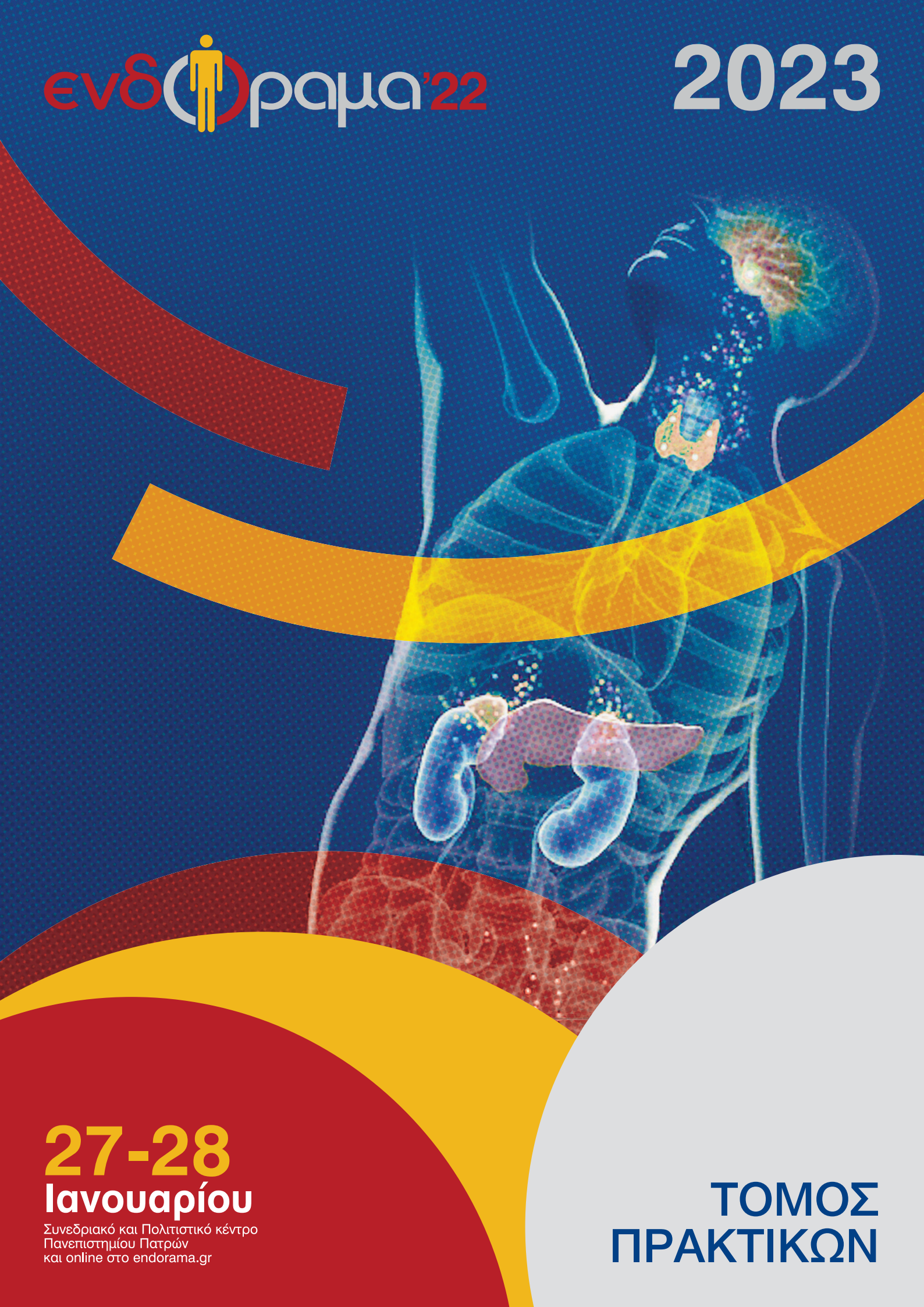
ενδοραμα'22

2023



27-28
Ιανουαρίου

Συνεδριακό και Πολιτιστικό κέντρο
Πανεπιστημίου Πατρών
και online στο endorama.gr

ΤΟΜΟΣ ΠΡΑΚΤΙΚΩΝ

Παρασκευή, 27 Ιανουαρίου 2023

15:30 – 16:30 Εγγραφές

16:30 – 17:30 Λιπίδια
Ομιλητής: **Διονύσιος Χαρτουμπέκης**
Πρόεδρος: **Βαγγέλης Λυμπερόπουλος**

17:30 – 18:30 Μεταβολισμός Οστών
Ομιλητής: **Σπύρος Καρράς**
Πρόεδρος: **Αντώνης Πολυμέρης**

18:30 – 18:45 Διάλλειμα

18:45 – 19:45 Παιδιατρική

Ενδοκρινολογία
Ομιλητής: **Χριστίνα Τάτση**
Πρόεδρος: **Κωνσταντίνος Στρατάκης**

19:45 – 20:45 Θυρεοειδής
Ομιλητής: **Σπυριδούλα Μαράκα**
Πρόεδρος: **Γρηγόριος Ευφραιμίδης**

21:00 – 21:00 Τιμητική βράβευση
Αθανάσιος Σουβατζόγλου

21:00 – 21:30 Πολιτιστικό ΕΝΔΟΡΑΜΑ
«Ναυάγια και ενάλιες αρχαιότητες»
Εισηγητής: **Γεώργιος Παπαθεοδώρου,**
Καθηγητής Γεωλογικού Τμ. Παν. Πατρών

21:30 Welcome Reception

Σάββατο, 28 Ιανουαρίου 2023

09:00 – 10:00 Υπόφυση
Ομιλητής: **Πλούταρχος Τζούλης**
Πρόεδρος: **Κρυσταλλένια Αλεξανδράκη**

10:00 – 11:00 Διατροφή
Ομιλητής: **Δημήτριος Κουρέτας**
Πρόεδρος: **Δημήτριος – Νικηφόρος Κιόρτσης**

11:00 – 11:30 Διάλειμμα

11:30 – 12:30 Ινσουλινο-εξαρτώμενος Σακχαρώδης Διαβήτης
Ομιλητής: **Νικόλαος Βάλβης**
Πρόεδρος: **Βαρβάρα Βλασοπούλου**

12:30 – 13:30 Μη Ινσουλινο-εξαρτώμενος Σακχαρώδης Διαβήτης
Ομιλητής: **Χαράλαμπος Μηλιώνης**
Πρόεδρος: **Δήμητρα Ζιάννη**

13:30 – 16:00 Ομάδες Εκπαίδευσης Αντλιών Ινσουλίνης

16:00 – 17:00 Επινεφρίδια
Ομιλητής: **Δανάη Δεληβάνη**
Πρόεδρος: **Σαράντης Λειβαδάς**

17:00 – 19:00 Νέα Φάρμακα
Ομιλητής: **Κωνσταντίνος Τουλής**
Πρόεδρος: **Γεώργιος Παπαγεωργίου**

19:00 – 20:00 Γυναικεία Αναπαραγωγή
Ομιλητής: **Παναγιώτης Αναγνωστής**
Πρόεδρος: **Κώστας Σαμαράς**

20:00 – 21:00 Ανδρική Αναπαραγωγή
Ομιλητής: **Γεώργιος Παπαδάκης**
Πρόεδρος: **Πέτρος Δρέττας**

Κυριακή, 29 Ιανουαρίου 2023

11:00 – 13:00 Παρουσίαση του βιβλίου της Αιμιλίας Σαλβάνου **"Μικρασιατική Καταστροφή και Πρόσφυγες: Αρρώστιες και Περίθαλψη"**
Εισαγωγή: **Αντώνης Λιάκος,**
Ομότιμος Καθηγητής Ιστορίας ΕΚΠΑ

Κλινικά Φροντιστήρια Φοιτητών

9:00 – 11:00
Κλινικό Φροντιστήριο Φοιτητών I

11:00 – 13:00
Κλινικό Φροντιστήριο Φοιτητών II

13:00 – 15:00
Κλινικό Φροντιστήριο Φοιτητών III

15:00 – 17:00
Κλινικό Φροντιστήριο Φοιτητών IV

Κρυσταλλένια Αλεξανδράκη
MD, PhD, MSc, MSc Ενδοκρινολόγος, Επιστημονικός Συνεργάτης, Β' Χειρουργική Κλινική, Αρεταίειο Νοσοκομείο, Ε.Κ.Π.Α.

Παναγιώτης Γ. Αναγνωστής
MD, MSc, PhD, FRSPH, Ενδοκρινολόγος Υπεύθυνος Ενδοκρινολογικού Τμήματος ΕΛ.ΑΣ., Επιστημονικός Συνεργάτης Α' Μαιευτική-Γυναικολογική Κλινική ΑΠΘ

Νικόλαος Βάλβης
Ειδικός Ενδοκρινολόγος - Διαβητολόγος

Βαρβάρα Βλασοπούλου
Ενδοκρινολόγος, τεως Διευθύντρια ΕΣΥ, Τμήμα Ενδοκρινολογίας & Μεταβολισμού - Διαβητολογικό Κέντρο ΓΝΑ "Ο Ευαγγελισμός", Αθήνα

Δανάη Δεληβάνη
Ειδικός Ενδοκρινολόγος, Mayo Clinic, Rochester USA, Certified American Board of Endo-crinology, Diabetes and Metabolism

Πέτρος Δρέττας
Χειρούργος Ουρολόγος-Ανδρολόγος

Γρηγόριος Ευφραιμίδης
Επίκουρος Καθηγητής Ενδοκρινολογίας, Ιατρική Σχολή Λάρισας, Πανεπιστήμιο Θεσσαλίας, Senior Re- searcher, Department of Endocrinology, Copenha- gen University Hospital Rigshospitalet, Denmark

Δήμητρα Ζιάννη
Ενδοκρινολόγος – Διαβητολόγος

Σπύρος Καρράς
Ενδοκρινολόγος, PHD, Εργαστήριο Βιολογικής Χημείας, Ιατρική Σχολή ΑΠΘ, Θεσσαλονίκη

Δημήτριος-Νικηφόρος Κιόρτσης
Ενδοκρινολόγος, Καθηγητής Τμήματος Ιατρικής Πανεπιστημίου Ιωαννίνων

Δημήτριος Κουρέτας
Καθηγητής Φυσιολογίας Ζωικών Οργανισμών – Τοξικολογίας στο Πανεπιστήμιο Θεσσαλίας

Σαράντης Λιβαδάς
Ενδοκρινολόγος – Διαβητολόγος

Βαγγέλης Λυμπερόπουλος
Καθηγητής Παθολογίας-Μεταβολικών Νοσημάτων Ιατρικής Σχολής Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

ΟΜΙΛΗΤΕΣ - ΠΡΟΕΔΡΟΙ

Σπυριδούλα Μαράκα
Endocrinologist, University of Arkansas for Medical Sciences

Χαράλαμπος Μηλιώνης
Ενδοκρινολόγος, Επιμελητής Β' ΕΣΥ, Γ.Ν. «ΕΛΕΝΑ ΒΕΝΙΖΕΛΟΥ»

Γεώργιος Παπαγεωργίου
Ενδοκρινολόγος

Γεώργιος Παπαδάκης
Ενδοκρινολόγος, Επίκουρος Καθηγητής Τμήμα Ενδοκρινολογίας, Διαβητολογίας και Μεταβολισμού Πανεπιστημιακό Νοσοκομείο Λωζάνης - Ελβετία

Αντώνης Πολυμέρης
Ενδοκρινολόγος, Διευθυντής Τμήματος Ενδοκρινολογίας, Μεταβολισμού και Σακχαρώδη Διαβήτη, ΓΝΑ Σισμανόγλειο - Αμαλία Φλέμινγκ

Κωνσταντίνος Σαμαράς
Μαιευτήρας-Γυναικολόγος, Ειδίκευση στην γυναικολογική Ενδοκρινολογία

Κωνσταντίνος Στρατάκης
Chief, Section on Endocrinology & Genetics, NICHD, NIH

Χριστίνα Τάτση
Assistant Clinical Investigator, Head of Section on Hy- pothalamic and Pituitary Disorders at Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

ΠλούταρχοςΤζούλης
MD, PhD
(UCL), FRCP (Lon), MSc (Hons), CCT (UK), Ενδοκρινολόγος – Διαβητολόγος, Επ. Αναπληρωτής Καθηγητής Ενδοκρινολογίας, Ιατρική Σχολή UCL (University College London)

Κωνσταντίνος Τουλής
Στρατιωτικός Ιατρός, Διδάκτωρ Ιατρικής Α.Π.Θ.

Διονύσης Χαρτουμπέκης
MD, MD, PhD, Ενδοκρινολόγος, επιμελητής (chef de clinique) και ερευνητής του τμήματος Ενδοκρινολογίας, Διαβητολογίας και Μεταβολισμού στο Πανεπιστημιακό Νοσοκομείο της Λωζάνης CHUV (Ελβετία)

ΧΟΡΗΓΟΙ

ΠΑΙΔΟ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ

ΧΡΙΣΤΙΝΑ ΤΑΤΣΗ

ASSISTANT CLINICAL INVESTIGATOR,
HEAD OF SECTION ON HY- POTHALAMIC AND PITUITARY DISORDERS
AT EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH
AND HUMAN DEVELOPMENT (NICHD)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 19, 2022 VOL. 386 NO. 20

Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events

D.R. Jacobs, Jr., J.G. Woo, A.R. Sinaiko, S.R. Daniels, J. Ikonen, M. Juonala, N. Kartiosuo, T. Lehtimäki, C.G. Magnussen, J.S.A. Viikari, N. Zhang, L.A. Bazzano, T.L. Burns, R.J. Prineas, J. Steinberger, E.M. Urbina, A.J. Venn, O.T. Raitakari, and T. Dwyer

ABSTRACT

BACKGROUND

Childhood cardiovascular risk factors predict subclinical adult cardiovascular disease, but links to clinical events are unclear.

METHODS

In a prospective cohort study involving participants in the International Childhood Cardiovascular Cohort (i3C) Consortium, we evaluated whether childhood risk factors (at the ages of 3 to 19 years) were associated with cardiovascular events in adulthood after a mean follow-up of 35 years. Body-mass index, systolic blood pressure, total cholesterol level, triglyceride level, and youth smoking were analyzed with the use of i3C-derived age- and sex-specific z scores and with a combined-risk z score that was calculated as the unweighted mean of the five risk z scores. An algebraically comparable adult combined-risk z score (before any cardiovascular event) was analyzed jointly with the childhood risk factors. Study outcomes were fatal cardiovascular events and fatal or nonfatal cardiovascular events, and analyses were performed after multiple imputation with the use of proportional-hazards regression.

RESULTS

In the analysis of 319 fatal cardiovascular events that occurred among 38,589 participants (49.7% male and 15.0% Black; mean [±SD] age at childhood visits, 11.8±3.1 years), the hazard ratios for a fatal cardiovascular event in adulthood ranged from 1.30 (95% confidence interval [CI], 1.14 to 1.47) per unit increase in the z score for total cholesterol level to 1.61 (95% CI, 1.21 to 2.13) for youth smoking (yes vs. no). The hazard ratio for a fatal cardiovascular event with respect to the combined-risk z score was 2.71 (95% CI, 2.23 to 3.29) per unit increase. The hazard ratios and their 95% confidence intervals in the analyses of fatal cardiovascular events were similar to those in the analyses of 779 fatal or nonfatal cardiovascular events that occurred among 20,656 participants who could be evaluated for this outcome. In the analysis of 115 fatal cardiovascular events that occurred in a subgroup of 13,401 participants (31.0±5.6 years of age at the adult measurement) who had data on adult risk factors, the adjusted hazard ratio with respect to the childhood combined-risk z score was 3.54 (95% CI, 2.57 to 4.87) per unit increase, and the mutually adjusted hazard ratio with respect to the change in the combined-risk z score from childhood to adulthood was 2.88 (95% CI, 2.06 to 4.05) per unit increase. The results were similar in the analysis of 524 fatal or nonfatal cardiovascular events.

CONCLUSIONS

In this prospective cohort study, childhood risk factors and the change in the combined-risk z score between childhood and adulthood were associated with cardiovascular events in midlife. (Funded by the National Institutes of Health.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Woo can be contacted at jessica.woo@cchmc.org or at the Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 5041, Cincinnati, OH 45229-3039.

Drs. Jacobs, Woo, and Sinaiko and Drs. Bazzano, Burns, Prineas, Steinberger, Urbina, Venn, Raitakari, and Dwyer contributed equally to this article.

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Clinical and genetic characterization of familial central precocious puberty

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Running title: Familial central precocious puberty

Keywords: familial central precocious puberty, autosomal inheritance, mode of transmission, genetic of puberty, MKRN3, DLK1.

Word count: 4876 **Tables:** 5 **Figures:** 2 **References:** 39

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Disclosure statement: The authors have nothing to disclose.

ABSTRACT

Context: Central precocious puberty (CPP) can have a familial form in one quarter of the children. The recognition of this inherited condition increased after the identification of autosomal dominant CPP with paternal transmission caused by mutations in the *MKRN3* and *DLK1* genes.

Objectives: To characterize the inheritance and estimate the prevalence of familial CPP in a large multiethnic cohort. To compare clinical and hormonal features, as well as treatment

response to GnRH analogs (GnRHa), in children with distinct modes of transmission. To investigate the genetic basis of familial CPP.

Methods: We retrospectively studied 586 children with diagnosis of CPP. Patients with familial CPP (n=276) were selected for clinical and genetic analysis. Data from previous studies were grouped, encompassing sequencing of *MKRN3* and *DLK1* genes in 204 patients. Large-scale parallel sequencing was performed in 48 individuals from 34 families.

Results: The prevalence of familial CPP was estimated in 22%, with a similar frequency of maternal and paternal transmission. Pedigree analyses of families with maternal transmission suggested an autosomal dominant inheritance. Clinical and hormonal features, as well as treatment response to GnRHa, were similar among patients with different forms of transmission of familial CPP. *MKRN3* loss-of-function mutations were the most prevalent cause of familial CPP, followed by *DLK1* loss-of-function mutations, affecting, respectively, 22% and 4% of the studied families; both affecting exclusively families with paternal transmission. Rare variants of uncertain significance were identified in CPP families with maternal transmission.

Conclusions: We demonstrated a similar prevalence of familial CPP with maternal and paternal transmission. *MKRN3* and *DLK1* loss-of-function mutations were the major causes of familial CPP with paternal transmission.

INTRODUCTION

Central precocious puberty (CPP) results from the premature reactivation of the hypothalamic-pituitary-gonadal axis, clinically manifested as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys (1). Familial CPP can be defined by diagnosis or clinical history of early sexual development in more than one family member of first-, second- or third-degree of a confirmed CPP case (2).

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

Sarah E. Hampl, MD, FAAP,[a] Sandra G. Hassink, MD, FAAP,[b] Asheley C. Skinner, PhD,[c] Sarah C. Armstrong, MD, FAAP,[d] Sarah E. Barlow, MD, MPH, FAAP,[e] Christopher F. Bolling, MD, FAAP,[f] Kimberly C. Avila Edwards, MD, FAAP,[g] Ihuoma Eneli, MD, MS, FAAP,[h] Robin Hamre, MPH,[i] Madeline M. Joseph, MD, FAAP,[j] Doug Lunsford, MEd,[k] Eneida Mendonca, MD, PhD, FAAP,[l] Marc P. Michalsky, MD, MBA, FAAP,[m] Nazrat Mirza, MD, ScD, FAAP,[n] Eduardo R. Ochoa, Jr, MD, FAAP,[o] Mona Sharifi, MD, MPH, FAAP,[p] Amanda E. Staiano, PhD, MPP,[q] Ashley E. Weedn, MD, MPH, FAAP,[r] Susan K. Flinn, MA,[s] Jeanne Lindros, MPH,[t] Kymika Okechukwu, MPA[u]

Greetings

You have in your hands, or at your fingertips, the first edition of the American Academy of Pediatrics clinical practice guideline for evaluation and management of children and adolescents with overweight and obesity. Putting together this guideline was no small task, and the Academy is grateful to the efforts of all the professionals who contributed to the production of this document. This work is a true testament to their passion and dedication to combatting childhood and adolescent overweight and obesity.

The Subcommittee responsible for developing this guideline comprises a diverse group of professionals from a variety of disciplines representing both governmental entities and private institutions. Experts all, they are united by a common desire to provide the finest, most effective care and treatment to children and adolescents with overweight and obesity. Over the course of several months, the members of the Subcommittee reviewed the technical reports produced from the study review, then worked in concert to develop the Key Action Statements and Expert Consensus Recommendations contained within this guideline. These were crafted with meticulous care by the Subcommittee members, to align with current literature and to place appropriate emphasis on each statement.

While representing such a broad spectrum of perspectives, the members of this committee are all keenly aware of the multitude of barriers to treatment that patients and their families face. These barriers impact not only their access to treatment, but their ability to follow prescribed treatment plans. Whereas some patients are able to adopt the lifestyle changes and habitualize elements of their prescribed treatment plans, so many others struggle to do so for a wide variety of reasons. The members of the Subcommittee understand all of this. To assist with optimizing health equity and overcoming these barriers, guidance on a number of multilevel factors related to barriers to treatment have been included in this guideline. During the course of their work, members of the Subcommittee acknowledged that, although so much has been learned to advance the treatment of children and adolescents with overweight and obesity, there is still so much we have yet

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ORIGINAL ARTICLE

JBMR®

Long Bone Fractures in Fibrous Dysplasia/ McCune-Albright Syndrome: Prevalence, Natural History, and Risk Factors

Raya E.S. Geels,[1] Maartje E. Meier,[1,2] Amanda Saikali,[3] Roula Tsonaka,[4] Natasha M. Appelman-Dijkstra,[1] and Alison M. Boyce[5]

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ABSTRACT

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare bone and endocrine disorder arising along a broad spectrum. Long-bone fractures are a common, painful, and potentially disabling complication. However, fracture prevalence and risk factors have not been well-established, making it difficult to predict which patients are at risk for a severe course. Clinical and imaging data were reviewed from two large, well-phenotyped cohorts (National Institutes of Health [NIH] in the United States and the Leiden University Medical Center [LUMC] in the Netherlands) to identify long-bone fractures at FD sites. Skeletal burden score was quantified using bone scintigraphy. Multiple linear regressions were performed to identify clinical associations with fractures. A total of 419 patients were included (186 NIH, 233 LUMC); 194 (46%) had MAS endocrinopathies. Median age at last follow-up was 30.2 years (range 3.2–84.6, interquartile range [IQR] 25.5), and median skeletal burden score was 16.6 (range 0–75, IQR 33). A total of 48 (59%) patients suffered one or more lifetime fracture (median 1, range 0–70, IQR 4). Median age at first fracture was 8 years (range 1–76, IQR 10). Fracture rates peaked between 6 and 10 years of age and decreased thereafter. Lifetime fracture rate was associated with skeletal burden score ($\beta = 0.40$, $p < 0.01$) and MAS hyperthyroidism ($\beta = 0.22$, $p = 0.01$). Younger age at first fracture was associated with skeletal burden score ($\beta = -0.26$, $p = 0.01$) and male sex ($\beta = -0.23$, $p = 0.01$). Both skeletal burden score >25 and age at first fracture ≤7 years were associated with a higher total number of lifetime fractures (median 4, range 1–70, IQR 5 versus median 1, range 1–13, IQR 1) ($p < 0.01$). In conclusion, higher skeletal burden score and MAS hyperthyroidism are associated with long-bone fractures in FD/MAS. Both skeletal burden score ≥25 and age at first fracture ≤7 years are associated with a higher lifetime long-bone fracture risk and may predict a more severe clinical course. These results may allow clinicians to identify FD/MAS patients at risk for severe disease who may be candidates for early therapeutic interventions. © 2021 American Society for Bone and Mineral Research (ASBMR). This article has been contributed to by US Government employees and their work is in the public domain in the USA.

