal stimulation from abnormally elevated ACTH levels, due to an ACTH-secreting pituitary tumour (Cushing's Disease, CD)

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VIEW POINT

COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology

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Keywords Covid-19 · Diabetes mellitus · Obesity · Malnourishment · Hypoadrenalism

Introduction

Coronavirus disease 2019 (COVID-19) outbreak requires that endocrinologists from all over Europe move on, even more, to the first line of care of our patients, also in collaboration with other physicians such as those in internal medicine and emergency units. This will preserve the health status and prevent the adverse COVID-19-related outcomes in people affected by different endocrine diseases. People with diabetes in particular are among those in high-risk categories who can have serious illness if they get the virus, according to the data published so far from the Chinese researchers, but other endocrine diseases such as obesity, malnutrition, and adrenal insufficiency may also be impacted by COVID-19. Therefore, since the responsibilities of endocrinologists worldwide due to the current COVID-19 outbreak are not minor we have been appointed by the European Society of Endocrinology (ESE) to write the current statement in order to support the ESE members and the whole endocrine community in this critical situation.

In addition, endocrinologists, as any other healthcare worker under the current COVID-19 outbreak, will need to self-protect from this viral disease, which is demonstrating to have a very high disseminating and devastating capacity. We urge Health Authorities to provide adequate protection to the whole workforce of health professionals and to consistently test for COVID-19 the exposed personnel. A decrease in the number of healthcare professionals available for active medical practice in case they contract the disease as it is happening in certain countries, is itself, a threat for the healthcare system and the well-being of our patients.

The virus seems to have spread from infected animals and human-to-human transmission is now more than evident, with a high suspicion that non-symptomatic individuals act as the major vectors. It spreads like any other respiratory infectious disease, through contaminated air-droplets that come out of the mouth of infected persons when talking, coughing, or sneezing. The virus can survive in the environment from a few hours to a few days, depending on surfaces and environmental conditions, and touching affected surfaces. The mouth, nose, and ocular mucosa appears to be the major way of transmission.

Symptoms of COVID-19 infection

General symptoms are relatively nonspecific and similar to other common viral infections targeting the respiratory system, and include fever, cough, myalgia, and shortness of breath. The clinical spectrum of the virus ranges from mild disease with nonspecific signs and symptoms of acute respiratory illness, to severe pneumonia with respiratory failure and septic shock. Possibly, an overreaction of the immune system leading to an autoimmune aggression of the lungs could be involved in the most severe cases of acute distress respiratory syndrome. There have also been reports of asymptomatic infection and research in this matter is currently ongoing worldwide to elucidate the real prevalence of the disease and the true relative mortality ratio.

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The Impact of SARS-Cov-2 Virus Infection on the Endocrine System

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has spread across the globe rapidly causing an unprecedented pandemic. Because of the novelty of the disease, the possible impact on the endocrine system is not clear. To compile a mini-review describing possible endocrine consequences of SARS-CoV-2 infection, we performed a literature survey using the key words Covid-19, Coronavirus, SARS CoV-1, SARS Cov-2, Endocrine, and related terms in medical databases including PubMed, Google Scholar, and MedARXiv from the year 2000. Additional references were identified through manual screening of bibliographies and via citations in the selected articles. The literature review is current until April 28, 2020. In light of the literature, we discuss SARS-CoV-2 and explore the endocrine consequences based on the experience with structurally-similar SARS-CoV-1. Studies from the SARS -CoV-1 epidemic have reported variable changes in the endocrine organs. SARS-CoV-2 attaches to the ACE2 system in the pancreas causing perturbation of insulin production resulting in hyperglycemic emergencies. In patients with preexisting endocrine disorders who develop COVID-19, several factors warrant management decisions. Hydrocortisone dose adjustments are required in patients with adrenal insufficiency. Identification and management of critical illness-related corticosteroid insufficiency is crucial. Patients with Cushing syndrome may have poorer outcomes because of the associated immunodeficiency and coagulopathy. Vitamin D deficiency appears to be associated with increased susceptibility or severity to SARS-CoV-2 infection, and replacement may improve outcomes. Robust strategies required for the optimal management of endocrinopathies in COVID-19 are discussed extensively in this mini-review.