KEY WORDS: DISEASES AND DISORDERS OF/RELATED TO BONE; OTHER

Introduction

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a rare, mosaic disorder with a broad and complex spectrum.[1] Disease may involve any part of the skeleton and may be associated with extraskeletal manifestations, including skin hyperpigmentation and hyperfunctioning endocrinopathies.[2,3] FD/MAS arises due to postzygotic mutations in *GNAS*, leading to $G\alpha_s$ activation and inappropriate production of intracellular cyclic adenosine monophosphate (AMP).[4] In bone, this results in impaired differentiation of skeletal progenitor cells, forming discrete, expansile fibrotic lesions.[4] Skeletal disease becomes apparent in the first few years of life, progresses during childhood and adolescence, and reaches final disease burden in early adulthood.[5] Patients present along a broad spectrum, ranging from trivial disease affecting one or a few bones, to severe disease affecting nearly the entire skeleton.

Fractures are a painful and potentially disabling complication of FD. They occur most commonly in childhood and may be the presenting sign.[3,4] Recurrent fractures can lead to progressive

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ΠΑΙΔΟ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ | ΧΡΙΣΤΙΝΑ ΤΑΤΣΗ

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Audrey Briscoe, Katherine Chen and Karen O. Klein*

No pubertal growth spurt, rapid bone maturation, and menarche post GnRHa treatment in girls with precocious puberty

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Abstract

Objectives: To study total growth, rate of bone maturation, and menarche after discontinuation of Gonadotropin releasing hormone agonist (GnRHa) treatment for central precocious puberty (CPP).
Methods: Twenty girls with CPP on treatment with GnRHa were followed from discontinuation of treatment to final height (FH). Height, height velocity (HV), and bone age were measured every 6 months. Age at menarche was collected.
Results: Once treatment is discontinued, rate of bone maturation (bone age [BA]/chronological [CA]) accelerated from 0.7 ± 0.3 at end of treatment to 1.2 ± 0.8 post treatment, similar to BA/CA prior to treatment. BA at treatment discontinuation ranged from 11–14 years. On average, treatment was stopped when CA was within 9 months of BA. All girls continued to grow from end of treatment to menarche averaging an increase of 4.7 ± 3.7 cm, with HV 3.2 ± 2.0 cm/year. Post-menarche they grew an additional 4.6 ± 2.1 cm, with HV 2.4 ± 1.9 cm/year. Acceleration of HV was not seen post treatment. The younger the BA at initiation or completion of treatment, the longer time to menarche. No one had menarche prior to a BA of 12.5 year.
Conclusions: A pubertal growth spurt does not usually occur after treatment with GnRHa in girls with CPP. Rate of bone maturation accelerates post treatment. These factors are important in assessing optimal height outcome and decisions regarding cessation of treatment. This study will help clinicians give patients and families better estimates of growth and onset of menarche post treatment.

Keywords: growth; leuprolide; LH; menarche; menses; precocious puberty.

Introduction

Gonadotropin releasing hormone agonist (GnRHa) treatment is standard of care for central precocious puberty (CPP) [1–4]. The treatment slows or halts pubertal progression, slows the rate of bone maturation, suppresses gonadotropins, and usually decreases height velocity (HV) to normal pre-pubertal levels. Predicted adult height (PAH) continues to improve while on treatment, and then slowly decreases post treatment as rapid bone maturation resumes.

The decision regarding when to stop treatment needs to be individualized [5] and is based on multiple factors. These include the child reaching an appropriate age for mid-puberty to resume and a PAH reasonable for genetic potential, with caution that PAH may decrease once treatment is discontinued [6]. After discontinuation of GnRHa, the pubertal growth spurt typically does not resume, however growth will continue at a slower velocity until cessation of growth. This emphasizes the importance of not stopping treatment prematurely, as the remaining growth may be minimal. There are limited studies of growth and HV after discontinuation of GnRHa, especially as related to onset of menses [7]. We studied rate of bone maturation and growth after GnRHa treatment was stopped. We hypothesized that HV will not accelerate after treatment is discontinued, and rate of bone maturation will accelerate. These results are helpful to parents anticipating pubertal development, growth and menses post treatment, and provide important information for the physician when deciding how long to continue GnRHa treatment based on anticipated growth and menarche post treatment.

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ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adolescents with Obesity

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ABSTRACT

BACKGROUND

A once-weekly, 2.4-mg dose of subcutaneous semaglutide, a glucagon-like peptide-1 receptor agonist, is used to treat obesity in adults, but assessment of the drug in adolescents has been lacking.

METHODS

In this double-blind, parallel-group, randomized, placebo-controlled trial, we enrolled adolescents (12 to <18 years of age) with obesity (a body-mass index [BMI] in the 95th percentile or higher) or with overweight (a BMI in the 85th percentile or higher) and at least one weight-related coexisting condition. Participants were randomly assigned in a 2:1 ratio to receive once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo for 68 weeks, plus lifestyle intervention. The primary end point was the percentage change in BMI from baseline to week 68; the secondary confirmatory end point was weight loss of at least 5% at week 68.

RESULTS

A total of 201 participants underwent randomization, and 180 (90%) completed treatment. All but one of the participants had obesity. The mean change in BMI from baseline to week 68 was –16.1% with semaglutide and 0.6% with placebo (estimated difference, –16.7 percentage points; 95% confidence interval [CI], –20.3 to –13.2; P<0.001). At week 68, a total of 95 of 131 participants (73%) in the semaglutide group had weight loss of 5% or more, as compared with 11 of 62 participants (18%) in the placebo group (estimated odds ratio, 14.0; 95% CI, 6.3 to 31.0; P<0.001). Reductions in body weight and improvement with respect to cardiometabolic risk factors (waist circumference and levels of glycated hemoglobin, lipids [except high-density lipoprotein cholesterol], and alanine aminotransferase) were greater with semaglutide than with placebo. The incidence of gastrointestinal adverse events was greater with semaglutide than with placebo (62% vs. 42%). Five participants (4%) in the semaglutide group and no participants in the placebo group had cholelithiasis. Serious adverse events were reported in 15 of 133 participants (11%) in the semaglutide group and in 6 of 67 participants (9%) in the placebo group.

CONCLUSIONS

Among adolescents with obesity, once-weekly treatment with a 2.4-mg dose of semaglutide plus lifestyle intervention resulted in a greater reduction in BMI than lifestyle intervention alone. (Funded by Novo Nordisk; STEP TEENS ClinicalTrials.gov number, NCT04102189.)

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

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ORIGINAL ARTICLE

Phentermine/Topiramate for the Treatment of Adolescent Obesity

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Abstract

BACKGROUND Antiobesity medication may be useful for the treatment of pediatric obesity, yet few safe and effective options exist. We evaluated phentermine/topiramate (PHEN/TPM) for weight management in adolescents with obesity.

METHODS This 56-week, randomized, double-blind trial enrolled adolescents 12 to less than 17 years of age with obesity. Participants were randomly assigned 1:1:2 to receive either placebo (n=56), mid-dose PHEN/TPM (7.5 mg/46 mg; n=54), or top-dose PHEN/TPM (15 mg/92 mg; n=113), respectively. All participants received lifestyle therapy. The primary end point was mean percent change in body-mass index (BMI) from randomization to week 56.

RESULTS Participants had a mean (±SD) age of 14.0±1.4 years and a mean (±SD) BMI of 37.8±7.1 kg/m^2; 54.3% were female. The primary end point of percent change in BMI at week 56 showed differences from placebo of −10.44 percentage points (95% CI, −13.89 to −6.99; P<0.001) and −8.11 percentage points (95% CI, −11.92 to −4.31; P<0.001) for the top and mid doses of PHEN/TPM, respectively. Differences from placebo in percent change in triglycerides nominally favored PHEN/TPM (mid dose, −21%; 95% CI, −40 to −2; and top dose, −21%; 95% CI, −38 to −4), as did differences in percent change in high-density lipoprotein cholesterol (HDL-C) (mid dose, 10%; 95% CI, 3 to 18; and top dose, 9%; 95% CI, 2 to 15). The incidence of participants reporting at least one adverse event was 51.8%, 37.0%, and 52.2% in the placebo, mid-dose, and top-dose groups, respectively. Serious adverse events were reported for two participants in the top-dose group.

CONCLUSIONS PHEN/TPM at both the mid and top doses offered a statistically significant reduction in BMI and favorably impacted triglyceride and HDL-C levels in adolescents with obesity. (Funded by VIVUS LLC, with project support provided by Covance LLC; ClinicalTrials.gov number, NCT03922945.)

*A complete list of investigators is provided in the Supplementary Appendix, available at evidence.nejm.org.

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BRIEF COMMUNICATION

Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

Ravi Savarirayan[1]✉, Louise Tofts[2], Melita Irving[3], William R. Wilcox[4], Carlos A. Bacino[5], Julie Hoover-Fong[6], Rosendo Ullot Font[7], Paul Harmatz[8], Frank Rutsch[9], Michael B. Bober[10], Lynda E. Polgreen[11], Ignacio Ginebreda[12], Klaus Mohnike[13], Joel Charrow[14], Daniel Hoernschemeyer[15], Keiichi Ozono[16], Yasemin Alanay[17], Paul Arundel[18], Yumiko Kotani[19], Natsuo Yasui[19], Klane K. White[20], Howard M. Saal[21], Antonio Leiva-Gea[22], Felipe Luna-González[22], Hiroshi Mochizuki[23], Donald Basel[24], Dania M. Porco[25], Kala Jayaram[25], Elena Fisheleva[26], Alice Huntsman-Labed[26] and Jonathan R. S. Day[26]

PURPOSE: Achondroplasia is caused by pathogenic variants in the fibroblast growth factor receptor 3 gene that lead to impaired endochondral ossification. Vosoritide, an analog of C-type natriuretic peptide, stimulates endochondral bone growth and is in development for the treatment of achondroplasia. This phase 3 extension study was conducted to document the efficacy and safety of continuous, daily vosoritide treatment in children with achondroplasia, and the two-year results are reported.
METHODS: After completing at least six months of a baseline observational growth study, and 52 weeks in a double-blind, placebo-controlled study, participants were eligible to continue treatment in an open-label extension study, where all participants received vosoritide at a dose of 15.0 µg/kg/day.
RESULTS: In children randomized to vosoritide, annualized growth velocity increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at week 104. In children who crossed over from placebo to vosoritide in the extension study, annualized growth velocity increased from 3.81 cm/year at week 52 to 5.43 cm/year at week 104. No new adverse effects of vosoritide were detected.
CONCLUSION: Vosoritide treatment has safe and persistent growth-promoting effects in children with achondroplasia treated daily for two years.

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INTRODUCTION

Achondroplasia is the most common form of disproportionate short stature in humans, caused by a common pathogenic variant in the fibroblast growth factor receptor 3 gene that confers a gain of function [1, 2]. People with achondroplasia experience significant medical and functional complications over their lifespan [2]. There are currently no approved precision therapies that target the underlying molecular etiology of this condition. Vosoritide, a modified C-type natriuretic peptide, stimulates endochondral ossification and is in clinical development to evaluate its safety and efficacy for the treatment of individuals with achondroplasia [3–5].

Studies in achondroplasia mouse models showed that subcutaneous administration of vosoritide increased long-bone and craniofacial growth [3, 4]. These data led to a growth study (to establish baseline growth over at least 6 months) and a phase 2, open-label study in children aged 5 to <14 years with achondroplasia [5]. The safety and efficacy data from this study supported further clinical development of vosoritide at a dose of 15.0-µg-per-kilogram-per-day in children with achondroplasia in pivotal, randomized controlled studies. This phase 3 study was a 52-week, randomized, double-blind, placebo-controlled design, and conducted in 121 children with achondroplasia aged 5 to <18 years. Eligible children were randomized 1:1 to treatment with vosoritide or an identical matching placebo [6]. The mean difference in annualized growth velocity between participants in the vosoritide group and placebo group was 1.57 cm per year in favor of vosoritide (95% CI: [1.22, 1.93], two-sided p value <0.0001) [6]. In total, 119 participants experienced at least one adverse event; 59 in the vosoritide group (98.3%), and 60 in the placebo group (98.4%) [6].

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Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

Safety and Efficacy of Lonapegsomatropin in Children With Growth Hormone Deficiency: enliGHten Trial 2-Year Results

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Abstract

Purpose: The objectives of the ongoing, Phase 3, open-label extension trial enliGHten are to assess the long-term safety and efficacy of weekly administered long-acting growth hormone lonapegsomatropin in children with growth hormone deficiency.

Methods: Eligible subjects completing a prior Phase 3 lonapegsomatropin parent trial (heiGHt or fliGHt) were invited to participate. All subjects were treated with lonapegsomatropin. Subjects in the United States switched to the TransCon hGH Auto-Injector when available. Endpoints were long-term safety, annualized height velocity, pharmacodynamics [insulin-like growth factor-1 SD score (SDS) values], and patient- and caregiver-reported assessments of convenience and tolerability.

Results: Lonapegsomatropin treatment during enliGHten was associated with continued improvements in height SDS through week 104 in treatment-naïve subjects from the heiGHt trial (−2.89 to −1.37 for the lonapegsomatropin group; −3.0 to −1.52 for the daily somatropin group). Height SDS also continued to improve among switch subjects from the fliGHt trial (−1.42 at fliGHt baseline to −0.69 at week 78). After 104 weeks, the average bone age/chronological age ratio for each treatment group was 0.8 (0.1), showing only minimal advancement of bone age relative to chronological age with continued lonapegsomatropin treatment among heiGHt subjects. Fewer local tolerability reactions were reported with the TransCon hGH Auto-Injector compared with syringe/needle.

Conclusions: Treatment with lonapegsomatropin continued to be safe and well-tolerated, with no new safety signals identified. Children treated with once-weekly lonapegsomatropin showed continued improvement of height SDS through the second year of therapy without excess advancement of bone age.

Key Words: growth hormone, growth hormone deficiency, growth hormone replacement therapy, long-acting growth hormone, TransCon hGH, lonapegsomatropin

Growth hormone deficiency (GHD), characterized by insufficient levels of GH to sustain normal growth and metabolism, has been treated for decades with recombinant human GH (rhGH) (1). For more than 35 years after its advent, rhGH therapy for children with GHD had remained available only as a daily injection formulation. The necessary regimen of daily injections, which may be painful as well as stressful and cumbersome for children and caregivers, is a probable cause of nonadherence and decreased compliance, both of which have been linked to suboptimal height outcomes (2, 3). Up to 77% of adolescents with GHD may be noncompliant with daily injections (4). There is an unmet need for a less burdensome GH therapeutic that offers a combination of efficacy and safety comparable to daily-administered hGH.

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Research Article

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Switching to Weekly Lonapegsomatropin from Daily Somatropin in Children with Growth Hormone Deficiency: The fliGHt Trial

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Keywords
Growth hormone · Growth hormone deficiency · Growth hormone replacement therapy · Long-acting growth hormone · Lonapegsomatropin · TransCon human growth hormone

Abstract

Introduction: The phase 3 fliGHt Trial evaluated the safety and tolerability of once-weekly lonapegsomatropin, a long-acting prodrug, in children with growth hormone deficiency (GHD) who switched from daily somatropin therapy to lonapegsomatropin. ***Methods:*** This multicenter, open-label, 26-week phase 3 trial took place at 28 sites across 4 countries (Australia, Canada, New Zealand, and the USA). The trial enrolled 146 children with GHD, 143 of which were previously treated with daily somatropin. All subjects received once-weekly lonapegsomatropin 0.24 mg human growth hormone/kg/week. The primary outcome measure was safety and tolerability of lonapegsomatropin over 26 weeks. Secondary outcome measures assessed annualized height velocity (AHV), height standard deviation score (SDS), and IGF-1 SDS at 26 weeks. ***Results:*** Subjects had a mean prior daily somatropin dose of 0.29 mg/kg/week. Treatment-emergent adverse events (AEs) reported were similar to the published AE profile of daily somatropin therapies. After switching to lonapegsomatropin, the least-squares mean (LSM) AHV was 8.7 cm/year (95% CI: 8.2, 9.2) at Week 26 and LSM height SDS changed from baseline to Week 26 of +0.25 (95% CI: 0.21, 0.29). Among switch subjects, the LSM for average IGF-1 SDS was sustained at Weeks 13 and 26, representing an approximate 0.7 increase from baseline (prior to switching from daily somatropin therapy). Patient-reported outcomes indicated a preference for weekly lonapegsomatropin among both children and their parents. ***Conclusions:*** Lonapegsomatropin treatment outcomes were as expected across a range of ages and treatment experiences. Switching to lonapegsomatropin resulted in a similar AE profile to daily somatropin therapy.

Reprint Requests: Reprint requests should be addressed to the corresponding author.
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ΠΑΙΔΟ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ | ΧΡΙΣΤΙΝΑ ΤΑΤΣΗ

Marcela Vargas Trujillo*, Peter A. Lee, Kent Reifschneider, Philippe F. Backeljauw, Sanja Dragnic, Stephen Van Komen, Jun Yu and Karen O. Klein

Using change in predicted adult height during GnRH agonist treatment for individualized treatment decisions in girls with central precocious puberty

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Abstract

Objectives: It is important to understand what variables influence change in predicted adult height (PAH) throughout GnRHa treatment for central precocious puberty (CPP) to individualize treatment decisions and optimize care.
Methods: Changes in PAH, chronological age (CA), bone age (BA), BA/CA, and height velocity (HV) were evaluated in girls with CPP throughout treatment with leuprolide acetate (n=77). A second analysis focused on changes in the 3 years preceding the first observed BA of ≥12 years. Relationships were characterized using plot inspection and linear mixed-effects analyses. Association between treatment duration and last assessed PAH was examined using multiple linear regression models.
Results: BA/CA and HV showed a nonlinear change during treatment, with the largest changes and improvement in PAH observed in the first 6–18 months. Rate of BA advancement tended to decrease more slowly in girls initiating treatment at a younger BA. On-treatment change in PAH was predicted by concurrent BA/CA change, HV, and BA, as well as CA at treatment initiation. Last assessed PAH was positively associated with longer treatment durations (primary/exploratory models cut-offs of ≥33/≥55 months).
Conclusions: These findings support individualized monitoring during GnRHa treatment. Initial response should be interpreted with caution until 6–18 months after treatment initiation and failure should not be assumed based on continued bone maturation in girls starting therapy at a younger age. Treatment cessation should not be automatically based on a diminishing change in PAH or HV, as ongoing treatment may result in continued increase or maintenance of PAH.

Keywords: bone age; central precocious puberty; duration of therapy; height velocity; leuprolide; predicted adult height.

Introduction

Gonadotropin-releasing hormone agonist (GnRHa) therapy is the standard of care for treatment of central precocious puberty (CPP). One goal of GnRHa therapy is to slow the rate of bone maturation while maintaining an adequate height velocity (HV) in order to maximize the impact on adult height (AH) [1, 2]. Decisions to discontinue GnRHa therapy have commonly been based on predetermined single-variable factors, such as bone age (BA) of >12 years, chronological age (CA) of >10 years, or slower HV, assuming additional height benefit is not anticipated [1, 3–7]. Because many factors contribute to height outcomes and further height gain has been reported with continued treatment beyond these single-variable cutoffs, no single factor should be used as the basis for deciding to discontinue GnRHa treatment [1, 8]. Prior research informing these decisions focused on change in predicted AH (PAH) from the start to end of treatment and compared

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Clinical Research Article

Clinical Research Article

Weekly Lonapegsomatropin in Treatment-Naïve Children With Growth Hormone Deficiency: The Phase 3 heiGHt Trial

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Abstract

Context: For children with growth hormone deficiency (GHD), treatment burden with daily somatropin injections [human growth hormone (hGH)] is high, which may lead to poor adherence and suboptimal overall treatment outcomes. Lonapegsomatropin (TransCon hGH) is an investigational long-acting, once-weekly prodrug for the treatment of GHD.

Objective: The objective of this study was to evaluate the efficacy and safety of once-weekly lonapegsomatropin *vs* daily somatropin.

Design: The heiGHt trial was a randomized, open-label, active-controlled, 52-week Phase 3 trial (NCT02781727).

Setting: This trial took place at 73 sites across 15 countries.

Patients: This trial enrolled and dosed 161 treatment-naïve, prepubertal patients with GHD.

Interventions: Patients were randomized 2:1 to receive lonapegsomatropin 0.24 mg hGH/kg/week or an equivalent weekly dose of somatropin delivered daily.

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Clinical Research Article

Clinical Research Article

Zoledronic Acid vs Placebo in Pediatric Glucocorticoid-induced Osteoporosis: A Randomized, Double-blind, Phase 3 Trial

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Abbreviations: AE, adverse event; BMC, bone mineral content; BMD, bone mineral density; BS-ALP, bone-specific alkaline phosphatase; CTX, serum cross-linked C-telopeptide of type I collagen; DMD, Duchenne muscular dystrophy; DXA, dual-energy x-ray absorptiometry; GC, glucocorticoid; GIO, glucocorticoid-induced osteoporosis; IV, intravenous; LS, lumbar spine; NSAA, North Star Ambulatory Assessment; NTX, cross-linked N-teleopeptide; P1NP, N-terminal propeptide of type I collagen; PedsQL, Pediatric Quality of Life; SAE, serious adverse event; TRAP5b, tartrate-resistant acid phosphatase isoform 5b; VF, vertebral fracture; ZA, zoledronic acid.

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ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ

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Α' ΜΑΙΕΥΤΙΚΗ-ΓΥΝΑΙΚΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΑΠΘ

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human reproduction **ORIGINAL ARTICLE** ***Reproductive epidemiology***

Menstrual cycle characteristics and incident cancer: a prospective cohort study

Siwen Wang [1,2], Yi-Xin Wang [1], Helena Sandoval-Insausti[1], Leslie V. Farland [3], Jan L. Shifren[4], Dan Zhang [2], JoAnn E. Manson[5,6,7], Brenda M. Birmann [7], Walter C. Willett[1,5,7], Edward L. Giovannucci [1,5,7], Stacey A. Missmer[8], and Jorge E. Chavarro [1,5,7,*]

STUDY QUESTION: Are menstrual cycle characteristics throughout the reproductive lifespan associated with cancer risk?

SUMMARY ANSWER: Irregular and long menstrual cycles throughout the reproductive lifespan were associated with increased risk of total invasive cancer, especially obesity-related cancers.

WHAT IS KNOWN ALREADY: Long and irregular menstrual cycles have been associated with lower risk of pre-menopausal breast cancer and higher risk of endometrial cancer, but associations with other malignancies are less clear.

STUDY DESIGN, SIZE, DURATION: Prospective cohort study. Prospective follow-up of 78 943 women participating in the Nurses' Health Study II between 1989 and 2015.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We followed 78 943 pre-menopausal women without cancer history who reported the usual length and regularity of their menstrual cycles at different ages (14–17, 18–22 and 29–46 years). Cancer diagnosis was confirmed through medical record review and classified as obesity-related (colorectal, gallbladder, kidney, multiple myeloma, thyroid, pancreatic, esophageal, gastric, liver, endometrial, ovarian and post-menopausal breast) or non-obesity-related. We fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs of the association between menstrual cycle characteristics and cancer incidence.

MAIN RESULTS AND THE ROLE OF CHANCE: We documented 5794 incident cancer cases during 1 646 789 person-years of follow-up. After adjusting for BMI and other potential confounders, women reporting irregular cycles at age 29–46 years had an 11% (95% CI: 2–21%) higher risk of total invasive cancer than women reporting very regular cycles at the same age. This association was limited to obesity-related cancers, with a 23% (95% CI: 9–39%) higher risk and was strongest for endometrial cancer (HR = 1.39; 95% CI: 1.09–1.77). Findings were comparable for cycle characteristics earlier in life and for menstrual cycle length. Very irregular cycles at age 14–17 years were associated with significant increase in risk of colorectal cancer (HR = 1.36; 95% CI: 1.02–1.81).

LIMITATIONS, REASONS FOR CAUTION: Our study might be subject to recall bias for findings pertaining to cycle characteristics in adolescence and early adulthood, as these were retrospectively reported. Generalizability to non-White women may be limited, as 96% of participants were White.

WIDER IMPLICATIONS OF THE FINDINGS: Women with irregular or long menstrual cycles in mid-adulthood had a statistically significantly higher risk of developing cancer, especially obesity-related cancers. This association was not limited to gynecological cancers. Obesity-related cancers may need to be added to the spectrum of long-term health consequences of long or irregular cycles, possibly warranting targeted screening among women who experience long or irregular cycles in mid-adulthood.

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human reproduction **ORIGINAL ARTICLE** ***Puberty, aging and HRT***

Maternal polycystic ovarian syndrome and pubertal development in daughters and sons: a population-based cohort study

Lea Lykke Harrits Lunddorf [1,*], Linn Håkonsen Arendt[1,2], Andreas Ernst[1,3], Nis Brix[1,4], Ulla Brent Knudsen[2,5], Jørn Olsen[1,6], and Cecilia Høst Ramlau-Hansen[1]

STUDY QUESTION: Does maternal polycystic ovarian syndrome (PCOS) affect the timing of pubertal development in daughters and sons?

SUMMARY ANSWER: Maternal PCOS was associated with earlier adrenarche in daughters.

WHAT IS KNOWN ALREADY: Female adolescents with PCOS often experience earlier adrenarche compared to adolescents without PCOS, due to hyperandrogenism. Likewise, they usually have hyperandrogenism during pregnancy, which might potentially affect the development of the foetus, including its future reproductive health.

STUDY DESIGN, SIZE, DURATION: In this population-based cohort study, we included 15 596 mothers–child pairs from the Danish National Birth Cohort (DNBC) Puberty Cohort, who were followed from foetal life until full sexual maturation or 18 years of age.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Using register-based and self-reported information on maternal PCOS and menstrual irregularities, collected during pregnancy, we categorized the mothers as having PCOS (n = 251), oligomenorhoea (n = 134), 'other menstrual irregularities' (n = 2411) or no menstrual abnormalities (reference group, n = 12 800). The children provided self-reported information on pubertal development every 6 months from the age of 11 years. The main outcome measures were adjusted mean age differences (in months) at attaining several individual pubertal milestones using an interval-censored regression model, as well as the average difference in age at attaining all pubertal milestones combined into a single estimate using Huber–White robust variance estimation.

MAIN RESULTS AND THE ROLE OF CHANCE: We found that maternal PCOS was associated with an accelerated pubertal development in daughters with an overall average difference of −3.3 (95% CI: −6.3; −0.4) months based on all pubertal milestones compared to the reference group. When further looking into the average difference for adrenarche only (pubarche, axillary hair and acne), the average difference was −5.4 (95% CI: −8.7; −2.1) months compared to the reference group; whereas thelarche and menarche did not occur earlier in daughters of mothers with PCOS (average difference: −0.8 (95% CI: −3.9; 2.4) months). Oligomenorrhoea and 'other menstrual irregularities' were not associated with pubertal development in daughters. Neither PCOS, oligomenorrhoea nor 'other menstrual irregularities' were associated with pubertal development in sons.

LIMITATIONS, REASONS FOR CAUTION: We expect some degree of non-differential misclassification of maternal PCOS and menstrual irregularities as well as pubertal development in the children.

WIDER IMPLICATIONS OF THE FINDINGS: Maternal PCOS might accelerate adrenarche in daughters. Whether this is due to genetics, epigenetics or prenatal programming by hyperandrogenism in foetal life remains unsolved. The results from the present study can be generalized to Caucasian populations.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

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human reproduction **ORIGINAL ARTICLE** ***Reproductive epidemiology***

Polycystic ovary syndrome and risk of adverse pregnancy outcomes: a registry linkage study from Massachusetts

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STUDY QUESTION: Do women with polycystic ovary syndrome (PCOS) have a greater risk of adverse pregnancy complications (gestational diabetes, preeclampsia, cesarean section, placental abnormalities) and neonatal outcomes (preterm birth, small for gestational age, prolonged delivery hospitalization) compared to women without a PCOS diagnosis and does this risk vary by BMI, subfertility and fertility treatment utilization?

SUMMARY ANSWER: Deliveries to women with a history of PCOS were at greater risk of complications associated with cardiometabolic function, including gestational diabetes and preeclampsia, as well as preterm birth and prolonged length of delivery hospitalization.

WHAT IS KNOWN ALREADY: Prior research has suggested that women with PCOS may be at increased risk of adverse pregnancy outcomes. However, findings have been inconsistent possibly due to lack of consistent adjustment for confounding factors, small samples size and other sources of bias.

STUDY DESIGN, SIZE, DURATION: Massachusetts deliveries among women ≥18 years old during 2013–2017 from state vital records linked to hospital discharges, observational stays and emergency department visits were linked to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) and the Massachusetts All-Payers Claims Database (APCD).

PARTICIPANTS/MATERIALS, SETTING, METHODS: PCOS was identified by ICD9 and ICD10 codes in APCD prior to index delivery. Relative risks (RRs) and 95% CI for pregnancy and delivery complications were modeled using generalized estimating equations with a log link and a Poisson distribution to take multiple cycles into account and were adjusted *a priori* for maternal age, BMI, race/ethnicity, education, plurality, birth year, chronic hypertension and chronic diabetes. Tests for homogeneity investigated differences between maternal pre-pregnancy BMI categories (<30, ≥30, <25 and ≥25 kg/m^2) and between non-infertile deliveries and deliveries that used ART or had a history of subfertility (defined by birth certificates, SART CORS records, APCD or hospital records).

MAIN RESULTS AND THE ROLE OF CHANCE: Among 91 825 deliveries, 3.9% had a history of PCOS. Women with a history of PCOS had a 51% greater risk of gestational diabetes (CI: 1.38–1.65) and a 25% greater risk of preeclampsia (CI: 1.15–1.35) compared to women without a diagnosis of PCOS. Neonates born to women with a history of PCOS were more likely to be born preterm (RR: 1.17, CI: 1.06–1.29) and more likely to have a prolonged delivery hospitalization after additionally adjusting for gestational age (RR: 1.23, CI: 1.09–1.40) compared to those of women without a diagnosis of PCOS. The risk for gestational diabetes for women with PCOS was greater among women with a pre-pregnancy BMI <30 kg/m^2.

LIMITATIONS, REASONS FOR CAUTION: PCOS was defined by ICD documentation prior to delivery so there may be women with undiagnosed PCOS or PCOS diagnosed after delivery included in the unexposed group. The study population is limited to deliveries within Massachusetts among most private insurance payers and inpatient or observational hospitalization in Massachusetts during the follow-up window, therefore there may be diagnoses and or deliveries outside of the state or outside of our sample that were not captured.

WIDER IMPLICATIONS OF THE FINDINGS: In this population-based study, women with a history of PCOS were at greater risk of pregnancy complications associated with cardiometabolic function and preterm birth. Obstetricians should be aware of patients' PCOS status and closely monitor for potential pregnancy complications to improve maternal and infant perinatal health outcomes.

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human reproduction **ORIGINAL ARTICLE** ***Reproductive epidemiology***

Association of PCOS with offspring morbidity: a longitudinal cohort study

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STUDY QUESTION: Do children whose mothers have polycystic ovary syndrome (PCOS) have an increased risk of morbidity?

SUMMARY ANSWER: Maternal PCOS is associated with an increased risk of infection, allergy and other childhood morbidity.

WHAT IS KNOWN ALREADY: PCOS is associated with higher rates of gestational diabetes, pre-eclampsia and preterm delivery, but the long-term impact on child health is poorly understood.

STUDY DESIGN, SIZE, DURATION: We conducted a retrospective longitudinal cohort study of 1 038 375 children in Quebec between 2006 and 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We included 7160 children whose mothers had PCOS and 1 031 215 unexposed children. Outcomes included child hospitalization for infectious, allergic, malignant and other diseases before 13 years of age. We estimated hazard ratios (HRs) and 95% CI for the association of PCOS with childhood morbidity in adjusted Cox proportional hazards regression models.

MAIN RESULTS AND THE ROLE OF CHANCE: Children exposed to PCOS were hospitalized at a rate of 68.9 (95% CI 66.2–71.8) per 1000 person-years, whereas unexposed children were hospitalized at a rate of 45.3 (95% CI 45.1–45.5) per 1000 person-years. Compared with no exposure, maternal PCOS was associated with 1.32 times the risk of any childhood hospitalization (95% CI 1.26–1.40), 1.31 times the risk of infectious disease hospitalization (95% CI 1.25–1.38) and 1.47 times the risk of allergy-related hospitalization (95% CI 1.31–1.66). Risk of hospitalization was also elevated for childhood metabolic (HR 1.59, 95% CI 1.16–2.18), gastrointestinal (HR 1.72, 95% CI 1.53–1.92), central nervous system (HR 1.74, 95% CI 1.46–2.07) and otologic disorders (HR 1.34, 95% CI 1.26–1.43). Subgroup analyses suggested that there was little difference in the association of PCOS with hospitalization among boys (HR 1.31, 95% CI 1.24–1.39) and girls (HR 1.34, 95% CI 1.26–1.43).

LIMITATIONS, REASONS FOR CAUTION: We analyzed severe childhood morbidity requiring hospitalization, not mild diseases treated in ambulatory clinics. We lacked data on ethnicity, education and physical activity, and cannot rule out residual confounding.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings suggest that maternal PCOS is associated with an increased risk of childhood morbidity.

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human reproduction **META-ANALYSIS** ***Reproductive epidemiology***

Live birth rate after female fertility preservation for cancer or haematopoietic stem cell transplantation: a systematic review and meta-analysis of the three main techniques; embryo, oocyte and ovarian tissue cryopreservation

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STUDY QUESTION: What are the chances of achieving a live birth after embryo, oocyte and ovarian tissue cryopreservation (OTC) in female cancer survivors?

SUMMARY ANSWER: The live birth rates (LBRs) following embryo and oocyte cryopreservation are 41% and 32%, respectively, while for IVF and spontaneous LBR after tissue cryopreservation and transplantation, these rates are 21% and 33%, respectively.

WHAT IS KNOWN ALREADY: Currently, fertility preservation (FP) has become a major public health issue as diagnostic and therapeutic progress has made it possible to achieve an 80% survival rate in children, adolescents and young adults with cancer. In the latest ESHRE guidelines, only oocyte and embryo cryopreservation are considered as established options for FP. OTC is still considered to be an innovative method, while it is an acceptable FP technique in the American Society for Reproductive Medicine guidelines. However, given the lack of studies on long-term outcomes after FP, it is still unclear which technique offers the best chance to achieve a live birth.

STUDY DESIGN, SIZE, DURATION: We performed a systematic review and meta-analysis of published controlled studies. Searches were conducted from January 2004 to May 2021 in Medline, Embase and the Cochrane Library using the following search terms: cancer, stem cell transplantation, FP, embryo cryopreservation, oocyte vitrification, OTC and reproductive outcome.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 126 full-text articles were preselected from 1436 references based on the title and abstract and assessed via the Newcastle–Ottawa Quality Assessment Scale. The studies were selected, and their data were extracted by two independent reviewers according to the Cochrane methods. A fixed-effect meta-analysis was performed for outcomes with high heterogeneity.

MAIN RESULTS AND THE ROLE OF CHANCE: Data from 34 studies were used for this meta-analysis. Regarding cryopreserved embryos, the LBR after IVF was 41% (95% CI: 34–48, I^2: 0%, fixed effect). Concerning vitrified oocytes, the LBR was 32% (95% CI: 26–39, I^2: 0%, fixed effect). Finally, the LBR after IVF and the spontaneous LBR after ovarian tissue transplantation were 21% (95% CI: 15–26, I^2: 0%, fixed-effect) and 33% (95% CI: 25–42, I^2: 46.1%, random-effect), respectively. For all outcomes, in the sensitivity analyses, the maximum variation in the estimated percentage was 1%.

LIMITATIONS, REASONS FOR CAUTION: The heterogeneity of the literature prevents us from comparing these three techniques. This meta-analysis provides limited data which may help clinicians when counselling patients.

WIDER IMPLICATIONS OF THE FINDINGS: This study highlights the need for long-term follow-up registries to assess return rates, as well as spontaneous pregnancy rates and birth rates after FP.

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human reproduction update

Fresh and cryopreserved ovarian tissue transplantation for preserving reproductive and endocrine function: a systematic review and individual patient data meta-analysis

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BACKGROUND: Ovarian tissue cryopreservation involves freezing and storing of surgically retrieved ovarian tissue in liquid or vapour nitrogen below −190°C. The tissue can be thawed and transplanted back with the aim of restoring fertility or ovarian endocrine function. The techniques for human ovarian tissue freezing and transplantation have evolved over the last 20 years, particularly in the context of fertility preservation in pre-pubertal cancer patients. Fresh ovarian tissue transplantation, using an autograft or donor tissue, is a more recent development; it has the potential to preserve fertility and hormonal function in women who have their ovaries removed for benign gynaecological conditions. The techniques of ovarian tissue cryopreservation and transplantation have progressed rapidly since inception; however, the evidence on the success of this intervention is largely based on case reports and case series.

OBJECTIVE AND RATIONALE: The aim of this study was to systematically review the current evidence by incorporating study-level and individual patient-level meta-analyses of women who received ovarian transplants, including frozen–thawed transplant, fresh or donor graft.

SEARCH METHODS: The review protocol was registered with PROSPERO (CRD42018115233). A comprehensive literature search was performed using MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials from database inception to October 2020. Authors were also contacted for individual patient data if relevant outcomes were not reported in the published manuscripts. Meta-analysis was performed using inverse-variance weighting to calculate summary estimates using a fixed-effects model.

OUTCOMES: The review included 87 studies (735 women). Twenty studies reported on ≥5 cases of ovarian transplants and were included in the meta-analysis (568 women). Fertility outcomes included pregnancy, live birth and miscarriage rates, and endocrine outcomes included oestrogen, FSH and LH levels. The pooled rates were 37% (95% CI: 32–43%) for pregnancy, 28% (95% CI: 24–34%) for live birth and 37% (95% CI: 30–46%) for miscarriage following frozen ovarian tissue transplantation. Pooled mean for pre-transplant oestrogen was 101.6 pmol/l (95% CI: 47.9–155.3), which increased post-transplant to 522.4 pmol/l (95% CI: 315.4–729; mean difference: 228.24; 95% CI: 180.5–276). Pooled mean of pre-transplant FSH was 66.4 IU/l (95% CI: 52.8–84), which decreased post-transplant to 14.1 IU/l (95% CI: 10.9–17.3; mean difference 61.8; 95% CI: 57–66.6). The median time to return of FSH to a value <25 IU/l was 19 weeks (interquartile range: 15–26 weeks; range: 0.4–208 weeks). The median duration of graft function was 2.5 years (interquartile range: 1.4–3.4 years; range: 0.7–5 years). The analysis demonstrated that ovarian tissue cryopreservation and transplantation could restore reproductive and hormonal functions in women. Further studies with larger samples of well-characterized populations are required to define the optimal retrieval, cryopreservation and transplantation processes.

WIDER IMPLICATIONS: Ovarian tissue cryopreservation and transplantation may not only be effective in restoring fertility but also the return of reproductive endocrine function. Although this technology was developed as a fertility preservation option, it may have the scope to be considered for endocrine function preservation.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

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human reproduction ORIGINAL ARTICLE *Reproductive endocrinology*

The effect of Covid-19 mRNA vaccine on serum anti-Müllerian hormone levels

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STUDY QUESTION: Does the administration of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine have an association with ovarian reserve as expressed by circulating anti-Müllerian hormone (AMH) levels?

SUMMARY ANSWER: Ovarian reserve as assessed by serum AMH levels is not altered at 3 months following mRNA SARS-CoV-2 vaccination.

WHAT IS KNOWN ALREADY: A possible impact of SARS-CoV-2 infection or vaccination through an interaction between the oocyte and the somatic cells could not be ruled out, however, data are limited.

STUDY DESIGN, SIZE, DURATION: This is a prospective study conducted at a university affiliated tertiary medical center between February and March 2021.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Study population included reproductive aged women (18–42 years) that were vaccinated by two Pfizer-BioNTech Covid-19 vaccines (21 days apart). Women with ovarian failure, under fertility treatments, during pregnancy, previous Covid-19 infection or vaccinated were excluded from the study. Blood samples were collected for AMH levels before the first mRNA vaccine administration. Additional blood samples after 3 months were collected for AMH and anti-Covid-19 antibody levels. Primary outcome was defined as the absolute and percentage change in AMH levels.

MAIN RESULTS AND THE ROLE OF CHANCE: The study group consisted of 129 women who received two mRNA vaccinations. Mean AMH levels were 5.3 (±SD 4.29) μg/l and 5.3 (±SD 4.50) μg/l at baseline and after 3 months, respectively ($P=0.11$). To account for possible age-specific changes of AMH, sub-analyses were performed for three age groups: <30, 30–35 and >35 years. AMH levels were significantly lower for women older than 35 years at all times ($P=0.001$ for pre and post vaccination AMH levels versus younger women). However, no significant differences for the changes in AMH levels before and after vaccinations (Delta AMH) were observed for the three age groups ($P=0.46$). Additionally, after controlling for age, no association was found between the degree of immunity response and AMH levels.

LIMITATIONS, REASONS FOR CAUTION: Although it was prospectively designed, for ethical reasons we could not assign a priori a randomized unvaccinated control group. This study examined plasma AMH levels at 3 months after the first vaccination. It could be argued that possible deleterious ovarian and AMH changes caused by the SARS-CoV-2 mRNA vaccinations might take effect only at a later time. Only longer-term studies will be able to examine this issue.

WIDER IMPLICATIONS OF THE FINDINGS: The results of the study provide reassurance for women hesitant to complete vaccination against Covid 19 due to concerns regarding its effect on future fertility. This information could be of significant value to physicians and patients alike.

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REVIEW AND SCHOLARLY DIALOG

Open camera or QR reader and scan code to access this article and other resources online.

Impact of Thyroid Autoimmunity on Assisted Reproductive Technology Outcomes and Ovarian Reserve Markers: An Updated Systematic Review and Meta-Analysis

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Background: Thyroid autoimmunity (TAI) has a high prevalence among women of reproductive age. Investigating its possible impact on ovarian function and fertility is, thus, of utmost relevance. The aim of this systematic review and meta-analysis was to elucidate the effect of TAI on both assisted reproductive technology (ART) outcomes and ovarian reserve.

Methods: This systematic review and meta-analysis was restricted to two groups of research articles investigating the association between TAI and: (1) autologous ART outcomes (i.e., fertilization rate [FR], implantation rate, clinical pregnancy rate [CPR], miscarriage rate, and live birth rate), (2) markers of ovarian reserve (i.e., anti-Müllerian hormone, basal follicle stimulating hormone, antral follicle count, and number of oocytes retrieved). Studies including women affected by overt hypo/hyperthyroidism were excluded. Relevant studies were identified by a systematic search in PubMed, MEDLINE, ClinicalTrials.gov, Embase, and Scopus, from database inception to May 1, 2022.

Results: From a total of 432 identified publications, 22 studies were included in Group 1 and 26 studies in Group 2. The presence of TAI was associated with a higher risk of miscarriage (7606 participants, odds ratio [OR] 1.52, confidence interval [CI 1.14–2.01], $p=0.004$, $I^2=53\%$), lower chance of embryo implantation (7118 participants, OR 0.72, [CI 0.59–0.88], $p=0.001$, $I^2=36\%$), and live birth (11417 participants, OR 0.73, [CI 0.56–0.94], $p=0.02$, $I^2=71\%$). These associations were no longer observed in a subgroup analysis of patients who exclusively underwent intracytoplasmic sperm injection (ICSI). The FR and CPR as well as the mean values of surrogate markers of oocyte quantity appeared not to be affected by TAI.

Conclusions: This data synthesis suggest a higher risk of adverse ART outcomes in women with positive TAI. However, the reliability of these findings is hampered by the relatively low quality of the evidence and significant heterogeneity in many of the meta-analyses. The possible protective effect of ICSI is promising but should be confirmed in controlled prospective clinical trials.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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See Comment page 299

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Summary

Background Women positive for thyroid peroxidase antibodies (TPO-Ab) have a higher risk of recurrent pregnancy loss. Evidence on whether levothyroxine treatment improves pregnancy outcomes in women who are TPO-Ab positive women with recurrent pregnancy loss is scarce. The aim of this study was to determine if levothyroxine increases live birth rates in women who were TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

Methods The T4LIFE trial was an international, double-blind, placebo-controlled, phase 3 study done in 13 secondary and tertiary hospitals in the Netherlands, one tertiary hospital in Belgium, and one tertiary hospital in Denmark. Women (18–42 years) who were TPO-Ab positive, had two or more pregnancy losses, and had a thyroid stimulating hormone (TSH) concentration within the institutional reference range were eligible for inclusion. Women were excluded if they had antiphospholipid syndrome (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or β2-glycoprotein-I IgG or IgM antibodies), other autoimmune diseases, thyroid disease, previous enrolment in this trial, or contraindications for levothyroxine use. Before conception, women were randomly assigned (1:1) to receive either levothyroxine or placebo orally once daily. The daily dose of levothyroxine was based on preconception TSH concentration and ranged from 0·5–1·0 µg/kg bodyweight. Levothyroxine or placebo was continued until the end of pregnancy. The primary outcome was live birth, defined as the birth of a living child beyond 24 weeks of gestation measured in the intention-to-treat population. The trial was registered within the Netherlands Trial Register, NTR3364 and with EudraCT, 2011-001820-39.

Results Between Jan 1, 2013, and Sept 19, 2019, 187 women were included in the study: 94 (50%) were assigned to the levothyroxine group and 93 (50%) were assigned to the placebo group. The trial was prematurely stopped when 187 (78%) of the 240 predefined patients had been included because of slow recruitment. 47 (50%) women in the levothyroxine group and 45 (48%) women in the placebo group had live births (risk ratio 1·03 [95% CI 0·77 to 1·38]; absolute risk difference 1·6% [95% CI −12·7 to 15·9]). Seven (7%) women in the levothyroxine group and seven (8%) in the placebo group reported adverse events, none of them were directly related to the study procedure.

Interpretation Compared with placebo, levothyroxine treatment did not result in higher live birth rates in euthyroid women with recurrent pregnancy loss who were positive for TPO-Ab. On the basis of our findings, we do not advise routine use of levothyroxine in women who are TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

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Clinical Research Article

Clinical Research Article

Early-Pregnancy Intermediate Hyperglycemia and Adverse Pregnancy Outcomes Among Women Without Gestational Diabetes

Yunzhen Ye,[1,2] Yu Xiong,[1,2] Qiongjie Zhou,[1,2] Xirong Xiao,[1,2,*] and Xiaotian Li[1,2,*]

Abstract

Context: Universal early-pregnancy screening for overt diabetes reveals intermediate hyperglycemia (fasting plasma glucose [FPG] [5.1-6.9 mM]).

Objective: We evaluated the association between early-pregnancy intermediate hyperglycemia and adverse pregnancy outcomes among women without gestational diabetes.

Methods: This retrospective cohort study was conducted at the Obstetrics and Gynecology Hospital, Shanghai, China, from 2013 to 2017. All singleton pregnancies with FPG less than or equal to 6.9 mM in early pregnancy and receiving a 75-g oral glucose tolerance test (OGTT) were included. Women with prepregnancy diabetes were excluded. Individuals with normal OGTT were analyzed. Pregnancy outcomes for FPG less than 5.1 mM and intermediate hyperglycemia were evaluated. The primary outcomes were large for gestational age (LGA) and primary cesarean delivery. Multivariate logistic regressions were conducted. Statistical significance was defined as *P* less than .05.

Results: In total, 24 479 deliveries were included, of which 23 450 (95.8%) had normal OGTTs later in pregnancy (NGT). There were 807 (3.4%) women who had an FPG of 5.1 to 6.9 mM in early pregnancy. Compared to the NGT group with an FPG of less than 5.1 mM in early pregnancy (N = 20692), the intermediate hyperglycemia NGT group (N = 693) had a higher age and body mass index (BMI), and significantly higher rates of LGA, primary cesarean delivery, preterm birth, preeclampsia, and neonatal distress. The rates of primary cesarean delivery (adjusted odds ratio [AOR] 1.24; 95% CI, 1.05-1.45), preterm birth (AOR 1.75; 95% CI, 1.29-2.36), and neonatal distress (AOR 3.29; 95% CI, 1.57-6.89) remained statistically significantly higher after adjustments for maternal age, BMI, and other potential confounding factors.