Key Words: SARS-CoV2, COVID-19, Endocrine

Coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, Hubei province, China, toward the end of 2019, swiftly spread around the globe and became a major

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CIRCI, critical illness-related corticosteroid insufficiency; COVID-19, coronavirus-19; CS, Cushing syndrome; DRA, dopamine receptor agonist; FGF2, fibroblast growth factor 2; HPA, hypothalamo-pituitary-adrenal axis; IFN-γ, interferon γ; MCP1, monocyte chemoattractant protein 1; MERS-CoV, Middle East respiratory syndrome-coronavirus; RAAS, renin-angiotensin-aldosterone system; S protein, Spike protein; SARS-CoV-1, severe acute respiratory syndrome-coronavirus-1; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TMPRSS2, transmembrane protease serine 2

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ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Baqsimi 3 mg ρινική κόνις σε περιέκτη μίας δόσης. **ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** Κάθε περιέκτης μίας δόσης χορηγεί ρινική κόνιν με 3 mg γλυκαγόνης. **Θεραπευτικές ενδείξεις:** Το Baqsimi ενδείκνυται για την αντιμετώπιση της σοβαρής υπογλυκαιμίας σε ενήλικες, εφήβους και παιδιά ηλικίας 4 ετών και άνω με σακχαρώδη διαβήτη. **Δοσολογία και τρόπος χορήγησης:** Ενήλικες, έφηβοι και παιδιά ηλικίας 4 ετών και άνω. Η συνιστώμενη δόση είναι 3 mg γλυκαγόνης, χορηγούμενη στον ένα ρώθωνα. **Ηλικιωμένοι:** (ηλικίας ≥ 65 ετών) Δεν απαιτείται προσαρμογή της δόσης με βάση την ηλικία. Υπάρχουν πολύ περιορισμένα δεδομένα αποτελεσματικότητας και ασφάλειας για ασθενείς ηλικίας 65 ετών και άνω και δεν υπάρχουν δεδομένα για ασθενείς ηλικίας 75 ετών και άνω. **Νεφρική και ηπατική δυσλειτουργία**: Δεν απαιτείται προσαρμογή της δόσης με βάση τη νεφρική και την ηπατική λειτουργία. **Παιδιατρικός πληθυσμός:** 0 - < 4 ετών. Η ασφάλεια και η αποτελεσματικότητα του Baqsimi σε βρέφη και παιδιά ηλικίας 0 έως < 4 ετών δεν έχουν ακόμα τεκμηριωθεί. Δεν υπάρχουν διαθέσιμα δεδομένα. Τρόπος χορήγησης. Για ρινική χρήση μόνο. Η ρινική κόνις γλυκαγόνης χορηγείται στον ένα ρώθωνα. Η γλυκαγόνη απορροφάται παθητικά μέσω του ρινικού βλεννογόνου. Δεν είναι απαραίτητη η εισπνοή ή η βαθιά αναπνοή μετά τη χορήγηση. **Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. Φαιοχρωμοκύτταμα. **Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση**: **Φαιοχρωμοκύτταμα:** Σε περίπτωση παρουσίας φαιοχρωμοκυττώματος, η γλυκαγόνη μπορεί να διεγείρει την απελευθέρωση κατεχολαμινών από τον όγκο. Εάν ο ασθενής παρουσιάσει σημαντική αύξηση της αρτηριακής πίεσης, η χρήση ενός μη εκλεκτικού α-αδρενεργικού αποκλειστή έχει καταδειχθεί ότι είναι αποτελεσματική στη μείωση της αρτηριακής πίεσης. Το Baqsimi αντενδείκνυται σε ασθενείς με φαιοχρωμοκύτταμα. Ινσουλίνωμα Σε ασθενείς με ινσουλίνωμα, η χορήγηση γλυκαγόνης μπορεί να οδηγήσει αρχικά σε αύξηση των επιπέδων γλυκόζης αίματος. Ωστόσο, η χορήγηση γλυκαγόνης μπορεί να διεγείρει άμεσα ή έμμεσα (μέσω μίας αρχικής αύξησης των επιπέδων γλυκόζης αίματος) υπερβολική απελευθέρωση ινσουλίνης από ένα ινσουλίνωμα και να προκαλέσει υπογλυκαιμία. Ένας ασθενής που αναπτύσσει συμπτώματα υπογλυκαιμίας μετά τη λήψη μίας δόσης γλυκαγόνης θα πρέπει να λάβει γλυκόζη από του στόματος ή ενδοφλεβίως. **Υπερευαισθησία και αλλεργικές αντιδράσεις:** Μπορεί να εκδηλωθούν αλλεργικές αντιδράσεις, οι οποίες έχουν αναφερθεί