Conclusion: Women with intermediate hyperglycemia in early pregnancy are at an increased risk for adverse maternal-fetal outcomes, even with normal future OGTTs.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

The NEW ENGLAND JOURNAL of MEDICINE
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Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

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ABSTRACT

BACKGROUND
Treatment of gestational diabetes improves maternal and infant health, although diagnostic criteria remain unclear.

METHODS
We randomly assigned women at 24 to 32 weeks' gestation in a 1:1 ratio to be evaluated for gestational diabetes with the use of lower or higher glycemic criteria for diagnosis. The lower glycemic criterion was a fasting plasma glucose level of at least 92 mg per deciliter (≥5.1 mmol per liter), a 1-hour level of at least 180 mg per deciliter (≥10.0 mmol per liter), or a 2-hour level of at least 153 mg per deciliter (≥8.5 mmol per liter). The higher glycemic criterion was a fasting plasma glucose level of at least 99 mg per deciliter (≥5.5 mmol per liter) or a 2-hour level of at least 162 mg per deciliter (≥9.0 mmol per liter). The primary outcome was the birth of an infant who was large for gestational age (defined as a birth weight above the 90th percentile according to Fenton–World Health Organization standards). Secondary outcomes were maternal and infant health.

RESULTS
A total of 4061 women underwent randomization. Gestational diabetes was diagnosed in 310 of 2022 women (15.3%) in the lower-glycemic-criteria group and in 124 of 2039 women (6.1%) in the higher-glycemic-criteria group. Among 2019 infants born to women in the lower-glycemic-criteria group, 178 (8.8%) were large for gestational age, and among 2031 infants born to women in the higher-glycemic-criteria group, 181 (8.9%) were large for gestational age (adjusted relative risk, 0.98; 95% confidence interval, 0.80 to 1.19; P=0.82). Induction of labor, use of health services, use of pharmacologic agents, and neonatal hypoglycemia were more common in the lower-glycemic-criteria group than in the higher-glycemic-criteria group. The results for the other secondary outcomes were similar in the two trial groups, and there were no substantial between-group differences in adverse events. Among the women in both groups who had glucose test results that fell between the lower and higher glycemic criteria, those who were treated for gestational diabetes (195 women), as compared with those who were not (178 women), had maternal and infant health benefits, including fewer large-for-gestational-age infants.

CONCLUSIONS
The use of lower glycemic criteria for the diagnosis of gestational diabetes did not result in a lower risk of a large-for-gestational-age infant than the use of higher glycemic criteria. (Funded by the Health Research Council of New Zealand and others; GEMS Australian New Zealand Clinical Trials Registry number, ACTRN12615000290594.)

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*The members of the GEMS Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

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Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

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Original article

Is premature ovarian insufficiency associated with mortality? A three-decade follow-up cohort

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ARTICLE INFO

Keywords:
Premature ovarian insufficiency
Risk factors
Death
Mortality
Cohort

ABSTRACT

Objective: To evaluate the association between premature ovarian insufficiency (POI) and mortality.
Materials and methods: This was a secondary analysis of a long-term cohort of Chilean women who received preventive health care between 1990 and 1993. The exposure variable was POI and the outcome was death, and follow-up time was 30 years. Patient data were extracted from medical records. Data related to deaths were obtained from the records of the official government registry as of January 2021. Cox regression proportional hazard models were used to estimate crude and adjusted hazard ratios (HR) and 95 % confidence intervals (CI).
Results: Data for a total of 1119 women were included in the analysis. Median age was 47 years (interquartile range: 44–52). The baseline prevalence of POI was 6.7 %. At the end of the follow-up, 34.7 % of women with POI had died, compared with 19.3 % of women without the condition ($p < 0.001$). A larger proportion of women with POI died from cardiovascular disease (12.0 % vs. 5.1 %; OR: 2.55, 95 % CI: 1.21–5.39) whereas there was no significant difference in cancer mortality (6.7 % vs. 7.7 %; OR: 0.86, 95 % CI: 0.34–2.19). In the adjusted Cox model, POI was among the main factors associated with mortality (hazard ratio [HR] 1.60, 95 % CI: 1.03–2.47), after diabetes (HR 2.51, 95 % CI: 1.40–4.51) and arterial hypertension (HR 1.75, 95 % CI: 1.29–2.37).
Conclusion: Although POI affects a small group of women, its association with mortality seems to be relevant; hence it is necessary to implement measures that reduce this risk.

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Association between reproductive lifespan and risk of incident type 2 diabetes and hypertension in postmenopausal women: Findings from a 20-year prospective study

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ARTICLE INFO

Keywords:
Type 2 diabetes
Hypertension
Reproductive lifespan
Menarche
Menopause

ABSTRACT

Background: This study examined the association between reproductive lifespan and incident type 2 diabetes mellitus (T2DM) and hypertension in mid-age women. Also, the combined effect of reproductive lifespan and body mass index (BMI) on the risks of T2DM and hypertension were explored.
Methods: Reproductive lifespan was defined as the difference between age at menopause and age at menarche and categorized as <35, 35–37, 38–40, and ≥41 years based on the quartile distribution. A multivariable Cox proportional hazard regression was used, adjusting for socio-demographic, lifestyle, and reproductive factors.
Results: Of 6357 postmenopausal women included (mean [SD] age at last follow-up, 66.3[3.3] years), a total of 655 developed incident T2DM (10.3%) and 1741 developed hypertension (30.0%) during 20 years of follow-up. The total sample had a mean (SD) reproductive lifespan of 37.9 (4.5). Compared with the women who had a reproductive lifespan of 38–40 years, those with a short reproductive lifespan (<35 years) had a 30% increased risk of T2DM and twice the risk of hypertension. Under the combined model, women who had a short reproductive lifespan (<35 years) and who had a BMI ≥30 kg/m^2 at baseline showed a higher risk of T2DM (HR: 6.30, 95% CI: 4.41–8.99) and hypertension (HR: 6.06, 4.86–7.55) compared with women who had a reproductive lifespan of 38–40 years and a BMI < 25 kg/m^2.
Conclusions: A higher risk of both incident T2DM and hypertension at midlife was found among women experiencing a shorter reproductive lifespan, with pronounced risk for women experiencing both a short reproductive lifespan (<35 years) and a higher baseline BMI (≥30 kg/m^2). Women with a short reproductive lifespan may benefit from maintaining healthy body weight in midlife.

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Clinical Research Article

Clinical Research Article

Associations of Age at Menopause With Postmenopausal Bone Mineral Density and Fracture Risk in Women

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Abstract

Context: Menopause before age 45 is a risk factor for fractures, but menopause occurs at age ≥45 in ~90% of women.
Objective: To determine, in women with menopause at age ≥45, whether (1) years since the final menstrual period (FMP) is more strongly associated with postmenopausal bone mineral density (BMD) than chronological age and (2) lower age at FMP is related to more fractures.
Design and Setting: The Study of Women's Health Across the Nation, a longitudinal cohort study of the menopause transition (MT).
Participants: A diverse cohort of ambulatory women (pre- or early perimenopausal at baseline, with 15 near-annual follow-up assessments).
Main Outcome Measures: Postmenopausal lumbar spine (LS) or femoral neck (FN) BMD (n = 1038) and time to fracture (n = 1554).
Results: Adjusted for age, body mass index (BMI), cigarette use, alcohol intake, baseline LS or FN BMD, baseline MT stage, and study site using multivariable linear regression, each additional year after the FMP was associated with 0.006 g/cm^2 ($P < 0.0001$) and 0.004 g/cm^2 ($P < 0.0001$) lower postmenopausal LS and FN BMD, respectively. Age was not related to FN BMD independent of years since FMP. In Cox proportional hazards regression, accounting for race/ethnicity, BMI, cigarette use, alcohol intake, prior fracture, diabetes status, exposure to bone-modifying medications/supplements, and study site, the hazard for incident fracture was 5% greater for each 1-year decrement in age at FMP ($P = 0.02$).
Conclusions: Years since the FMP is more strongly associated with postmenopausal BMD than chronological age, and earlier menopause is associated with more fractures.

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human reproduction **ORIGINAL ARTICLE** ***Reproductive epidemiology***

Menopause, hysterectomy, menopausal hormone therapy and cause-specific mortality: cohort study of UK Biobank participants

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STUDY QUESTION: What is the association between menopausal hormone therapy (MHT) and cause-specific mortality?

SUMMARY ANSWER: Self-reported MHT use following early natural menopause, surgical menopause or premenopausal hysterectomy is associated with a lower risk of breast cancer mortality and is not consistently associated with the risk of mortality from cardiovascular disease or other causes.

WHAT IS KNOWN ALREADY: Evidence from the Women's Health Initiative randomized controlled trials showed that the use of estrogen alone is not associated with the risk of cardiovascular mortality and is associated with a lower risk of breast cancer mortality, but evidence from the Million Women Study showed that use of estrogen alone is associated with a higher risk of breast cancer mortality.

STUDY DESIGN, SIZE, DURATION: Cohort study (the UK Biobank), 178 379 women, recruited in 2006–2010.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Postmenopausal women who had reported age at menopause (natural or surgical) or hysterectomy, and information on MHT and cause-specific mortality. Age at natural menopause, age at surgical menopause, age at hysterectomy and MHT were exposures of interest. Natural menopause was defined as spontaneous cessation of menstruation for 12 months with no previous hysterectomy or oophorectomy. Surgical menopause was defined as the removal of both ovaries prior to natural menopause. Hysterectomy was defined as removal of the uterus before natural menopause without bilateral oophorectomy. The study outcome was cause-specific mortality.

MAIN RESULTS AND THE ROLE OF CHANCE: Among the 178 379 women included, 136 790 had natural menopause, 17 569 had surgical menopause and 24 020 had hysterectomy alone. Compared with women with natural menopause at the age of 50–52 years, women with natural menopause before 40 years (hazard ratio (HR): 2.38, 95% CI: 1.64, 3.45) or hysterectomy before 40 years (HR: 1.60, 95% CI: 1.23, 2.07) had a higher risk of cardiovascular mortality but not cancer mortality. MHT use was associated with a lower risk of breast cancer mortality following surgical menopause before 45 years (HR: 0.17, 95% CI: 0.08, 0.36), at 45–49 years (HR: 0.15, 95% CI: 0.07, 0.35) or at ≥50 years (HR: 0.28, 95% CI: 0.13, 0.63), and the association between MHT use and the risk of breast cancer mortality did not differ by MHT use duration (<6 or 6–20 years). MHT use was also associated with a lower risk of breast cancer mortality following natural menopause before 45 years (HR: 0.59, 95% CI: 0.36, 0.95) or hysterectomy before 45 years (HR: 0.49, 95% CI: 0.32, 0.74).

LIMITATIONS, REASONS FOR CAUTION: Self-reported data on age at natural menopause, age at surgical menopause, age at hysterectomy and MHT.

WIDER IMPLICATIONS OF THE FINDINGS: The current international guidelines recommend women with early menopause to use MHT until the average age at menopause. Our findings support this recommendation.

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Vasomotor symptoms and carotid artery intima-media thickness among Korean midlife women

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ABSTRACT

Objectives: To evaluate the association between vasomotor symptoms (VMS) and carotid intima-media thickness (CIMT) in Korean midlife women.
Study design: This cross-sectional study included 918 Korean women aged 45–65 years who attended their routine health checkup at a single institution between 2013 and 2016.
Main outcome measures: All participants' results on the Menopause Rating Scale were used to assess the VMS. Severe and very severe VMS were combined into severe VMS. CIMT and blood flow velocities were measured on the common carotid arteries using duplex ultrasound.
Results: All participants' mean age was 54.73 ± 5.37 years, and 627 (68.3%) were postmenopausal. A total of 401 (43.7%) women reported VMS: 217 (23.6%), mild; 109 (11.9%), moderate; and 75 (8.2%), severe. The mean CIMT was 0.062 ± 0.017 mm and 0.064 ± 0.019 mm in premenopausal and menopausal women, respectively. In the multivariate linear regression analysis, the CIMT of women with moderate VMS was 0.102 mm (95% confidence interval [CI] – 0.002–0.009) more than that of women with no VMA, and the CIMT of women with severe VMS was 0.246 mm (95% CI – 0.012–0.021) more than that of women with no VMS, after adjusting for several confounders, including age, body mass index, and lifestyle factors. Severe VMS were associated with the risk of thickened CIMT (≥0.075 mm) and/or plaques (odds ratio – 2.90, 95% CI – 1.74–4.84) in the logistic regression analysis after adjusting for the same variables.
Conclusions: Moderate and severe VMS are independently associated with increased CIMT in otherwise healthy Korean midlife women. Clinicians managing midlife women with bothersome VMS should consider screening for subclinical cardiovascular diseases.

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Clinical Research Article

Clinical Research Article

Oral Contraceptive and Menopausal Hormone Therapy Use and Risk of Pituitary Adenoma: Cohort and Case-Control Analyses

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Abbreviations: BMI, body mass index; OC, oral contraceptive; ICD, International Classification of Diseases; MHT, menopausal hormone therapy; MVHR, multivariable-adjusted hazard ratio; MVOR, multivariable-adjusted odds ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RPDR, Mass General Brigham Research Patient Data Registry.

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Abstract

Context: No prospective epidemiologic studies have examined associations between use of oral contraceptives (OCs) or menopausal hormone therapy (MHT) and risk of pituitary adenoma in women.

Objective: Our aim was to determine the association between use of OC and MHT and risk of pituitary adenoma in two separate datasets.

Methods: We evaluated the association of OC/MHT with risk of pituitary adenoma in the Nurses' Health Study and Nurses' Health Study II by computing multivariable-adjusted hazard ratios (MVHR) of pituitary adenoma by OC/MHT use using Cox proportional hazards models. Simultaneously, we carried out a matched case-control study using an institutional data repository to compute multivariable-adjusted odds ratios (MVOR) of pituitary adenoma by OC/MHT use.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

Results: In the cohort analysis, during 6 668 019 person-years, 331 participants reported a diagnosis of pituitary adenoma. Compared to never-users, neither past (MVHR = 1.05; 95% CI, 0.80-1.36) nor current OC use (MVHR = 0.72; 95% CI, 0.40-1.32) was associated with risk. For MHT, compared to never-users, both past (MVHR = 2.00; 95% CI, 1.50-2.68) and current use (MVHR = 1.80; 95% CI, 1.27-2.55) were associated with pituitary adenoma risk, as was longer duration (MVHR = 2.06; 95% CI, 1.42-2.99 comparing more than 5 years of use to never, *P* trend = .002). Results were similar in lagged analyses, when stratified by body mass index, and among those with recent health care use. In the case-control analysis, we included 5469 cases. Risk of pituitary adenoma was increased with ever use of MHT (MVOR = 1.57; 95% CI, 1.35-1.83) and OC (MVOR = 1.27; 95% CI, 1.14-1.42) compared to never.

Conclusion: Compared to never use, current and past MHT use and longer duration of MHT use were positively associated with higher risk of pituitary adenoma in 2 independent data sets. OC use was not associated with risk in the prospective cohort analysis and was associated with only mildly increased risk in the case-control analysis.

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Original article

EMAS position statement: Vitamin D and menopausal health

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ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ | ΠΑΝΑΓΙΩΤΗΣ Γ. ΑΝΑΓΝΩΣΤΗΣ

ABSTRACT

Introduction: There is increasing evidence that vitamin D has widespread tissue effects. In addition to osteoporosis, vitamin D deficiency has been associated with cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease. However, the effect of vitamin D supplementation on non-skeletal outcomes requires clarification, especially in postmenopausal women.

Aim: This position statement provides an evidence-based overview of the role of vitamin D in the health of postmenopausal women based on observational and interventional studies.

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

Results and conclusions: Vitamin D status is determined by measuring serum 25-hydroxyvitamin D levels. Concentrations <20 ng/ml (<50 nmol/l) and <10 ng/ml (<25 nmol/l) are considered to constitute vitamin D deficiency and severe deficiency, respectively. Observational data suggest an association between vitamin D deficiency and adverse health outcomes in postmenopausal women, although they cannot establish causality. The evidence from randomized controlled trials concerning vitamin D supplementation is not robust, since many studies did not consider whether people were deficient at baseline. Moreover, high heterogeneity exists in terms of the population studied, vitamin D dosage, calcium co-administration and duration of intervention.

Concerning skeletal health, vitamin D deficiency is associated with low bone mass and an increased risk of fractures. Vitamin D supplementation at maintenance doses of 800–2000 IU/day (20–50 μg/day), after repletion of vitamin D status with higher weekly or daily doses, may be of benefit only when co-administered with calcium (1000–1200 mg/day), especially in the elderly populations and those with severe vitamin D deficiency.

Concerning cardiovascular disease, vitamin D deficiency is associated with an increased prevalence of cardiovascular risk factors, mainly metabolic syndrome, type 2 diabetes mellitus and dyslipidemia. Vitamin D deficiency, especially its severe form, is associated with an increased risk of cardiovascular events (coronary heart disease, stroke, mortality), independently of traditional risk factors. Vitamin D supplementation may have a modestly beneficial effect on lipid profile and glucose homeostasis, especially in obese individuals or those ≥60 years old and at doses of ≥2000 IU/day (≥50 μg/day). However, it has no effect on the incidence of cardiovascular events.

Concerning cancer, vitamin D deficiency is associated with increased incidence of and mortality from several types of cancer, such as colorectal, lung and breast cancer. However, the data on other types of gynecological cancer are inconsistent. Vitamin D supplementation has no effect on cancer incidence, although a modest reduction in cancer-related mortality has been observed.

Concerning infections, vitamin D deficiency has been associated with acute respiratory tract infections, including coronavirus disease 2019 (COVID-19). Vitamin D supplementation may decrease the risk of acute respiratory tract infections and the severity of COVID-19 (not the risk of infection).

Concerning menopausal symptomatology, vitamin D deficiency may have a negative impact on some aspects, such as sleep disturbances, depression, sexual function and joint pains. However, vitamin D supplementation has no effect on these, except for vulvovaginal atrophy, at relatively high doses, i.e., 40,000–60,000 IU/week (1000–1500 IU/week) orally or 1000 IU/day (25 μg/day) as a vaginal suppository.

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Περιληψη Χαρακτηριστικων Του Προϊοντος (SmPC)

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ
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Για τον πλήρη κατάλογο των εκδόχων βλ. παράγραφο 6.1 «Κατάλογος εκδόχων».
3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ
Ενέσιμο διάλυμα
4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ
4.1. Θεραπευτικές ενδείξεις
Θεραπεία με υποκατάσταση τεστοστερόνης για ανδρικό υπογοναδισμό, όταν έχει επιβεβαιωθεί ανεπάρκεια τεστοστερόνης μέσω κλινικών χαρακτηριστικών και βιοχημικών εξετάσεων.
4.2. Δοσολογία και τρόπος χορήγησης
Δοσολογία: Για την ανάπτυξη και διέγερση υποπλαστικών ανδρογονοεξαρτώμενων οργάνων-στόχων και για την αρχική θεραπεία συμπτωμάτων ανεπάρκειας: 250 mg ενδομυϊκά ανά 2-3 εβδομάδες. Για τη διατήρηση επαρκούς ανδρογονικού αποτελέσματος: 250 mg ενδομυϊκώς ανά 3-4 εβδομάδες. Ανάλογα με την εκάστοτε εξατομικευμένη διαφορετική ορμονική έλλειψη, ίσως να είναι αναγκαία συντομότερα χρονικά διαστήματα μεταξύ των ενέσεων. Σε πολλές περιπτώσεις επαρκούν και μεγαλύτερα μέχρι 6 εβδομάδων, χρονικά διαστήματα μεταξύ των ενέσεων.
Πριν την έναρξη της θεραπείας και περιστασιακά κατά τη διάρκεια της θεραπείας στο τέλος του μεσοδιαστήματος των ενέσεων, πρέπει να γίνεται μέτρηση των επιπέδων της τεστοστερόνης στον ορό. Τα επίπεδα ορού κάτω του φυσιολογικού ορίου δηλώνουν την ανάγκη για ένα πιο σύντομο μεσοδιάστημα ενέσεων. Σε περίπτωση υψηλών επιπέδων ορού μπορεί να ληφθεί υπόψη μια παράταση του μεσοδιαστήματος ενέσεων.
Επιπρόσθετες πληροφορίες για τους ειδικούς πληθυσμούς
Ηλικιωμένοι Ασθενείς
Περιορισμένα βιβλιογραφικά δεδομένα δεν δείχνουν την ανάγκη για κάποια προσαρμογή της δόσης σε ηλικιωμένους ασθενείς (βλ. παράγραφο 4.4. «Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση»).
Ασθενείς με ηπατική δυσλειτουργία
Δεν έχουν διεξαχθεί μελέτες σε ασθενείς με ηπατική δυσλειτουργία. Η χρήση του **Testosterone Enanthate/Norma®** αντενδείκνυται σε άνδρες που είχαν ή έχουν όγκους στο ήπαρ (βλ. παράγραφο 4.3. «Αντενδείξεις»).
Ασθενείς με νεφρική δυσλειτουργία
Δεν έχουν διεξαχθεί μελέτες σε ασθενείς με νεφρική δυσλειτουργία.
Παιδιατρικός πληθυσμός
Η χρήση του **Testosterone Enanthate/Norma®** δεν ενδείκνυται σε παιδιά και εφήβους (βλ. παράγραφο 4.4. «Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση»).
Τρόπος χορήγησης
Διάλυμα για ενδομυϊκή ένεση.
Η ένεση πρέπει να χορηγείται εξαιρετικά αργά (βλ. παράγραφο 4.4. «Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση» και 4.8. «Ανεπιθύμητες ενέργειες»). Το ελαιώδες διάλυμα ενίεται αμέσως μετά την αναρρόφησή του στη σύριγγα.
4.3. Αντενδείξεις
– Εξαρτώμενος από ανδρογόνα καρκίνος του προστάτη ή των ανδρικών μαζικών αδένων [μαστός].
– Υπερασβεστιαιμία που συνοδεύει κακοήθεις όγκους.
– Ιατρικά ή παρουσία ηπατικών όγκων.
– Υπερευαισθησία στην δραστική ουσία ή σε κάποιο από τα έκδοχα.
4.4. Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση
Πριν από την έναρξη θεραπείας υποκατάστασης με τεστοστερόνη, όλοι οι ασθενείς πρέπει να υποβληθούν σε ενδελεχή εξέταση προκειμένου να αποκλειστεί ο κίνδυνος προϋπάρχοντος καρκίνου του προστάτη. Σε ασθενείς που λαμβάνουν θεραπεία με τεστοστερόνη πρέπει να διενεργείται προσεκτική και τακτική παρακολούθηση του προστατικού αδένα και του μαστού σύμφωνα με τις συνιστώμενες μεθόδους (βασικολική διαβίκη εξέταση και προσδιορισμός του ειδικού προστατικού αντιγόνου ορού (PSA) τουλάχιστον μια φορά το χρόνο και δύο φορές το χρόνο σε ηλικιωμένους ασθενείς και ασθενείς υψηλού κινδύνου (εκείνους με κλινικούς ή οικογενείς παράγοντες)). Τα ανδρογόνα μπορεί να επιταχύνουν την ανάπτυξη του υποκλινικού καρκινώματος του προστάτη και της καλοήθους υπερτροφίας του προστάτη. Η αιμοσφαιρίνη και ο αιματοκρίτης πρέπει να ελέγχονται ανά τακτά χρονικά διαστήματα στους ασθενείς που λαμβάνουν μακροχρόνια θεραπεία με ανδρογόνα προκειμένου να ανιχνευθούν περιπτώσεις πολυκυτταραιμίας (βλέπε παράγραφο 4.8. «Ανεπιθύμητες ενέργειες»). Μετά τη χρήση ενανθικής τεστοστερόνης έχουν παρατηρηθεί περιπτώσεις με καλοήθεις και κακοήθεις όγκους στο ήπαρ που μπορεί να οδηγήσουν σε ενδοκοιλιακή αιμορραγία απειλητική για τη ζωή. Εάν υπάρχουν σοβαρές ενοχλήσεις στην άνω κοιλία, διόγκωση του ήπατος ή ενδείξεις ενδοκοιλιακής αιμορραγίας, πρέπει στη διαφορική διάγνωση να συμπεριληφθεί η πιθανότητα όγκου του ήπατος. Πρέπει να δίνεται προσοχή σε ασθενείς που έχουν προδιάθεση για ανάπτυξη οιδήματος, καθότι η θεραπεία με ανδρογόνα μπορεί να συνοδεύεται από αυξημένη κατακράτηση νατρίου (βλ. παράγραφο 4.8 «Ανεπιθύμητες ενέργειες»).
Διαταραχές πήξης
Η τεστοστερόνη πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με βρομβοφιλία, καθώς υπήρξαν μελέτες μετά την κυκλοφορία και αναφορές θρομβωτικών επεισοδίων σε αυτούς τους ασθενείς κατά τη διάρκεια θεραπείας με τεστοστερόνη.
Σε ασθενείς που πάσχουν από σοβαρή καρδιακή, ηπατική ή νεφρική ανεπάρκεια ή ισχαιμική καρδιακή νόσο, η θεραπεία με τεστοστερόνη μπορεί να προκαλέσει σοβαρές επιπλοκές που χαρακτηρίζονται από οίδημα με ή χωρίς συμφορητική καρδιακή ανεπάρκεια. Σε τέτοια περίπτωση, η θεραπεία πρέπει να διακοπεί αμέσως. Η τεστοστερόνη ενδέχεται να προκαλέσει αύξηση της αρτηριακής πίεσης και το **Testosterone Enanthate/Norma®** θα πρέπει να χρησιμοποιείται με προσοχή σε άνδρες με υπέρταση. Το επίπεδο τεστοστερόνης θα πρέπει να παρακολουθείται κατά την έναρξη και σε τακτά χρονικά διαστήματα κατά τη διάρκεια της θεραπείας. Οι κλινικοί ιατροί θα πρέπει να προσαρμόζουν τη δοσολογία σε ατομική βάση προκειμένου να διασφαλίζουν τη διατήρηση ευγενοειδών επιπέδων τεστοστερόνης. Σε ασθενείς που λαμβάνουν μακροχρόνια θεραπεία με ανδρογόνα, οι ακόλουθες εργαστηριακές παράμετροι θα πρέπει επίσης να παρακολουθούνται τακτικά: αιματοκρίτη και αιμοσφαιρίνη, δοκιμασίες ηπατικής λειτουργίας και λιπιδαιμικό προφίλ. Υπάρχει περιορισμένη εμπειρία σχετικά με την ασφάλεια και την αποτελεσματικότητα της χρήσης του **Testosterone Enanthate/Norma®** σε ασθενείς ηλικίας άνω των 65 ετών. Επί του παρόντος, δεν υπάρχει αμφιβολία σχετικά με τις ειδικές για την ηλικία τιμές αναφοράς για την τεστοστερόνη. Ωστόσο θα πρέπει να λαμβάνεται υπόψη ότι τα φυσιολογικά επίπεδα τεστοστερόνης στον ορό μειώνονται με την αυξανόμενη ηλικία. Η χρήση ενέσιμης τεστοστερόνης δεν ενδείκνυται σε παιδιά και εφήβους (βλ. παράγραφο 4.2 «Δοσολογία και τρόπος χορήγησης»).
Στα παιδιά η τεστοστερόνη, εκτός από την αρρενοποίηση, μπορεί να προκαλέσει επιτάχυνση της σωματικής ανάπτυξης και πρόωρη σύγκλειση των επιφύσεων των οστών, με συνέπεια μείωση του τελικού ύψους. Η ενανθική τεστοστερόνη δεν πρέπει να χρησιμοποιείται σε γυναίκες διότι, ανάλογα με την ατομική ευαισθησία στη δράση των ανδρογόνων, οι γυναίκες μπορεί να εμφανίσουν σημεία αρρενοποίησης, π.χ. ακμή, δασυτρισμός, αλλαγές στη χροιά της φωνής. Προϋπάρχουσα άπνοια στον ύπνο μπορεί να επιδεινωθεί. Τα ανδρογόνα δεν ενδείκνυνται για την προαγωγή της μυϊκής ανάπτυξης και την αύξηση της σωματικής ικανότητας (απόδοσης) σε υγιή άτομα. Όπως με όλα τα ελαιώδη διαλύματα, το **Testosterone Enanthate/Norma®** πρέπει να ενίεται συστηματικά ενδομυϊκά και πολύ αργά. Πνευμονικός μικροεμβολισμός από ελαιώδη διαλύματα μπορεί να οδηγήσει σε σημεία και συμπτώματα όπως βήχας, δύσπνοια και πόνος στο θώρακα. Μπορεί να υπάρχουν και άλλα σημεία και συμπτώματα συμπεριλαμβανομένων βαγοτονικών αντιδράσεων όπως αδιαθεσία, υπεριδρωσία, ζάλη, παραισθησία, ή συγκοπή. Αυτές οι αντιδράσεις μπορεί να προκύψουν κατά τη διάρκεια ή αμέσως μετά την ένεση και είναι αναταφέρμες. Η θεραπεία είναι συνήθως υποστηρικτική π.χ. χορήγηση οξυγόνου.
4.5. Αλληλεπιδράσεις με άλλα φαρμακευτικά προϊόντα και άλλες μορφές αλληλεπίδρασης
Η φαινοβαρβιτάλη αυξάνει το μεταβολισμό των στεροειδών ορμονών στο ήπαρ (πιθανή μείωση αποτελεσματικότητας).
Η κατάσταση της πήξης του αίματος πρέπει να παρακολουθείται ιδιαίτερα στενά, όταν το **Testosterone Enanthate/Norma®** χορηγείται ταυτόχρονα με αντιπηκτικά παράγωγα κουμαρίνης.
4.6. Γονιμότητα, Κύηση και γαλουχία
Η θεραπεία υποκατάστασης με τεστοστερόνη μπορεί αναστρέψιμα να μειώσει τη σπερματογένεση (βλ. παράγραφο 4.8. «Ανεπιθύμητες ενέργειες» και 5.3. «Προκλινικά δεδομένα ασφάλειας»).
Το **Testosterone Enanthate/Norma®** προορίζεται για χρήση μόνο από άνδρες. Το **Testosterone Enanthate/Norma®** δεν ενδείκνυται σε εγκύους ή γυναίκες που θηλάζουν (βλ. παράγραφο 5.3. «Προκλινικά δεδομένα ασφάλειας»).
4.7. Επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανημάτων
Δεν εφαρμόζεται.
4.8. Ανεπιθύμητες ενέργειες
Αναφορικά με τις ανεπιθύμητες ενέργειες σε σχέση με τη χρήση των ανδρογόνων παρακαλούμε δείτε επίσης την παράγραφο 4.4. «Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση».
Οι πιο συχνά αναφερόμενες ανεπιθύμητες ενέργειες με την ενέσιμη ενανθική τεστοστερόνη είναι ο πόνος στο σημείο ένεσης, ερύθημα στο σημείο ένεσης και βήχας και / ή δύσπνοια κατά τη διάρκεια ή αμέσως μετά την ένεση.
Ο παρακάτω πίνακας περιλαμβάνει ανεπιθύμητες ενέργειες από αυθόρμητες αναφορές και από επιστημονική βιβλιογραφία για τις οποίες η συχνότητα δεν μπορεί να υπολογισθεί από τα διαθέσιμα δεδομένα.

Κατηγορία Οργάνου Συστήματος σύμφωνα με τη Βάση δεδομένων MedDRA	Άγνωστη συχνότητα
Νεοπλάσματα καλοήθη και κακοήθη	Καλοήθεις και κακοήθεις όγκοι του ήπατος
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	Πολυκυτταραιμία
Διαταραχές του ανοσοποιητικού συστήματος	Υπερευαισθησία
Διαταραχές του ήπατος και χολοφόρων	Παθολογικός έλεγχος ηπατικής λειτουργίας Ίκτερος
Διαταραχές του δέρματος και του υποδέρμιου ιστού	Ακμή, Αλωπεκία, Εξάνθημα, Κνίδωση, Κνησμός
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	Ποικίλα είδη αντιδράσεων στο σημείο ένεσης*
Έρευνες	Αυξημένο ειδικό προστατικό αντιγόνο
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	Αύξηση της λίμνιτο, Μείωση της λίμνιτο, Γυναικομαστία

* Πόνος στο σημείο ένεσης, ερύθημα στο σημείο ένεσης, σκλήρυνση στο σημείο ένεσης, οίδημα στο σημείο ένεσης, φλεγμονή στο σημείο ένεσης

Ενέσεις ελαιωδών διαλυμάτων όπως το **Testosterone Enanthate/Norma®** έχουν συσχετισθεί με συστηματικές αντιδράσεις: βήχα, δύσπνοια, πόνο στο θώρακα. Μπορεί να υπάρχουν και άλλα σημεία και συμπτώματα συμπεριλαμβανομένων βαγοτονικών αντιδράσεων όπως: αδιαθεσία, υπεριδρωσία, ζάλη, παραισθησία, ή συγκοπή.
Συχνή συχνότητα παρουσιάζουν: αιματοκρίτης αυξημένος, αριθμός ερυθροκυττάρων αυξημένος, αιμοσφαιρίνη αυξημένη.
Υψηλή δοσολογία ή μακροχρόνια χορήγηση τεστοστερόνης συμπεριλαμβανομένου του **Testosterone Enanthate/Norma®**, αυξάνει την τάση για κατακράτηση ύδατος και δημιουργία οιδήματος.
Η απεριποίητη ανατελλάται από τη μακροχρόνια χρήση και τη θεραπεία με υψηλή δόση του **Testosterone Enanthate/Norma®**.
Εάν, σε μεμονωμένες περιπτώσεις, εμφανισθούν συχνές ή επίμονες στύσεις, πρέπει να ελαττωθεί η δόση ή να διακοπεί η θεραπεία ώστε να αποφευχθεί βλάβη του πέους.
Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών
Η αναφορά πιθανολογούμενων ανεπιθύμητων ενέργειων 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 του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς
Εθνικός Οργανισμός Φαρμάκων
Μεσογείων 284
GR-15562 Χολαργός, Αθήνα
Τηλ. + 30 21 32040380/337
Φαξ: + 30 21 06549585
Ιστότοπος: http://www.eof.gr
4.9. Υπερδοσολογία
Μετά από υπερδοσολογία δεν είναι απαραίτητη η λήψη ειδικών θεραπευτικών μέτρων εκτός από τη διακοπή της θεραπείας με το φάρμακο ή μείωση της δόσης.
Τα δεδομένα οξείας τοξικότητας δείχνουν ότι η ενανθική τεστοστερόνη, ο εστέρας που περιέχεται στο **Testosterone Enanthate/Norma®**, καταπόσεται σε μη-τοξικές ουσίες, μετά από εφάπαξ χορήγηση. Ακόμη και μετά από εφάπαξ χορήγηση δόσης πολλαπλάσιας της θεραπευτικής, δεν αναμένεται κίνδυνος τοξικότητας.
5. ΦΑΡΜΑΚΟΛΟΓΙΚΕΣ ΙΔΙΟΤΗΤΕΣ
5.1. Φαρμακοδυναμικές ιδιότητες
Φαρμακοθεραπευτική κατηγορία. Ανδρογόνα
Κωδικός ΑΤC G03BA03
Το **Testosterone Enanthate/Norma®** περιέχει ως δραστικό συστατικό ένα παράγωγο της φυσικής ανδρικής ορμόνης του φύλου, της τεστοστερόνης. Η ενανθική τεστοστερόνη μπορεί να εξαλείψει τα συμπτώματα που παρουσιάζονται όταν υπάρχει ανεπάρκεια ανδρογόνων. Η ενεργός μορφή, τεστοστερόνη, δημιουργείται με διάσπαση του εστερικού δεσμού.
5.2. Φαρμακοκινητικές ιδιότητες
Ενανθική τεστοστερόνη
Απορρόφηση
Μετά από ενδομυϊκή χορήγηση, η ενανθική τεστοστερόνη γίνεται απόλυτα διαθέσιμη για συστηματική απορρόφηση. Η ουσία απελευθερώνεται από την περιοχή αποθήκευσής της σταδιακά με χρόνο ημίσειας ζωής περίπου 4,5 ημέρες και διασπάται σε τεστοστερόνη και ενανθικό οξύ. Με μία δόση 250 mg ενανθικής τεστοστερόνης, οι ασθενείς λαμβάνουν μια συνολική δόση 180 mg τεστοστερόνης. Κατά το χρόνο που επιτυγχάνονται οι μέγιστες τιμές στον ορό, οι κατά προσέγγιση ημερήσιες δόσεις μετά από 1 και 2 εβδομάδες αντιστοιχούν σε 12 και 4 mg τεστοστερόνης, αντίστοιχα. Η τεστοστερόνη απελευθερώνεται πλήρως από την περιοχή αποθήκευσής της μέσα σε περίπου 4 εβδομάδες από τη χορήγηση του φαρμάκου.
Κατανομή
Μέγιστες συγκεντρώσεις, περίπου 20 ng/ml, τεστοστερόνης μετρήθηκαν 1,5 – 3 ημέρες μετά την ενδομυϊκή χορήγηση 250 mg ενανθικής τεστοστερόνης σε νέους άνδρες. Από εκεί και πέρα, τα επίπεδα τεστοστερόνης στο πλάσμα μειώθηκαν με χρόνο ημίσειας ζωής περίπου 4,5 ημέρες, που αντιστοιχεί στο ρυθμό απελευθέρωσης από την περιοχή αποθήκευσης. Οι συγκεντρώσεις τεστοστερόνης ≥ 2 ng/ml διατηρήθηκαν για 20 ημέρες και εκείνες ≥1 ng/ml για 26 ημέρες.
Η τεστοστερόνη είναι ισχυρά συνδεδεμένη με τις πρωτεΐνες του ορού, ιδιαίτερα με την αλβουμίνη και την SHBG.
Μεταβολισμός
Η τεστοστερόνη που προέρχεται από τη διάσπαση του εστέρα της ενανθικής τεστοστερόνης μεταβολίζεται και απεκκρίνεται όπως και η ενδογενής τεστοστερόνη.
Η απόλυτη βιοδιαθεσιμότητα της τεστοστερόνης από τον εστέρα είναι σχεδόν πλήρης, καταδεικνύοντας με αυτό τον τρόπο μια γρήγορη και αποτελεσματική διάσπαση του εστέρα.
Το ενανθικό οξύ μεταβολίζεται μέσω β-οξείδωσης με τον ίδιο τρόπο όπως άλλα αλειφατικά καρβοξυλικά οξέα.
Απέκκριση
Η μεταβολική κάθαρση της τεστοστερόνης υπολογίζεται σε 16±7 ml/min/kg και αναφέρεται στον ηπατικά και εξωηπατικό μεταβολισμό της τεστοστερόνης. Οι μεταβολίτες της τεστοστερόνης απεκκρίνονται με χρόνο ημίσειας ζωής 7,8 ημερών. Περίπου το 90% απεκκρίνεται μέσω της νεφρικής οδού και περίπου το 10% με τη χολή.
Συνθήκες σταθεροποιημένης κατάστασης
Η έγκαιρη 250 mg ενανθικής τεστοστερόνης κάθε 3-4 εβδομάδες δεν οδηγεί σε κλινικά σημαντική συσσώρευση τεστοστερόνης στον ορό.
5.3. Προκλινικά δεδομένα για την ασφάλεια
Εφόσον η ενανθική όπως και η προπιονική τεστοστερόνη διασπώνται πλήρως με τη βοήθεια εστεραζών σε ελεύθερη τεστοστερόνη, η αβιολόγηση έχει γίνει λαμβάνοντας υπόψη τα αποτελέσματα και των δύο εστέρων.
Οξεία τοξικότητα
Όπως γενικά με τις στεροειδείς ορμόνες, η οξεία τοξικότητα της τεστοστερόνης είναι πολύ χαμηλή.
Χρόνια τοξικότητα
Μελέτες για συστηματική ανεκτικότητα, μετά από επανειλημμένη χορήγηση, δεν ανέδειξαν ευρήματα τα οποία να απαγορεύουν τη χρήση των δραστικών ουσιών, στις δόσεις που είναι απαραίτητες για τη θεραπεία.
Μεταλλαξιογόνο και ογκογόνο δυναμικό
In vitro μελέτες για μεταλλαξιογόνο δράση χρησιμοποιώντας την τεστοστερόνη που απελευθερώνεται από τους εστέρες δεν έδωσαν κάποια ένδειξη για μεταλλαξιογόνο δυναμικό. Επιπροσθέτως, με βάση τα αρνητικά αποτελέσματα μελετών μεταλλαξογένεσης με άλλες στεροειδείς ορμόνες, δεν αναμένεται τέτοιο δυναμικό στην περίπτωση της ενανθικής τεστοστερόνης.
Δεν έχουν διεξαχθεί με την ενανθική τεστοστερόνη μελέτες με στόχο την αξιολόγηση μιας πιθανής ογκογεννητικής δράσης μετά από επανειλημμένη χορήγηση. Αυτού του είδους οι μελέτες δεν θεωρήθηκαν απαραίτητες, εφόσον, σε μελέτες συστηματικής ανεκτικότητας μετά από επανειλημμένη χορήγηση, σε αρουραίους και σκύλους για χρονικό διάστημα 6 μηνών, δεν παρουσιάστηκαν ενδείξεις ογκογεννητικής δράσης. Επιπλέον, πολλά χρόνια κλινικής εμπειρίας με την ενανθική τεστοστερόνη δεν έχουν δώσει ενδείξεις ογκογεννητικής δράσης στον άνθρωπο. Ωστόσο, πρέπει να υπενθυμιστεί γενικότερα ότι τόσο οι στεροειδείς ορμόνες του φύλου που απαντώνται στη φύση όσο και οι συνθετικές στεροειδείς ορμόνες του φύλου μπορούν να προάγουν την αύξηση ορισμένων ορμονοεξαρτώμενων ιστών και όγκων.
Αναπαραγωγική τοξικότητα
Μελέτες γονιμότητας σχετικά με την πιθανή πρόκληση βλάβης στα γεννητικά κύτταρα δεν έχουν διεξαχθεί με την ενανθική τεστοστερόνη. Δεν θεωρήθηκε απαραίτητο να διεξαχθούν τέτοιου είδους μελέτες, εφόσον οι μελέτες μακροχρόνιας συστηματικής ανεκτικότητας δεν έδωσαν ενδείξεις τοξικής βλάβης στους όρχεις, αλλά μόνο μία κεντρικά-σχετιζόμενη αναστολή της σπερματογένεσης και της ωογένεσης. Επίσης, η προσωρινή αναστολή της σπερματογένεσης μετά από τη θεραπεία με την ενέσιμη ενανθική τεστοστερόνη 250 mg/ml στους ανθρώπους δεν έδωσε ενδείξεις ότι τα σπερματοζωάρια υφίστανται οποιαδήποτε βλάβη, η οποία μπορεί να οδηγήσει σε διαμαρτίες ή μείωση της γονιμότητας στους απογόνους. Η ενέσιμη ενανθική τεστοστερόνη δεν πρέπει να χορηγείται κατά τη διάρκεια της κύησης, λόγω της πιθανότητας αρρενοποίησης των θηλυκών εμβρύων. Ωστόσο, έρευνες εμβρυοτοξικότητας, ιδιαίτερα τερατογένεσης, δεν έδωσαν ενδείξεις ότι πρέπει να αναμένονται άλλες βλάβες στην ανάπτυξη των οργάνων.
Τοπική ανεκτικότητα
Μελέτες τοπικής ανεκτικότητας, μετά από ενδομυϊκή χορήγηση, έδειξαν ότι η προπιονική και η ενανθική τεστοστερόνη δεν αυξάνουν τον ερεθισμό που προκαλεί από μόνος του ο διαλύτης. Ο διαλύτης που περιέχεται στο **Testosterone Enanthate/Norma®** έχει χρησιμοποιηθεί επί πολλά χρόνια σε πολυάριθμες φαρμακοτεχνικές μορφές που προορίζονται για ανθρώπινη χρήση. Σε αυτό το διάστημα δεν παρουσιάστηκαν φαινόμενα τοπικού ερεθισμού, που να αντιθέτεται στην περαιτέρω χρήση του.
Οι έρευνες που διεξήχθησαν με τον ελαιώδη διαλύτη που περιέχεται στο **Testosterone Enanthate/Norma®** δεν έδωσαν ενδείξεις ευαισθητοποίησης. Δεν έχουν διεξαχθεί επιπρόσθετες έρευνες ευαισθητοποίησης για την προπιονική και την ενανθική τεστοστερόνη. Αρκετά έτη κλινικής εμπειρίας έδειξαν μόνο σποραδικές περιπτώσεις, στις οποίες υπήρξε υποψία αλλεργικών αντιδράσεων. Δεν έχει, ωστόσο αποδειχτεί ξεκάθαρη δραστηριότητα ευαισθητοποίησης.
Συνολικά, τα διαθέσιμα τοξικολογικά ευρήματα δεν φανερώνουν αντιρρήσεις ως προς τη συνταγογραφημένη χρήση του **Testosterone Enanthate/Norma®** στον άνθρωπο, στις προτεινόμενες ενδείξεις και δοσολογίες.
6. ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ
6.1. Κατάλογος των εκδόχων
Βενζυλεστέρας Βενζοϊκός/Benzyl benzoate
Κικέλαιο/Oleum Ricine
6.2. Ασυμβατότητες
Με υδατικά διαλύματα.
6.3. Διάρκεια ζωής
24 μήνες για προϊόν διατηρημένο σύμφωνα με τις οδηγίες.
6.4. Ιδιαίτερες προφυλάξεις κατά τη φύλαξη του προϊόντος
Να μη φυλάσσεται σε θερμοκρασία μεγαλύτερη των 25º C. Να προφυλάσσεται από το φως.
Κάθε ακρησιμοποίητο φαρμακευτικό προϊόν ή υπόλειμμα πρέπει να απορρίπτεται σύμφωνα με τις κατά τόπους ισχύουσες σχετικές διατάξεις.
6.5. Φύση και συστατικά του περιέκτη
Χάρτινο κουτί που περιέχει καφέ γυάλινη φύσιγγα και φύλλο οδηγιών χρήσης.
7. ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ
ΝΟΡΜΑ ΕΛΛΑΣ Α.Ε.
Μενάνδρου 54,10431 Αθήνα.
Τηλ. 210 52 22 282 Fax: 210 52 41 368
email: info@normahellas.gr
8. ΑΡΙΘΜΟΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ
Testosterone Enanthate/Norma® inj.sol. 250mg/ml 45945/03-10-2008
9. ΗΜΕΡΟΜΗΝΙΑ ΠΡΩΤΗΣ ΕΓΚΡΙΣΗΣ/ΑΝΑΝΕΩΣΗΣ ΤΗΣ ΑΔΕΙΑΣ
20-08-2003/03-10-2008
10. ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ
17/11/2017

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

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ΑΝΔΡΙΚΗ ΑΝΑΠΑΡΑΓΩΓΗ

ΓΕΩΡΓΙΟΣ ΠΑΠΑΔΑΚΗΣ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ, ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ ΤΜΗΜΑ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑΣ,
ΔΙΑΒΗΤΟΛΟΓΙΑΣ ΚΑΙ ΜΕΤΑΒΟΛΙΣΜΟΥ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΝΟΣΟΚΟΜΕΙΟ ΛΩΖΑΝΗΣ - ΕΛΒΕΤΙΑ

PNAS RESEARCH ARTICLE | ANTHROPOLOGY

Evidence for an adolescent sensitive period to family experiences influencing adult male testosterone production

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Across vertebrates, testosterone is an important mediator of reproductive trade-offs, shaping how energy and time are devoted to parenting versus mating/competition. Based on early environments, organisms often calibrate adult hormone production to adjust reproductive strategies. For example, favorable early nutrition predicts higher adult male testosterone in humans, and animal models show that developmental social environments can affect adult testosterone. In humans, fathers' testosterone often declines with caregiving, yet these patterns vary within and across populations. This may partially trace to early social environments, including caregiving styles and family relationships, which could have formative effects on testosterone production and parenting behaviors. Using data from a multidecade study in the Philippines ($n = 966$), we tested whether sons' developmental experiences with their fathers predicted their adult testosterone profiles, including after they became fathers themselves. Sons had lower testosterone as parents if their own fathers lived with them and were involved in childcare during adolescence. We also found a contributing role for adolescent father–son relationships: sons had lower waking testosterone, before and after becoming fathers, if they credited their own fathers with their upbringing and resided with them as adolescents. These findings were not accounted for by the sons' own parenting and partnering behaviors, which could influence their testosterone. These effects were limited to adolescence: sons' infancy or childhood experiences did not predict their testosterone as fathers. Our findings link adolescent family experiences to adult testosterone, pointing to a potential pathway related to the intergenerational transmission of biological and behavioral components of reproductive strategies.

fathers | hormones | androgens | psychobiology | developmental plasticity

Significance

Testosterone influences how animals devote energy and time toward reproduction, including opposing demands of mating and competition versus parenting. Reflecting this, testosterone often declines in new fathers and lower testosterone is linked to greater caregiving. Given these roles, there is strong interest in factors that affect testosterone, including early-life experiences. In this multidecade study, Filipino sons whose fathers were present and involved with raising them when they were adolescents had lower testosterone when they later became fathers, compared to sons whose fathers were present but uninvolved or were not coresident. Sons' own parenting behaviors did not explain these patterns. These results connect key social experiences during adolescence to adult testosterone, and point to possible intergenerational effects of parenting style.