με τη χορήγηση ενέσιμης γλυκαγόνης και περιλαμβάνουν γενικευμένο εξάνθημα και, σε κάποιες περιπτώσεις, αναφυλακτικό σοκ με αναπνευστικές δυσκολίες, καθώς και υπόταση. Εάν ο ασθενής αντιμετωπίσει δυσκολία στην αναπνοή, ζητήστε άμεση ιατρική βοήθεια. **Αποθήκες γλυκογόνου και υπογλυκαιμία:** Η γλυκαγόνη είναι αποτελεσματική στην αντιμετώπιση της υπογλυκαιμίας μόνο εάν υφίστανται επαρκής παρουσία γλυκογόνου στο ήπαρ. Επειδή η γλυκαγόνη παρέχει λίγη ή καθόλου βοήθεια σε καταστάσεις ασιτίας, επινεφριδιακής ανεπάρκειας, χρόνιας κατάχρησης αλκοόλ ή χρόνιας υπογλυκαιμίας, αυτές οι παθήσεις θα πρέπει να αντιμετωπίζονται με χορήγηση γλυκόζης. Για την πρόληψη της επανεμφάνισης της υπογλυκαιμίας, θα πρέπει να χορηγούνται υδατάνθρακες από του στόματος για την αποκατάσταση του γλυκογόνου στο ήπαρ, όταν ο ασθενής έχει ανταποκριθεί στη θεραπεία. **Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης:** Δεν έχουν πραγματοποιηθεί μελέτες αλληλεπιδράσεων. **Ινσουλίνη** Δρα ανταγωνιστικά προς τη γλυκαγόνη. **Ινδομεθακίνη:** Όταν χρησιμοποιείται μαζί με ινδομεθακίνη, η γλυκαγόνη μπορεί να απωλέσει την ικανότητα αύξησης των επιπέδων γλυκόζης αίματος ή μπορεί ακόμη και να προκαλέσει υπογλυκαιμία. **Β-αποκλειστές:** Οι ασθενείς που λαμβάνουν β-αποκλειστές αναμένεται να έχουν μεγαλύτερη αύξηση τόσο των σφυγμών όσο και της αρτηριακής πίεσης, μία αύξηση η οποία θα είναι παροδική λόγω του μικρού χρόνου ημίσειας ζωής της γλυκαγόνης. **Βαρφαρίνη:** Η γλυκαγόνη μπορεί να αυξήσει την αντιπηκτική δράση της βαρφαρίνης. **Γονιμότητα, κύηση και γαλουχία: Κύηση:** Μελέτες αναπαραγωγής και γονιμότητας με ρινική κόνιν γλυκαγόνης δεν διεξήχθησαν σε ζώα. Το Baqsimi μπορεί να χρησιμοποιείται κατά τη διάρκεια της εγκυμοσύνης. Η γλυκαγόνη δεν διαπερνά τον ανθρώπινο πλακουντιακό φραγμό. Η χρήση γλυκαγόνης έχει αναφερθεί σε έγκυες γυναίκες με διαβήτη και δεν υπάρχουν γνωστές επιβλαβείς επιδράσεις σε σχέση με την πορεία της εγκυμοσύνης και την υγεία του εμβρύου και του νεογνού. **Θηλασμός:** Το Baqsimi μπορεί να χρησιμοποιείται κατά τη διάρκεια του θηλασμού. Η γλυκαγόνη απομακρύνεται από την κυκλοφορία του αίματος πολύ γρήγορα και κατά συνέπεια, η ποσότητα που απεκκρίνεται στο γάλα μητέρων που θηλάζουν μετά τη θεραπεία σοβαρών υπογλυκαιμικών αντιδράσεων αναμένεται να είναι εξαιρετικά μικρή. Καθώς η γλυκαγόνη αποδομείται στην πεπτική οδό και δεν μπορεί να απορροφηθεί στην ολική μορφή της, δεν θα εκλύει οποιαδήποτε μεταβολική επίδραση στο παιδί. **Γονιμότητα:** Δεν έχουν διεξαχθεί μελέτες γονιμότητας με τη ρινική κόνιν γλυκαγόνης. Μελέτες σε αρουραίους έχουν καταδείξει ότι η γλυκαγόνη δεν προκαλεί διαταραχή της γονιμότητας. Επιδράσεις στην ικανότητα οδήγησης και χειρισμού μηχανημάτων Το Baqsimi έχει ασήμαντη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων. **Ανεπιθύμητες ενέργειες:** Οι πιο συχνά αναφερθείσες ανεπιθύμητες ενέργειες είναι η αυξημένη δακρύρροια (36 %), ο ερεθισμός της ανώτερης αναπνευστικής οδού (34 %), η ναυτία (27 %), η κεφαλαλγία (21 %) και ο έμετος (16 %). Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς. **ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, Ολλανδία. **ΑΡΙΘΜΟΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** EU/1/19/1406/001. **ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ:** 16 ΔΕΚΕΜΒΡΙΟΥ 2019. **ΤΡΟΠΟΣ ΔΙΑΘΕΣΗΣ:** Με ιατρική συνταγή. 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