There is widespread interest in the role of early-life environments in shaping later health, biological function, and behavior (1–8). The hypothalamic–pituitary–gonadal (HPG) axis and its production of testosterone (T) are widely studied across vertebrates for their roles in reproductive function, life-history strategies, and health outcomes, but little is known about the range of early-life environmental stimuli involved in HPG programming (9–12). Across taxa, T contributes to costly somatic forms of reproductive investment, including sexually dimorphic ornamentations and muscle mass, along with reproduction-linked behaviors like competition and risk taking (9–13). Thus, any effects of early experiences on later T production could have lasting impacts on adult patterns of energy allocation and on reproductively important somatic and behavioral phenotypes.

In humans, markers of favorable early-life nutrition, such as rapid infancy growth, have been linked to higher circulating T in adult males (14, 15). This is consistent with the hypothesis that energetic conditions during sensitive periods of growth and development help calibrate HPG axis production of T and its downstream energetically costly reproductive expenditures in adulthood (2, 14, 15). Human life history also involves a unique, extended window of development during which children are adaptively attuned to social relationships and processes as key calibrators of their own emerging social and cultural competencies (16). Intertwined with this prolonged, accentuated importance of social context to humans, early-life social experiences are foundational environmental inputs to sensitive periods for numerous biological systems, extending beyond infancy to include later childhood and adolescence (4, 6, 7, 17, 18). In this vein, developmental social environments have also been proposed to affect human adult T production (3, 4, 19). Yet, few prospective, longitudinal studies have focused on the implications of early-life social experiences for human T production (20–23). This gap persists despite the important interrelationships between the HPG axis and adult social and reproductive behaviors in humans that have likewise been linked to early social environments in separate research (24–33). Studies have also

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Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis

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Summary

Background Testosterone is the standard treatment for male hypogonadism, but there is uncertainty about its cardiovascular safety due to inconsistent findings. We aimed to provide the most extensive individual participant dataset (IPD) of testosterone trials available, to analyse subtypes of all cardiovascular events observed during treatment, and to investigate the effect of incorporating data from trials that did not provide IPD.

Methods We did a systematic review and meta-analysis of randomised controlled trials including IPD. We searched MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Epub Ahead of Print, Embase, Science Citation Index, the Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, and Database of Abstracts of Review of Effects for literature from 1992 onwards (date of search, Aug 27, 2018). The following inclusion criteria were applied: (1) men aged 18 years and older with a screening testosterone concentration of 12 nmol/L (350 ng/dL) or less; (2) the intervention of interest was treatment with any testosterone formulation, dose frequency, and route of administration, for a minimum duration of 3 months; (3) a comparator of placebo treatment; and (4) studies assessing the pre-specified primary or secondary outcomes of interest. Details of study design, interventions, participants, and outcome measures were extracted from published articles and anonymised IPD was requested from investigators of all identified trials. Primary outcomes were mortality, cardiovascular, and cerebrovascular events at any time during follow-up. The risk of bias was assessed using the Cochrane Risk of Bias tool. We did a one-stage meta-analysis using IPD, and a two-stage meta-analysis integrating IPD with data from studies not providing IPD. The study is registered with PROSPERO, CRD42018111005.

Findings 9871 citations were identified through database searches and after exclusion of duplicates and of irrelevant citations, 225 study reports were retrieved for full-text screening. 116 studies were subsequently excluded for not meeting the inclusion criteria in terms of study design and characteristics of intervention, and 35 primary studies (5601 participants, mean age 65 years, [SD 11]) reported in 109 peer-reviewed publications were deemed suitable for inclusion. Of these, 17 studies (49%) provided IPD (3431 participants, mean duration 9·5 months) from nine different countries while 18 did not provide IPD data. Risk of bias was judged to be low in most IPD studies (71%). Fewer deaths occurred with testosterone treatment (six [0·4%] of 1621) than placebo (12 [0·8%] of 1537) without significant differences between groups (odds ratio [OR] 0·46 [95% CI 0·17–1·24]; p=0·13). Cardiovascular risk was similar during testosterone treatment (120 [7·5%] of 1601 events) and placebo treatment (110 [7·2%] of 1519 events; OR 1·07 [95% CI 0·81–1·42]; p=0·62). Frequently occurring cardiovascular events included arrhythmia (52 of 166 *vs* 47 of 176), coronary heart disease (33 of 166 *vs* 33 of 176), heart failure (22 of 166 *vs* 28 of 176), and myocardial infarction (10 of 166 *vs* 16 of 176). Overall, patient age (interaction 0·97 [99% CI 0·92–1·03]; p=0·17), baseline testosterone (interaction 0·97 [0·82–1·15]; p=0·69), smoking status (interaction 1·68 [0·41–6·88]; p=0.35), or diabetes status (interaction 2·08 [0·89–4·82; p=0·025) were not associated with cardiovascular risk.

Interpretation We found no evidence that testosterone increased short-term to medium-term cardiovascular risks in men with hypogonadism, but there is a paucity of data evaluating its long-term safety. Long-term data are needed to fully evaluate the safety of testosterone.

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Research in context

Evidence before this study

Testosterone treatment is most often given to men aged 40–65 years. Testosterone has potentially favourable effects on cardiovascular risk such as increased lean-to-fat body mass and improved insulin sensitivity and glycaemia. Conversely, testosterone treatment increases haematocrit, might lower high-density lipoprotein (HDL) cholesterol, and some studies have observed increased cardiovascular event risk. The US Food & Drugs Administration (FDA) has mandated a box label warning of potential cardiovascular risks for all testosterone products. Uncertainty regarding the safety of testosterone might unduly influence decision making regarding the management of men with hypogonadism who could otherwise derive substantial benefits from treatment. We designed highly sensitive search strategies to identify reports of published, ongoing, and unpublished randomised controlled trials assessing the clinical effectiveness of testosterone treatment in men with hypogonadism. Searches were restricted to reports published in English from 1992. We searched major electronic databases (MEDLINE, Embase, Science Citation Index, and CENTRAL), clinical trial registries, and contacted clinical experts. We focused on trials with at least 3-month treatment duration and mean baseline total testosterone of 12 nmol/L or less (or equivalent) before treatment. We established a collaborative group of investigators of all identified trials (35 trials) and collected individual patient data (IPD) from 17 trials (3431 participants in total). In general, the risk of bias of IPD trials was low.

Added value of this study

This individual IPD meta-analysis allowed us to conduct a reliable assessment of the frequency of mortality and cardiovascular events (including subtypes) during testosterone treatment in men with hypogonadism. Few deaths have occurred during trials of testosterone in men. Furthermore, testosterone treatment is not associated with an increased risk of any recorded cardiovascular event subtype in the short to medium term. The only detected adverse effects of testosterone were oedema and a modest lowering of HDL cholesterol.

Implications of all the available evidence

Men with hypogonadism should be counselled that there is no current evidence that testosterone treatment increases cardiovascular risk in the short to medium term. Long-term safety of testosterone is not yet established; an FDA-mandated study is ongoing.

Introduction

The steroid hormone testosterone is fundamental to male physical development and sexual behaviour. Deficiency of testosterone causes male hypogonadism, including diminished secondary sexual characteristics, sexual dysfunction, muscle wasting and weakness, osteoporosis, and reduced quality of life. Testosterone treatment is the standard of care for reversing the consequences of hypogonadism. Testosterone sales increased 12-fold globally from USD$150 million in 2000 to $1·8 billion in 2011.[1] During this period, testosterone has been used increasingly in men aged 40–65 years, and has been over-prescribed by some clinicians.[2,3] Despite the increasing use of testosterone, the USA Endocrine Society, American College of Physicians, and Endocrine Society of Australia have independently concluded that the cardiovascular safety of testosterone has not been adequately established.[4–6] Furthermore, the European Urology Association (EAU) and the European Academy of Andrology (EAA) have recommended the assessment of cardiovascular risk before initiation of testosterone therapy.[7,8]

Testosterone exerts diverse effects on cardiovascular physiology. Some physiological testosterone effects could potentially reduce cardiovascular risk, including coronary vasodilatation and increased coronary blood flow, improved vascular reactivity, increased muscle mass, reduced whole body and visceral fat mass, shorter QTc interval, and normalisation of glycaemia during lifestyle interventions for prediabetes.[4,9] Other testosterone actions could increase cardiovascular risk, including increased haematocrit, reduced high density lipoprotein (HDL) cholesterol, induction of platelet aggregation by stimulation of thromboxane A2, sodium and water retention, and smooth muscle proliferation and increased expression of vascular cell adhesion molecules.[4,10,11]

Two large observational studies have reported increased risks of myocardial infarction, stroke, and death in men taking testosterone compared with non-users, but the study designs have been widely criticised.[12–14] Furthermore, a placebo-controlled trial was stopped early by its data and safety monitoring board following increased cardiovascular events in men aged 65 years and older who received 6 months of testosterone treatment.[15] Other controlled trials have not observed significant effects of testosterone on cardiovascular events, but none were sufficiently powered to detect excess cardiovascular risks.[16,17] Nevertheless, the US Food and Drug Administration (FDA) mandated box label warnings of potential cardiovascular risks for all testosterone products. The FDA also restricted testosterone approval to hypogonadism caused by documented pituitary or testicular disease, specifically excluding age-related hypogonadism.[18] Following the FDA's advisory about potential cardiovascular risk, testosterone prescription sales have declined in the USA.[2] Conversely, the European Medicines Agency, EAU, and EAA have concluded that when hypogonadism is properly diagnosed and managed, there is currently no consistent evidence that testosterone therapy causes

increased cardiovascular risk.[7,8,19] Uncertainty about the cardiovascular safety of testosterone might be unduly influencing decision making regarding the management of men with hypogonadism who might otherwise derive substantial benefits from the treatment.

Previous meta-analyses of cardiovascular safety of testosterone treatment have been restricted to published, aggregate data, limiting the ability to confirm quality and categorisation of source data, or analyse whether specific clinical benefits or adverse effects are associated with distinct subgroups such as patient age, baseline total and free testosterone, smoking, and diabetes status.[20–28]

To address ongoing uncertainly about the safety of testosterone, the Testosterone Efficacy and Safety Consortium was established as a global collaboration of principal investigators of testosterone trials. We report results of the most extensive individual participant dataset (IPD) of testosterone trials available and aimed to analyse subtypes of all cardiovascular events observed during treatment, and analyse the effect of incorporating data from trials not providing IPD.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, placebo-controlled trials evaluating the effects of at least 3 months of testosterone treatment in men with low testosterone were considered for inclusion. The following criteria were used for study selection: (1) men aged 18 years and older with a screening testosterone concentration of 12 nmol/L (350 ng/dL) or less. Studies restricted to conditions not resulting from hypogonadism likely to affect cardiovascular or thrombotic risk (eg, cancer, HIV, cirrhosis, Klinefelter syndrome, type 1 diabetes), or studies restricted to men with congenital hypogonadotrophic hypogonadism were not deemed suitable for inclusion. (2) The intervention of interest was treatment with any testosterone formulation, dose frequency, and route of administration, for a minimum duration of 3 months. Studies in which participants received non-testosterone drugs to increase androgen levels (eg, human chorionic gonadotropin, selective oestrogen receptor modulators) or concomitant interventions were not included. (3) A comparator of placebo treatment. (4) Studies assessing the pre-specified primary or secondary outcomes of interest.

Highly sensitive search strategies were applied by an information specialist on Aug 27, 2018, to the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Epub Ahead of Print, Embase, Science Citation Index, and the Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, and Database of Abstracts of Review of Effects (appendix pp 1–2). Furthermore, the Health Technology Assessment databases were searched for evidence syntheses. Recent conference proceedings of key professional organisations in the fields of endocrinology, cardiology, and men's health were also searched. Searches were restricted to reports published from 1992. Articles published in languages other than English were translated when possible. Reference lists of included studies were checked, and expert panellists assembled for this review were contacted for further potentially relevant reports. We did not consider unpublished evidence or evidence published in a non-commercial form.

Two reviewers independently screened titles and abstracts of all citations identified by the search strategies (MC and MB or MA-M). All potentially relevant reports were retrieved in full and assessed by one reviewer (MC) with 10% independently checked by a second reviewer (MA-M). Additionally, all selected reports were independently assessed by a clinical expert (CNJ or RQ). Any disagreements during the selection process were resolved by consensus.

This study was done according to Centre for Reviews and Dissemination guidance for undertaking reviews in health care and the Cochrane Handbook for Systematic Reviews of Interventions.[29,30] Results were reported according to the PRISMA IPD checklist.[31] Methods were pre-specified in a research protocol.

Data collection and risk of bias assessment

MC extracted details of study design, interventions, participants, and outcome measures from published articles using a bespoke data extraction form. In cases of multiple duplications, the most recent or complete article was selected for data extraction. MA-M cross-checked a random sample of 10% of selected studies. Extracted data were further checked for accuracy by the project statistician (JH). Anonymised IPD was requested from investigators of all identified trials, following the completion of a Data Sharing Agreement. A Standard Operating Procedure ensured secure receipt and storage of all IPD. Data sets received were checked for accuracy with published data and discrepancies were clarified with the collaborator. If this was not possible, the research team discussed discrepancies and decided whether data should be included. When applicable, variables were standardised to the same scale.

Primary outcomes were all-cause mortality and cardiovascular or cerebrovascular events, or both, at any time during the study period, irrespective of whether they were assessed as primary or secondary outcomes in the individual trials. Physiological markers were reported as secondary outcomes (appendix p 3). At baseline, data on age, body-mass index (BMI), ethnicity, hormone concentrations, cardiovascular history, and other medical history were extracted. We also collected data on additional outcomes including diabetes and prostate cancer (appendix p 4). Many secondary outcomes (eg, blood pressure) were measured serially. All but two eligible studies had durations of 12 months or less; to aid data comparison between studies, secondary outcomes were assessed at 12 months or the time-point closest to 12 months. Primary outcomes and additional secondary

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For the **published research protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=111005

See Online for appendix

outcomes were categorised independently by two clinical review authors (CJ, RQ). All American College of Cardiology (ACC) cardiovascular endpoints for clinical trials (death, heart failure, myocardial infarction, unstable angina, coronary intervention, and peripheral vascular disease)[32] were assessed; we also assessed any other cardiovascular endpoints reported within disclosed IPD. Stroke was the only reported cerebrovascular event. For simplicity, in the text of this Article, a reference to cardiovascular events indicates both cardiovascular and cerebrovascular events. A full list of secondary outcomes is available in the appendix (p 3).

The risk of study bias was assessed independently by MC and MA-M using the original version of the Cochrane Collaboration's risk of bias tool for randomised controlled trials.[33] Follow-up enquiries were made with collaborators providing IPD for cases in which details required were unclear or not reported. The following domains were assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

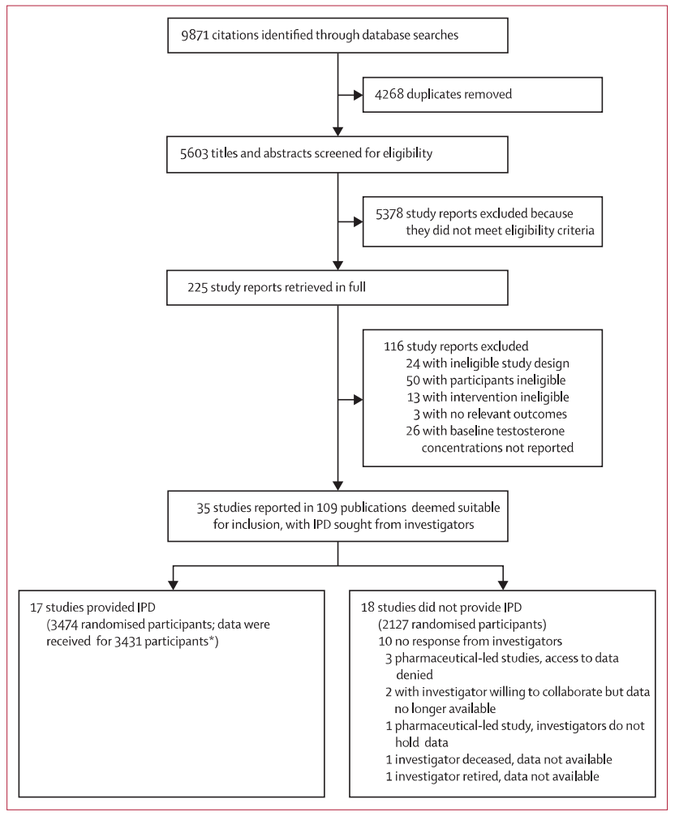

Figure 1: **Study selection**
IPD=individual participant dataset. *Reasons for discrepancies listed in the appendix (pp 18–24).

Other bias was judged to be high if the study was sponsored or done by a pharmaceutical company. The overall risk of bias was considered high if one or both key domains (selection bias, detection bias) were judged at high risk of bias; was considered unclear if either key domain was judged as unclear; or considered low if both domains were judged at low risk of bias. Reviewer disagreements were resolved by consensus. Risk of bias was presented using RevMan software (version 5.4.1).

Data analysis

All analyses were done according to intention-to-treat and at the participant level, in accordance with a pre-specified statistical analysis plan (appendix pp 5–17). Both one-stage and two-stage meta-analyses were undertaken as IPD were not available from all included studies. For the one-stage meta-analysis, we used a fixed-effects logistic regression model accounting for clustering and allowing a separate intercept per study, with treatment effects presented as odds ratios (ORs) for the primary outcomes due to non-converge of a random-effects analysis. Secondary continuous outcomes were analysed used a random-effects linear regression accounting for clustering and allowing separate baseline adjustment per study as well as a separate residual variance using restricted maximum likelihood (REML). Effect estimates were presented as mean differences. Estimated between-study variance, τ^2, is reported to assess heterogeneity. For the two-stage meta-analysis, IPD were analysed separately for each study. For the first stage, primary outcomes were analysed with logistic regression (while linear regression was adjusted for baseline value) and with REML for secondary outcomes. For studies without IPD, we obtained effect estimates and standard errors according to current methodological recommendations.[33] The second stage pooled the effect estimates using a random-effects model with REML. For models not converging using REML, we used a random-effects model using the DerSimonian and Laird method.[34] No adjustment for zero events was required due to the use of a parametric model and because both the one-stage and two-stage analysis approaches use information from across all the studies.

Heterogeneity was assessed by use of the I^2 statistic. Counter-enhanced funnel plots and Peters' test for asymmetry were used for primary outcomes to assess small-study effects and publication bias.[35] A χ^2 test was used to assess additional secondary outcomes. For cardiovascular (or cerebrovascular) events, pre-specified subgroup analyses according to current methodological recommendations were done to assess effects of diabetes diagnosis, smoking status, testosterone, and free testosterone concentrations.

A post-hoc subgroup analysis was done for age and baseline cardiovascular or cerebrovascular event status.[36] We also did sensitivity analyses according to age (<50, 50–75, >75 years), testosterone concentrations (<8, 8–10, >10 nmol/L), and free testosterone

concentrations (<180, 180–220, >220 pmol/L). Analysis of mortality was unfeasible due to the limited number of total recorded deaths. Due to low numbers of mortality events, we did a sensitivity analysis using the Mantel-Haenszel method and including unknown cause of death for cardiovascular (or cerebrovascular) events.

Treatment effects were presented with 95% CIs apart from in the subgroup analyses, for which stricter levels of significance (99% CIs) were used. No adjustment for multiple secondary outcomes was performed. To allow direct comparison, SF-36 and SF-12 scores were transformed into *T*-scores.[37] All statistical analyses were done with Stata software (version 16). The study is registered on the PROSPERO database, CRD42018111005.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Results

9871 citations were identified through all database searches, and following the removal of 4268 duplicates, 5603 titles and abstracts were screened for inclusion; 5378 study reports were subsequently excluded as they did not meet the eligibility criteria, and 225 were retrieved for full-text assessment. A total of 116 studies were then excluded because they did not meet the inclusion criteria in terms of study design and characteristics of the intervention and 35 primary studies (5601 participants) reported in 109 peer-reviewed publications were deemed suitable for inclusion. IPD were sought from the investigators of the 35 clinical studies. 17 studies (49%) from nine countries provided IPD (3431 participants; figure 1; appendix pp 18–24) and the remaining 18 studies did not provide IPD.

Among the 17 studies that provided IPD, 1750 participants were allocated to the testosterone group and 1681 to the placebo group. Mean participant age was 65 years (SD 11) and most participants were White (testosterone, 915 [87·5%] of 1046; placebo, 888 [87·6%] of 1014) and non-smokers (testosterone, 838 [88·9%] of 943; placebo, 756 [87·2%] of 867). Mean BMI was 30 kg/m² (SD 5). At baseline, 432 (27·4%) of 1574 men had diabetes, 5 (23·8%) of 21 had angina, and 81 (8·4%) of 970 had previous myocardial infarction in the testosterone group and 402 (26·9%) of 1492 had diabetes, 5 (26·3%) of 19 had angina, and 83 (8·6%) of 964 had previous myocardial infarction in the placebo group (table 1; appendix pp 25–27). Across studies, the mean duration of testosterone treatment was 9·5 months (range, 12 weeks–3 years). The rate of cardiovascular or cerebrovascular events was not a primary endpoint in any of the included trials. Overall, the risk of bias was judged to be low for 12 (71%) of the 17 IPD studies and unclear for the remaining five studies. For the 18 non-IPD studies, the overall risk of bias was judged to be low for three (17%) studies, unclear for 13 (72%) studies, and high for two (11%) studies (appendix pp 28–34).

	Number of studies	Testosterone treatment group	Placebo group
Demographics			
Age, years	16	64·5 (11·0); 1724	65·3 (10·8); 1656
Body-mass index, kg/m²	17	30·3 (4·7); 1746	30·2 (4·5); 1677
Ethnicity	6	..	..
Caucasian	..	915/1046 (87·5%)	888/1014(87·6%)
Asian	..	63/1046 (6·0%)	62/1014 (6·1%)
Black or African American	..	16/1046 (1·5%)	12/1014 (1·2%)
Other	..	9/1046 (0·9%)	7/1014 (0·7%)
Missing	..	43/1046 (4·1%)	45/1014 (4·4%)
Smoking status	10	..	..
No	..	838/943 (88·9%)	756/867 (87·2)
Yes	..	103/943 (10·9%)	107/867 (12·3%)
Missing	..	2/943 (0·2%)	4/867 (0·5%)
Hormone concentrations			
Albumin, g/L	9	42·6 (3·2); 817	42·7 (3·1); 783
Estradiol, pmol/L	8	80·8 (38·6); 782	77·1 (33·6); 710
Follicle stimulating hormone, IU/L	8	14·7 (16·7); 711	14·2 (16·0); 683
Luteinising hormone, IU/L	8	6·0 (5·6); 435	6·3 (5·6); 362
Sex hormone binding globulin, nmol/L	15	33·8 (16·6); 1256	32·7 (16·2); 1190
Cardiovascular reported medical history			
Unspecified	1	13/45 (28·9%)	5/43 (11·6%)
Angina	1	5/21 (23·8%)	5/19 (26·3%)
Coronary heart disease	7	95/803 (11·8%)	82/771 (10·6%)
Myocardial infarction	6	81/970 (8·4%)	83/964 (8·6%)
Arrhythmia	6	36/713 (5·0%)	25/677 (3·7%)
Peripheral vascular disease	4	12/500 (2·4%)	9/472 (1·9%)
Atherosclerosis	3	16/531 (3·0%)	7/527 (1·3%)
Heart failure	6	13/624 (2·1%)	3/591 (0·5%)
Valvular heart disease	4	2/586 (0·3%)	9/55 (16·4%)
Stable angina	3	4/530 (0·8%)	8/533 (1·5%)
Aortic aneurysm	2	2/379 (0·5%)	5/376 (1·3%)
Unstable angina	2	0/513	1/508 (0·2%)
Cardiac arrest	1	0/113	1/110 (0·9%)
Other medical conditions			
Cerebrovascular reported medical history	8	37/1139 (3·2%)	58/1085 (5·3%)
Diabetes*	12	432/1574 (27·4%)	402/1492 (26·9%)
Prostate cancer	17	0/1750	0/1681
Sexual function			
IIEF-15	5	..	..
Total	..	33·47 (20·65); 800	31·11 (20·84); 818
Erectile function	..	13·12 (10·03); 814	12·02 (10·00); 838
Orgasmic function	..	5·28 (3·91); 820	4·76 (4·02); 841
Sexual desire	..	5·18 (2·12); 819	5·03 (2·12); 839
Intercourse satisfaction	..	5·27 (5·00); 818	4·65 (4·96); 844
Overall satisfaction	..	4·65 (2·48); 808	4·59 (2·52); 826
IIEF-5	5	14·66 (7·16); 273	14·74 (7·01); 206
Androgen deficiency in the aging men	1	4·06 (2·21); 113	3·69 (2·43); 110

(Table 1 continues on next page)

	Number of studies	Testosterone treatment group	Placebo group
(Continued from previous page)			
Physiological marker			
Testosterone, nmol/L	16	9·21 (2·85); 1387	9·21 (2·83); 1318
Free testosterone, pmol/L	12	196·02 (66·46); 120	198·92 (70·87); 116
Fasting glucose, mmol/L	12	6·55 (2·18); 1421	6·66 (2·36); 1353
Cholesterol, mmol/L	15	4·71 (1·12); 1670	4·73 (1·10); 1606
Low-density lipoproteins, mmol/L	15	2·81 (1·02); 1644	2·78 (1·00); 1584
High-density lipoproteins, mmol/L	15	1·20 (0·36); 1664	1·21 (0·39); 1599
Triglycerides, mmol/L	15	1·87 (1·39); 1653	1·91 (1·50); 1584
Haemoglobin, g/L	14	145·26 (12·64); 160	144·30 (12·89); 151
HbA_{1c} (%)	10	6·35 (1·08); 1067	6·36 (1·12); 1059
Haematocrit (%)	16	43·29 (3·68); 1694	42·99 (3·83); 1621
Systolic blood pressure, mm Hg	12	133·13 (17·30); 130	133·52 (16·62); 127
Diastolic blood pressure, mm Hg	12	77·21 (10·74); 1300	77·08 (10·72); 1274

Data are mean (SD) with number of participants, or n/N (%). IIEF=International Index of Erectile Function. *Type 1, 2, and unknown type.

Table 1: **Baseline characteristics of the participants enrolled in the 17 individual participant dataset studies**

14 (82%) studies provided IPD on mortality. The one-stage analysis indicated that fewer deaths were reported in the testosterone group (six [0·4%] of 1621) than in the placebo group (12 [0·8%] of 1537) with no significant differences between groups (OR 0·46 [95% CI 0·17–1·24]; p=0·13). Causes of death included myocardial infarction, cancer, and ruptured aortic aneurysm; in three studies (seven deaths in total) cause was undetermined (table 2). The two-stage analysis (figure 2A) and Mantel-Haenszel sensitivity analysis showed similar results (appendix p 35). Both contour-enhanced funnel plots as well as Peters' test on small-study effects for IPD (Peters' test p=0·28), aggregate, and all studies combined (Peters' test p=0·46) showed no evidence of significant small-study bias (appendix p 36).

13 studies (76%) provided IPD for cardiovascular or cerebrovascular events (table 2). There were 120 (7·5%) of 1601 events in the testosterone group and 110 (7·2%) of 1519 events in the placebo group; there was no significant difference between groups (OR 1·07 [95% CI 0·81–1·42]; p=0·62). Most reported events were arrhythmia, coronary heart disease, heart failure, myocardial infarction, and valvular heart disease (table 2). Sensitivity analysis, including unknown cause of death, did not change observed results (OR 1·05 [95% CI 0·79–1·38]; p=0·74). Results were not changed significantly by including follow-up time as a weight in the model (cardiovascular or cerebrovascular events unadjusted OR 1·07 [95% CI 0·81–1·42] to OR 1·02 [0·92–1·14]; death unadjusted OR 0·46 [0·17–1·24] to OR 0·42 [0·28–0·62]). Two-stage analysis showed differences between IPD (OR 1·03 [95% CI 0·77–1·38]) and aggregate data (OR 0·35 [0·12–1·01]) (figure 2B; appendix p 37). Both contour-enhanced funnel plots (appendix p 38), as well as Peters' test on small-study effects for IPD (Peters' test p=0·82), aggregate, and all studies combined (Peters' test p=0·70), showed no significant small-study bias. There was no evidence of treatment-covariate interaction for diabetes or smoking status, age, or baseline cardiovascular or cerebrovascular events (appendix p 37). Furthermore, pre-specified analysis showed no evidence that baseline total or free testosterone were associated with risks of cardiovascular or cerebrovascular event risk during testosterone treatment. However, post-hoc sensitivity analyses suggested that cardiovascular or cerebrovascular event risk favoured testosterone treatment when free testosterone was between 180 and 220 pmol/L (appendix p 40).

Regarding physiological markers, as expected, the one-stage analysis showed evidence of higher serum total testosterone concentrations in the testosterone group than the placebo group (mean difference 7·24 nmol/L [95% CI 5·07–9·41]; p<0·0001; τ^2=17·01; table 3). Similar findings were observed for free testosterone but with substantial heterogeneity. Furthermore, the one-stage analysis showed evidence of lower HDL cholesterol in the testosterone group than the placebo group (mean difference –0·06 nmol/L [95% CI –0·08 to –0·04]; p<0·0001; τ^2=0·0). Both serum total cholesterol and triglycerides were significantly lower in the testosterone group than the placebo group; there was evidence of some difference and a degree of homogeneity (mean difference for total cholesterol, –0·15 mmol/L [95% CI –0·20 to –0·10]; p<0·001; τ^2=0·00 and mean difference for triglycerides, –0·09 nmol/L [95% CI –0·18 to –0·00]; p=0·04; τ^2=0·01). Significant differences were observed for haemoglobin and haematocrit. For fasting glucose sensitivity, HbA_{1c}, and blood pressure, there was no difference between treatment groups. However, fasting glucose and HbA_{1c} analyses were not limited to patients with diabetes. Results for the one-stage analysis for the remaining physiological marker outcomes are presented in the appendix (p 41). The two-stage analysis showed similar results to the one-stage analysis; however, for some outcomes there was a difference between the studies with and without IPD (appendix p 42–61).

Results of additional outcomes are presented in table 4. In the testosterone group, 14 (1·9%) of 752 men had new diabetes or diabetes complications, but there was no evidence of difference between groups (χ^2 test, p>0·05). Similarly, there was no evidence of difference between groups in terms of incidence of prostate cancer, hypertension, venous thromboembolism, and non-stroke cerebrovascular pathology. More men treated with testosterone had oedema and high haematocrit than treated with placebo.

Discussion

Our IPD meta-analysis of more than 3000 patients with hypogonadism from randomised placebo-controlled trials done by 17 research groups indicates that testosterone treatment is not associated with increased risk of various subtypes of cardiovascular events compared with placebo in the short to medium term. The small total number of deaths within our IPD analysis precluded a meaningful evaluation of the impact of testosterone treatment on mortality; furthermore, there was little available data evaluating the cardiovascular safety of testosterone beyond a 12-month duration of administration. Testosterone treatment did not have adverse effects on blood pressure or glycaemic markers compared with placebo; furthermore, it did not increase thrombotic events despite increased haematocrit. Testosterone treatment was associated with a modest lowering of total and HDL cholesterol and triglyceride concentrations compared with placebo.

Men with hypogonadism included in this IPD analysis had a higher prevalence of cardiovascular risk factors compared with the general population. Despite these risk factors, the overall incidence of cardiovascular events was not significantly higher during testosterone treatment than for placebo. Because most trials do not publish details of individual adverse events, the exact frequency of cardiovascular events occurring during testosterone treatment, up until this point, has been unclear. Two previous meta-analyses, which used different inclusion and exclusion criteria, have quantified the total numbers of reported cardiovascular events of any subtype, during testosterone therapy.[21,22] Xu and colleagues[21] reported 180 (6·0%) cardiovascular-related events among 2994 men from 27 trials while Corona and colleagues[22] reported 210 (3·8%) cardiovascular events among 5464 men from 75 trials. Within our IPD analysis, two masked clinical investigators identified a total of 342 cardiovascular events from the included IPD, which to date is the highest published rate of cardiovascular events. There is currently no consensus on the components of cardiovascular endpoint constituting a major adverse cardiovascular event, which might prohibit the comparison, replication, and aggregation of data.[56] Here, we have reported every cardiovascular event (including those classified by ACC[12]) encountered within several clinical trials providing IPD. Focusing on all cardiovascular events has enabled us to evaluate all aspects of cardiovascular safety for clinicians and patients, without making assumptions about the mechanisms of any potential association between testosterone and cardiovascular disease.

The most frequently recorded cardiovascular event categories in the identified trials were arrhythmia, coronary heart disease (without further description provided), heart failure, cerebrovascular events, and myocardial infarction. We have also identified and reported frequencies of stable angina, peripheral vascular disease, aortic aneurysm, and aortic dissection, which have not been reported by any previous meta-analysis.[5,20–22,28,57–59] None of the cardiovascular event subtypes were significantly more common in patients assigned to testosterone treatment than in patients assigned to placebo. Neither patient age nor the previous diagnosis of cardiovascular events were associated with an increased risk of cardiovascular events. Several thresholds for serum total testosterone (ranging between 8 and 12 nmol/L) have been proposed for the diagnosis of hypogonadism.[60] A post-hoc subgroup analysis showed a lower risk of cardiovascular events with testosterone treatment when calculated free testosterone was 180–220 pmol/L. However, no overall association was observed between cardiovascular events and either free or total serum testosterone at baseline or during testosterone treatment. No clear factors associated with cardiovascular risk were identified during testosterone treatment. Two previous studies (one of which is included in our IPD analysis) have reported that testosterone treatment is associated with reduced mortality in hypogonadal men with type 2 diabetes.[61,62] Our IPD analysis reported a non-significant increase in cardiovascular event risk in men

	Number of studies	Testosterone treatment group	Placebo group	OR (95% CI)	p value
Mortality from any cause					
Number of participants*	14	6/1621 (0·4%)	12/1537 (0·8%)	0·46 (0·17–1·24)	0·13
Myocardial Infarction	3	2/6 (33·3%)	2/12 (16·7%)	..	..
Cancer	1	0	3/12 (25·0%)	..	..
Ruptured aortic aneurysm	1	0	1/12 (8·3%)	..	..
Constrictive pericarditis	1	1/6 (16·7%)	0	..	..
Multiple organ failure	1	1/6 (16·7%)	0	..	..
Venous thromboembolism	1	0	1/12 (8·3%)	..	..
Unknown	3	2/6 (33·3%)	5/12 (41·7%)	..	..
Cardiovascular or cerebrovascular events					
Number of participants†	13	120/1601 (7·5)	110/1519 (7·2)	1·07 (0·81, 1·42)	0·62
Total number of events	13	182	183	..	..
Number of participants with a cardiovascular event	11	107/120 (89·2%)	105/110 (95·5%)	..	..
Total number of cardiovascular events‡	11	166	176	..	..
Arrhythmia	6	52/166 (31·3%)	47/176 (26·7%)	..	..
Coronary heart disease	6	33/166 (19·9%)	33/176 (18·8%)	..	..
Heart failure	6	22/166 (13·3%)	28/176 (15·9%)	..	..
Myocardial infarction	7	10/166 (6·0%)	16/176 (9·1%)	..	..
Valvular heart disease	2	18/166 (10·8%)	12/176 (6·8%)	..	..
Peripheral vascular disease	4	8/166 (4·8%)	14/176 (8·0%)	..	..
Stable angina	5	7/166 (4·2%)	7/176 (4·0%)	..	..
Aortic aneurysm§	5	6/166 (3·6%)	7/176 (4·0%)	..	..
New angina	3	5/166 (3·0%)	5/176 (2·8%)	..	..
Unstable angina	3	2/166 (1·2%)	4/176 (2·3%)	..	..
Aortic dissection	1	2/166 (1·2%)	0	..	..
Atherosclerosis	1	1/166 (0·6%)	1/176 (0·6%)	..	..
Cardiac arrest	2	0	2/176 (1·1%)	..	..
Number of participants with a cerebrovascular event	11	15/120 (12·5%)	7/110 (6·4%)	..	..
Total number of cerebrovascular events‡	11	16	7	..	..

Data are n/N (%), unless otherwise specified. For one study[28] outcomes were reported up to 3 years and the date of events could not be confirmed. OR=odds ratio. *Of the 14 studies, eight reported no deaths[13,16,39–44] and six reported deaths.[13,32,38,45–47] We were unable to confirm whether any deaths occurred for the remaining three studies;[48–50] therefore, they were not included. †Of the 13 studies, two[47,61] reported no cardiovascular or cerebrovascular events. We were unable to confirm whether cardiovascular or cerebrovascular events occurred for the remaining four studies.[44,48–50] ‡Some participants had more than one event. §One event was a ruptured aortic aneurysm.

Table 2: **One-stage individual participants dataset meta-analysis for all-cause mortality and cardiovascular or cerebrovascular events**

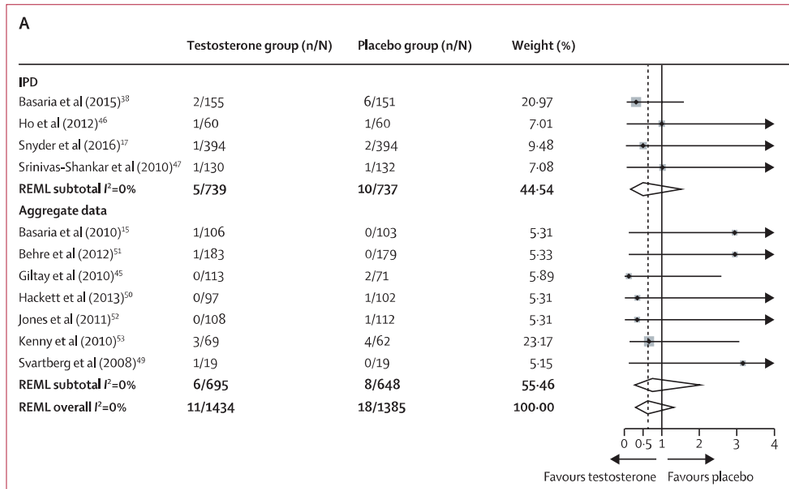

Figure 2: **Two-stage IPD meta-analysis for all-cause mortality (A) and cardiovascular or cerebrovascular events (B)**
IPD=individual participant dataset. OR=odds ratio. REML=restricted maximum likelihood.

	Number of studies	Testosterone treatment group	Placebo group	Mean difference (95% CI)	τ^2
Testosterone, nmol/L	16	17·27 (10·34); 1211	9·87 (3·98); 1156	7·24 (5·07 to 9·41)	17·01
Free testosterone, pmol/L	12	426·70 (368·42); 1058	203·57 (86·24); 1027	186·40 (115·91 to 256·90)	13 741·90
Fasting glucose, mmol/L	12	6·50 (2·09); 1259	6·75 (2·38); 1181	−0·16 (−0·24 to −0·07)	0·00
Fasting glucose sensitivity*, mmol/L	11	6·04 (1·69); 946	6·24 (2·04); 897	−0·13 (−0·28 to 0·02)	0·04
Cholesterol, mmol/L	14	4·51 (1·05); 1388	4·67 (1·11); 1314	−0·15 (−0·20 to −0·10)	0·00
Low-density lipoproteins cholesterol, mmol/L	14	2·69 (0·98); 1378	2·70 (0·98); 1299	−0·03 (−0·08 to 0·01)	0·00
High-density lipoproteins cholesterol, mmol/L	14	1·15 (0·33); 1384	1·21 (0·39); 1312	−0·06 (−0·08 to −0·04)	0·00
Triglycerides, mmol/L	14	1·73 (1·30); 1368	1·89 (1·51); 1297	−0·09 (−0·18 to −0·00)	0·01
Haemoglobin, g/L	13	153·53 (14·71); 1291	143·58 (12·67); 1206	10·87 (8·19 to 13·55)	20·80
Haematocrit (%)	15	46·06 (4·37); 1399	42·94 (3·77); 1309	3·15 (2·42 to 3·88)	1·77
HbA_{1c} (%)	8	6·46 (1·12); 748	6·58 (1·21); 742	−0·09 (−0·25 to 0·06)	0·03
HbA_{1c} (%) sensitivity*	7	6·14 (0·94); 519	6·24 (1·08); 523	−0·89 (−2·43 to 0·64)	4·29
Systolic blood pressure, mmHg	10	134·11 (17·14); 1069	133·31 (16·64); 1041	0·99 (−0·08 to 2·06)	0·00
Diastolic blood pressure, mmHg	10	77·20 (11·03); 1069	76·84 (10·98); 1041	0·48 (−0·30 to 1·26)	0·15

Data are mean (SD), unless otherwise specified. Outcomes were analysed using a random-effects model. *Participants with diabetes at baseline were excluded.

Table 3: **One-stage analysis for secondary outcome of physiological markers**

with diabetes during testosterone treatment, suggesting potential heterogeneity in the results of participating studies. In summary, our findings indicate that testosterone treatment did not increase risks of any subtype of cardiovascular event in men with hypogonadism and did not identify any patient characteristics that were associated with a significantly increased risk of cardiovascular events during testosterone treatment. Furthermore, we observed a similar mortality rate during testosterone treatment when compared with placebo, which was reassuring. A meta-analysis of several observational studies[63] reported an association between low endogenous testosterone concentrations and increased risk of cardiovascular events, suggesting, notwithstanding the possibility of reverse causality, that testosterone therapy might result in some beneficial effects on the cardiovascular system. According to the results of our analysis, the overall short to medium-term effect of testosterone seems neutral.

In view of the lack of consistent cardiovascular event classification, adjudication, or reporting within trials, we did a masked analysis of each individual adverse event by two independent clinicians to classify cardiovascular events from all IPD studies objectively. We successfully obtained data from 3431 (61·3%) of the 5601 participants included in eligible published trials, but IPD from some studies could not be included due to data loss, retirement or death of lead investigators, or unwillingness of two pharmaceutical sponsors (Bayer AG, Kyowa Kirin) to disclose them. To assess the effect of studies for which IPD were not available, we extracted appropriate aggregate study-level data and incorporated them alongside the IPD using two-stage IPD random-effect meta-analyses.[64] Our aggregate meta-analysis suggested that outcome data were not significantly discrepant between our IPD and non-IPD studies. Nevertheless, we cannot exclude that a high number of unreported cardiovascular events in the non-IPD studies could ultimately change the conclusions of our analysis. The very small total number of deaths recorded during testosterone trials limits our ability to analyse why they occurred. The mean follow-up of included randomised controlled trials was 9·5 months, which might be too short for atherosclerotic plaque progression to accrue. This is important, since the Testosterone Trials observed that a 12-month duration of testosterone treatment was associated with a significantly greater increase in coronary artery non-calcified plaque volume versus placebo, in older men.[65] This finding has led some to advocate coronary artery calcium scoring before treatment of high-risk individuals with underlying cardiovascular disease, due to the remaining possibility that testosterone might be riskier in such individuals.

	Number of studies	Testosterone treatment group	Placebo group
Diabetes or diabetes complications	2	14/752 (1·9%)	19/751 (2·5%)
Prostate cancer	8	10/1293 (0·8%)	3/1059 (0·3%)
Oedema	7	34/1301 (2·6%)	17/1290 (1·3%)
Hypertension	7	28/1195 (2·3%)	20/1182 (1·7%)
High haematocrit	7	30/1079 (2·8%)	5/993 (0·5%)
Venous thromboembolism	4	5/1037 (0·5%)	7/1034 (0·7%)
Non-stroke cerebrovascular pathology*	3	4/655 (0·6%)	11/648 (1·7%)

Data are n/N (%). *Examples include carotid occlusion and carotid stenosis.

Table 4: **Summary of additional outcomes**

However, we observed no significant associations between existing (baseline) cardiovascular or cerebrovascular events and risks of future events during the first 9·5 months after initiation of testosterone treatment.

The secondary objective of this IPD analysis was to assess the physiological effects of testosterone treatment. Testosterone had no significant effect on HbA_{1c}. Testosterone reduced serum fasting glucose concentrations in cases for which this was recorded, but this effect became non-significant when patients with known diabetes were excluded. Consistent with some published studies, minor reductions in serum total cholesterol, HDL cholesterol, and triglycerides were observed. Testosterone significantly elevated haematocrit and haemoglobin, which is in keeping with its role of suppressing hepcidin, a tonic, negative regulator of haematopoiesis. Furthermore, testosterone treatment was associated with a five-times higher risk of polycythemia. However, only five cases of deep vein thromboses were recorded during testosterone treatment, compared with seven in the placebo group. We observed no overall effect of testosterone on systolic or diastolic blood pressure.

An important strength of this IPD meta-analysis is its large size compared with individual testosterone trials, which have provided limited and situation-dependent information on cardiovascular safety. This IPD meta-analysis draws data from multiple, geographically diverse studies with approximately five-times more participants than the largest single participating trial. Definitive conclusions about the long-term cardiovascular safety of testosterone therapy cannot be made without results of an adequately powered clinical trial. However, this study has allowed us to more precisely estimate the incidence of cardiovascular events associated with testosterone treatment, which might be generalisable to patients worldwide. Furthermore, utilising previously collected data, we have actively reduced research waste.[66] We did not detect any significant funnel plot asymmetry in our analyses, suggesting that publication bias is not likely to be present in the overall IPD set. Several meta-analyses of published aggregate data have investigated the cardiovascular safety of testosterone treatment in men. Xu and colleagues analysed cardiovascular episodes of any type within the international statistical classification of diseases (ICD-10) and observed an increased cardiovascular risk during testosterone treatment.[21] By contrast, Corona and colleagues and Diem and colleagues did three separate meta-analyses of five-point major adverse cardiovascular events as the primary outcome, and any cardiovascular event as a secondary outcome; testosterone treatment was neither associated with major adverse cardiovascular events nor other cardiovascular events in any meta-analysis.[5,22,59] Fernandez-Balsells and colleagues reported that testosterone treatment did not significantly modify risks of myocardial infarction, all-cause mortality, coronary artery bypass, and arrhythmia, but did reduce HDL cholesterol concentrations.[20] Both Alexander and colleagues and Elliot and colleagues analysed risks of discrete major adverse cardiovascular event subtypes during testosterone treatment; neither myocardial infarction, stroke, nor mortality risks were associated with testosterone therapy.[28,58] Guo and colleagues observed a reduction in total cholesterol during testosterone therapy, but did not analyse lipid subtypes, or cardiovascular event risk.[57] Most of these meta-analyses failed to observe increased cardiovascular event risk with testosterone; however, many guidelines recommend that cardiovascular risk is considered when commencing testosterone treatment.

The current study has several strengths compared with all previous meta-analyses. Firstly, our access to unpublished cardiovascular events, which were independently adjudicated by investigators masked to the treatment allocation, allows for more robust scrutiny of cardiovascular safety. Secondly, we have been able to investigate whether subgroups of patients have distinct cardiovascular risk profiles during testosterone administration. Some previous meta-analyses of published data have comprised studies in which the relatively high baseline serum testosterone concentrations have allowed non-hypogonadal patients to be included.[5,20,28,57] By contrast, this IPD meta-analysis is restricted to patients with serum testosterone <12 nmol/L (350 ng/dL) using a validated mass spectrometry or immunoassays; this threshold was chosen after consideration that all current clinical guidelines on testosterone treatment recommend serum testosterone thresholds of between 8 and 12 nmol/L to ensure the inclusion of hypogonadal men exclusively. Variation among testosterone assay measurements limits the extent to which results from different studies can be compared.[67] Our IPD approach was further strengthened by subgroup analyses to assess whether any observed effect of testosterone was consistent across subgroups of patients. We did not observe any significant association between baseline testosterone and risks of any adverse outcome. Unlike some other meta-analyses, we excluded studies of patient groups with distinct risk profiles such as cancer, HIV, and cirrhosis,[22,27] or those with less than 3 months of testosterone exposure.[28] Finally, our analysis compared physiological markers in a more standardised manner compared with previous meta-analyses, by analysing the outcome at the timepoint closest to 12 months of testosterone treatment, regardless of whether that data had been previously published. Two meta-analyses have reported that testosterone improves glycaemic parameters in men.[68,69] Furthermore, Corona and colleagues reported an improvement in blood pressure during testosterone treatment.[70] However, our study suggests that testosterone has no significant effects on either blood pressure or glycaemic indices.

Results of this meta-analysis have potentially important implications for the management of men with hypogonadism. Worldwide prescribing of testosterone

for hypogonadism is increasing;[2] however, conflicting messages on testosterone safety might have caused variations in treatment among patients. We have conducted the most comprehensive study to date investigating the safety of testosterone treatment of hypogonadism. Testosterone treatment did not increase cardiovascular event risk in the short term to medium term. Furthermore, we did not identify subgroups with high cardiovascular risk. An ongoing trial (NCT03518034) is investigating the longer-term safety of testosterone, and future studies are needed to analyse the risk–benefit and cost-effectiveness of testosterone therapy. However, the current results provide some reassurance about the short-term to medium-term safety of testosterone to treat male hypogonadism.

Contributors

MB, CNJ, KG, LA, WSD, NO, RQ, and SBhat were involved in conceptualisation and study design. MC, CNJ, MB, FW, and RQ were involved in data collection and management. MC and MA-M extracted data. SBhas, PJS, SSE, MG, TGT, EJGil, YTvderS, MHE-V, EJGia, GH, SR, JS, KLH, KGA, GBB, JLT, HMT, CHCK, WST, LSM, RJR, RSS, SR, MSA, and LVM were involved in trial data collection and data transfer. JH formatted the data and did the statistical analyses. LA provided statistical advice. JH, MC, CNJ, MB, FW, WSD, NO, and RQ wrote the first draft of the manuscript. JH, MC, MB, CNJ, KG, LA, WSD, RH, NO, FW, RQ, SBhat, SBhas, PJS, SSE, MG, TGT, EG, YTS, MHE-V, EJGil, GH, and KGA revised the manuscript. PM did the literature searches and formatted the manuscript. JH and MB verified the underlying data. All authors have critically reviewed and approved the final manuscript version. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

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Data sharing

The statistical analysis plan used for this study is included in the appendix (pp 5–17). All aggregate patient data are presented either in the manuscript or appendix. Individual patient data cannot be made publicly available because they are protected by a confidentiality agreement.

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Metformin, testosterone, or both in men with obesity and low testosterone: A double-blind, parallel-group, randomized controlled trial

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ABSTRACT

Background: Men with obesity tend to be insulin resistant and often have low-normal testosterone concentrations. We conducted a clinical trial aimed to evaluate potential therapeutic strategies for low testosterone in men with obesity.

Methods: We did a 1-year, parallel, randomized, double-blind, placebo-controlled trial, where we evaluated the independent and combined effects of metformin and testosterone in 106 men with obesity, aged 18–50 years, who had low levels of testosterone and no diabetes mellitus. The primary outcome was change in insulin resistance, measured as Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) index. Secondary outcomes included changes in total and free serum testosterone, body composition, metabolic variables, erectile function, and health-related quality of life (HRQoL).

Results: In the intention-to-treat analysis, the HOMA-IR index decreased significantly in all active groups compared to placebo (metformin −2.4, 95 % CI −4.1 to −0.8, $p = 0.004$; testosterone −2.7, 95 % CI −4.3 to −1.1, $p = 0.001$; combination −3.4, 95 % CI −5.0 to −1.8, $p < 0.001$). Combination therapy was not superior to testosterone alone in decreasing insulin resistance (−0.7, 95 % CI −2.3 to 0.9, $p = 0.383$). Only the combination of metformin plus testosterone significantly increased total and free testosterone concentrations, compared to placebo. No significant changes in body composition (except for a higher decrease in fat mass in the metformin and combination group), metabolic variables, erectile function, or HRQoL were found with any treatment.

Conclusions: Among men with obesity and low testosterone concentrations, the combination of metformin plus testosterone, metformin only, and testosterone only, compared to placebo, reduced insulin resistance with no evidence of additive benefit.

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Clinical Study | D J Handelsman and others | Recovery of serum testosterone, LH and FSH | 186:3 | 307–318

Recovery of male reproductive endocrine function after ceasing prolonged testosterone undecanoate injections

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Abstract

Context: The time course of male reproductive hormone recovery after stopping injectable testosterone undecanoate (TU) treatment is not known.

Objective: The aim of this study was to investigate the rate, extent, and determinants of reproductive hormone recovery over 12 months after stopping TU injections.

Materials and Methods: Men (n = 303) with glucose intolerance but without pathologic hypogonadism who completed a 2-year placebo (P)-controlled randomized clinical trial of TU treatment were recruited for further 12 months while remaining blinded to treatment. Sex steroids (testosterone (T), dihydrotestosterone, oestradiol, oestrone) by liquid chromatography-mass sprectometry, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone-binding globulin (SHBG) by immunoassays and sexual function questionnaires (Psychosexual Diary Questionnaire, International Index of Erectile Function, and short form survey (SF-12)) were measured at entry (3 months after the last injection) and 6, 12, 18, 24, 40, and 52 weeks later.

Results: In the nested cohort of TU-treated men, serum T was initially higher but declined at 12 weeks remaining stable thereafter with serum T and SHBG at 11 and 13%, respectively, lower than P-treated men. Similarly, both questionnaires showed initial carry-over higher scores in T-treated men but after 18 weeks showed no difference between T- and P-treated men. Initially, fully suppressed serum LH and FSH recovered slowly towards the participant's own pre-treatment baseline over 12 months since the last injection.

Conclusions: After stopping 2 years of 1000 mg injectable TU treatment, full reproductive hormone recovery is slow and progressive over 15 months since the last testosterone injection but may take longer than 12 months to be complete. Persistent proportionate reduction in serum SHBG and T reflects lasting exogenous T effects on hepatic SHBG secretion rather than androgen deficiency.

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Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries

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Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis

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BACKGROUND: The beneficial effects of hormonal therapy in stimulating spermatogenesis in patients with non-obstructive azoospermia (NOA) and either normal gonadotrophins or hypergonadotropic hypogonadism prior to surgical sperm retrieval (SSR) is controversial. Although the European Association of Urology guidelines state that hormone stimulation is not recommended in routine clinical practice, a significant number of patients undergo empiric therapy prior to SSR. The success rate for SSR from microdissection testicular sperm extraction is only 40–60%, thus hormonal therapy could prove to be an effective adjunctive therapy to increase SSR rates.

†These authors contributed equally to this work.

OBJECTIVE AND RATIONALE: The primary aim of this systematic review and meta-analysis was to compare the SSR rates in men with NOA (excluding those with hypogonadotropic hypogonadism) receiving hormone therapy compared to placebo or no treatment. The secondary objective was to compare the effects of hormonal therapy in normogonadotropic and hypergonadotropic NOA men.

SEARCH METHODS: A literature search was performed using the Medline, Embase, Web of Science and Clinicaltrials.gov databases from 01 January 1946 to 17 September 2020. We included all studies where hormone status was confirmed. We excluded non-English language and animal studies. Heterogeneity was calculated using I^2 statistics and risk of bias was assessed using Cochrane tools. We performed a meta-analysis on all the eligible controlled trials to determine whether hormone stimulation (irrespective of class) improved SSR rates and also whether this was affected by baseline hormone status (hypergonadotropic versus normogonadotropic NOA men). Sensitivity analyses were performed when indicated.

OUTCOMES: A total of 3846 studies were screened and 22 studies were included with 1706 participants. A higher SSR rate in subjects pre-treated with hormonal therapy was observed (odds ratio (OR) 1.96, 95% CI: 1.08–3.56, $P=0.03$) and this trend persisted when excluding a study containing only men with Klinefelter syndrome (OR 1.90, 95% CI: 1.03–3.51, $P=0.04$). However, the subgroup analysis of baseline hormone status demonstrated a significant improvement only in normogonadotropic men (OR 2.13, 95% CI: 1.10–4.14, $P=0.02$) and not in hypergonadotropic patients (OR 1.73, 95% CI: 0.44–6.77, $P=0.43$). The literature was at moderate or severe risk of bias.

WIDER IMPLICATIONS: This meta-analysis demonstrates that hormone therapy is not associated with improved SSR rates in hypergonadotropic hypogonadism. While hormone therapy improved SSR rates in eugonadal men with NOA, the quality of evidence was low with a moderate to high risk of bias. Therefore, hormone therapy should not be routinely used in men with NOA prior to SSR and large scale, prospective randomized controlled trials are needed to validate the meta-analysis findings.

Key words: non-obstructive azoospermia / testicular extraction sperm surgery / hypergonadotropic hypogonadism / selective oestrogen receptor modulators / aromatase inhibitors / gonadotrophins

Introduction

Non-obstructive azoospermia (NOA) is the absence of sperm in the ejaculate secondary to impaired spermatogenesis (Schlegel, 2004) and represents the most severe form of male infertility. NOA is estimated to affect 1% of the male population and 10–20% of patients presenting with infertility (Jarow *et al.*, 1989). Biochemical hypogonadism is present in almost half of all patients with NOA (Bobjer *et al.*, 2012; Reifsnyder *et al.*, 2012).

The use of hormone therapy in men with NOA and hypergonadotropic hypogonadism (i.e. primary hypogonadism) or eugonadism is controversial (Kim and Schlegel, 2008; Reifsnyder *et al.*, 2012; Kumar, 2013; Shiraishi, 2015) with mixed outcomes reported in the literature although it is widely practiced.

Intratesticular testosterone (ITT) is required for spermiogenesis and serum testosterone has been shown to be an inaccurate surrogate for ITT level with differences ranging from 40- to 181-fold (Jarow *et al.*, 2001; McLachlan, 2002; Coviello *et al.*, 2004; Roth *et al.*, 2010).

In hypergonadotropic hypogonadism, both human and animal data suggest a pathological desensitization of the FSH receptor (FSHR) caused by high circulating levels of gonadotrophins (Gnanaprakasam *et al.*, 1979; Namiki *et al.*, 1985, 1987; Themmen *et al.*, 1991; Foresta *et al.*, 2004). It has been postulated that hormone therapy may benefit patients with hypergonadotropic hypogonadism by using GnRH to suppress gonadotrophin levels and thereby overcoming Sertoli cell receptor desensitization caused by chronically raised FSH levels (Foresta *et al.*, 2004, 2009). Foresta *et al.* (2009) conducted a randomized controlled trial (RCT) in hypergonadotropic men in which treatment with GnRH to induce hypogonadotropism followed by recombinant LH and FSH improved semen parameters and pregnancy rates.

The existence of a testosterone independent pathway for spermatogenesis, through supraphysiological FSH stimulation, provides a rationale for hormone stimulation therapy in both eugonadal and hypergonadotropic hypogonadism patients (Huhtaniemi, 2018; Oduwole et al., 2018a,b). Oduwole *et al.* (2018b) observed that constitutively activating FSHR mutations in mice were able to maintain spermatogenesis even in the absence of androgen signalling including treatment with the anti-androgen Flutamide. Furthermore, a case report (Gromoll *et al.*, 1996) of a male with an FSHR-D567G mutation who exhibited normal spermatogenesis after hypophysectomy suggests that a strong constitutive FSH stimulation can compensate for a deficiency in LH and testosterone.

The current European Association of Urology (EAU) guidelines on Male Sexual and Reproductive Health do not advocate hormone stimulation therapy in idiopathic NOA (Salonia et al., 2021). However, a survey reported that 64.9% of urologists prescribe empiric hormone therapy to treat idiopathic male infertility, with clomiphene citrate the most commonly prescribed drug for both general and fertility-trained urologists (Ko *et al.*, 2012). This may be attributable to the fact that surgical sperm retrieval (SSR) rates in patients with NOA have remained static (40–60%) over the last 10 years (Shiraishi *et al.*, 2012; Corona *et al.*, 2019). Therefore, hormone therapy has been proposed as an adjunctive therapy to improve fertility outcomes (i.e. SSR rates and production of sperm into the ejaculate) in men with NOA.

This is the first systematic review and meta-analysis to investigate the effects of hormone therapy on SSR rate. The primary outcome of the meta-analysis was the SSR rate in men with NOA who were treated with hormone therapy. The secondary outcome was comparison of SSR rates according to baseline hormone status (hypergonadotropic versus normogonadotropic NOA men).

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines and was registered in the international

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human reproduction **ORIGINAL ARTICLE** ***Andrology***

Sperm count is increased by diet-induced weight loss and maintained by exercise or GLP-1 analogue treatment: a randomized controlled trial

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STUDY QUESTION: Does diet-induced weight loss improve semen parameters, and are these possible improvements maintained with sustained weight loss?

SUMMARY ANSWER: An 8-week low-calorie diet-induced weight loss was associated with improved sperm concentration and sperm count, which were maintained after 1 year in men who maintained weight loss.

WHAT IS KNOWN ALREADY: Obesity is associated with impaired semen quality. Weight loss improves metabolic health in obesity, but there is a lack of knowledge on the acute and long-term effects of weight loss on semen parameters.

STUDY DESIGN, SIZE, DURATION: This is a substudy of men with obesity enrolled in a randomized, controlled, double-blinded trial (the S-LITE trial). The trial was conducted between August 2016 and November 2019. A total of 56 men were included in the study and assigned to an initial 8-week low-calorie diet (800 kcal/day) followed by randomization to 52 weeks of either: placebo and habitual activity (placebo), exercise training and placebo (exercise), the Glucagon Like Peptide 1 (GLP-1) analogue liraglutide and habitual activity (liraglutide) or liraglutide in combination with exercise training (combination).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Inclusion criteria were men who delivered semen samples, 18 to 65 years of age, and a body mass index between 32 and 43 kg/m^2, but otherwise healthy. The study was carried out at Hvidovre Hospital and at the University of Copenhagen, and the participants were from the Greater Copenhagen Area. We assessed semen parameters and anthropometrics and collected blood samples before (T0), after the 8-week low-calorie dietary intervention (T1), and after 52 weeks (T2).

MAIN RESULTS AND THE ROLE OF CHANCE: The men lost on average 16.5 kg (95% CI: 15.2–17.8) body weight during the low-calorie diet, which increased sperm concentration 1.49-fold (95% CI: 1.18–1.88, $P < 0.01$) and sperm count 1.41-fold (95% CI: 1.07–1.87, $P < 0.01$). These improvements were maintained for 52 weeks in men who maintained the weight loss, but not in men who regained weight. Semen volume, sperm motility and motile sperm count did not change.

LIMITATIONS, REASONS FOR CAUTION: The S-LITE trial was a randomized controlled trial of weight loss maintenance. Analysis of semen was preregistered to explore the effects of weight loss and weight loss maintenance on semen parameters, but definite inferences cannot be made.

[†]The authors consider that the first two authors should be regarded as joint First Authors.

WIDER IMPLICATIONS OF THE FINDINGS: This study shows that sperm concentration and sperm count were improved after a diet-induced weight loss in men with obesity. Our findings indicate that either or both liraglutide and exercise as weight maintenance strategies may be used to maintain the improvements in sperm concentration and count.

STUDY FUNDING/COMPETING INTEREST(S): This work is supported by an excellence grant from the Novo Nordisk Foundation (NNF16OC0019968), a Challenge Programme Grant from the Novo Nordisk Foundation (NNF18OC0033754) and a grant from Helsefonden. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research centre at the University of Copenhagen, partially funded by an unrestricted donation from the Novo Nordisk Foundation (NNF18CC0034900). Saxenda (liraglutide) and placebo pens were provided by Novo Nordisk. Cambridge Weight Plan diet products for the 8-week low-calorie diet were provided by Cambridge Weight Plan. E.A.: shareholder, employee of ExSeed Health Ltd. Grant Recipient from ExSeed Health Ltd and listed on Patents planned, issued or pending with ExSeed Health Ltd; J.J.H.: consultant for Eli Lilly A/S and Novo Nordisk A/S. Lecture fees for Novo Nordisk A/S. Listed on Patents planned, issued or pending with the University of Copenhagen, Advocacy group for Antag Therapeutics and Bainan Biotech; S.M.: lecture fees for Novo Nordisk A/S. Recipient of Support for attending meetings from Novo Nordisk A/S. Advisory boards of Novo Nordisk A/S; Sanofi Aventis and Merck Sharp & Dohme. S.S.T.: research grant recipient Novo Nordisk. The remaining authors have no conflicts of interest to declare.

TRIAL REGISTRATION NUMBER: The trial was approved by the Ethical Committee of the Capital Region of Denmark (H-16027082) and the Danish Medicines Agency (EudraCT Number: 2015-005585-32). ClinicalTrials.gov identifier (NCT number): NCT04122716.

TRIAL REGISTRATION DATE: 11 May 2016.

DATE OF FIRST PATIENT'S ENROLMENT: August 2016.

Key words: male reproduction / spermatozoa / obesity / weight loss / GLP-1 agonist / liraglutide / semen quality

Introduction

The prevalence of obesity is increasing globally (Bentham *et al.*, 2017), while meta-analyses indicate declining sperm count over time (Carlsen *et al.*, 1992; Levine *et al.*, 2017). A decline in utero exposure to maternal smoking has not reflected an overall improvement of semen quality at the population level in Danish men, which suggests that other adverse factors may maintain the low semen quality (Priskorn *et al.*, 2018). Increasing BMI levels, overweight and obesity are associated with decreased sperm concentration, total sperm count, progressive sperm motility and sperm morphology (Andersen *et al.*, 2015; Salas-Huetos *et al.*, 2021). Increased BMI of both the woman and the male partner is also associated with subfertility (time-to-pregnancy > 12 months or use of assisted reproductive technology) (Hernáez *et al.*, 2021). In line with these observations, results from a meta-analysis showed an increased risk of low (oligozoospermia) and very-low (azoospermia) sperm count in men with obesity compared to men with normal weight. Thus, compared to men with a BMI between 18.5 and 24.9 kg/m^2, the odds ratio for low sperm count increased to 1.28 for men with a BMI between 30.0 and 39.9 kg/m^2 and to 2.04 with a BMI above 40.0 kg/m^2 (Sermondade *et al.*, 2013). Obesity is therefore considered a risk factor for development of male infertility.

The S-LiTE study, a diet-induced weight loss intervention followed by exercise, GLP-1 receptor agonist therapy or the combination to maintain weight loss, has shown that the detrimental metabolic effects of obesity are reversed, to a large extent, by weight loss (Lundgren *et al.*, 2021). While studies in women have shown that weight loss achieved by combining diet and exercise interventions was associated with increased pregnancy rates, only a limited number of studies have investigated the effect of weight loss on male fertility (Best *et al.*, 2017). Initial case reports of men with obesity who underwent bariatric surgery suggested that the dramatic weight loss was associated with an impairment of semen parameters (Lazaros *et al.*, 2012), while a more recent and larger study suggests a modest improvement (Samavat *et al.*, 2018). Likewise, combined diet and exercise-induced weight loss interventions have shown promising effects on sperm count, semen volume, sperm morphology and decreased sperm DNA fragmentation (Håkonsen *et al.*, 2011; Faure *et al.*, 2014; Mir *et al.*, 2018). Higher self-reported moderate-to-vigorous physical activity was associated with higher levels of progressive and total motility in 746 potential sperm donors from China (Sun *et al.*, 2019). Furthermore, the frequency of 10 min bouts of moderate-to-vigorous-intensity physical activity performed and assessed by accelerometers was associated with higher sperm concentration, sperm count, motile concentration and total motile sperm in a cross-sectional study (Pärn *et al.*, 2015). However, it is unclear whether weight loss *per se* improves semen parameters and, if so, whether these improvements can be upheld with sustained weight loss.

Here, we investigated the effect of an 8-week diet-induced weight loss followed by randomization to one of four different 52 weeks weight maintenance strategies: placebo and habitual activity, placebo and exercise, liraglutide and habitual activity or liraglutide and exercise on semen parameters. The use of a GLP-1 receptor agonist, which induces and maintains weight loss, is of particular interest since a case report suggested that liraglutide therapy was detrimental to sperm concentration and motility (Fontoura *et al.*, 2014).

Materials and methods

Study cohort

This study was performed as a substudy of the S-LiTE trial (Synergy effect of the appetite hormone GLP-1 (Liraglutide) and Exercise on maintenance of weight loss and health after a low-calorie diet). The S-LiTE trial protocol with details of the design, a full list of inclusion and exclusion criteria and methods has been published (Jensen *et al.*, 2019) as well as the results of the primary endpoint, weight change

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ARTICLE

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A de novo paradigm for male infertility

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De novo mutations are known to play a prominent role in sporadic disorders with reduced fitness. We hypothesize that de novo mutations play an important role in severe male infertility and explain a portion of the genetic causes of this understudied disorder. To test this hypothesis, we utilize trio-based exome sequencing in a cohort of 185 infertile males and their unaffected parents. Following a systematic analysis, 29 of 145 rare (MAF < 0.1%) protein-altering de novo mutations are classified as possibly causative of the male infertility phenotype. We observed a significant enrichment of loss-of-function de novo mutations in loss-of-function-intolerant genes (p-value = 1.00×10^{-5}) in infertile men compared to controls. Additionally, we detected a significant increase in predicted pathogenic de novo missense mutations affecting missense-intolerant genes (p-value = 5.01×10^{-4}) in contrast to predicted benign de novo mutations. One gene we identify, *RBM5*, is an essential regulator of male germ cell pre-mRNA splicing and has been previously implicated in male infertility in mice. In a follow-up study, 6 rare pathogenic missense mutations affecting this gene are observed in a cohort of 2,506 infertile patients, whilst we find no such mutations in a cohort of 5,784 fertile men (p-value = 0.03). Our results provide evidence for the role of de novo mutations in severe male infertility and point to new candidate genes affecting fertility.

A full list of author affiliations appears at the end of the paper.

ΑΝΔΡΙΚΗ ΑΝΑΠΑΡΑΓΩΓΗ | ΓΕΩΡΓΙΟΣ ΠΑΠΑΔΑΚΗΣ

Male infertility contributes to approximately half of all cases of infertility and affects 7% of the male population. For the majority of these men the cause remains unexplained[1]. Despite a clear role for genetic causes in male infertility, there is a distinct lack of diagnostically relevant genes and at least 40% of all cases are classified as idiopathic[1–4]. Previous studies in other conditions with reproductive lethality, such as neurodevelopmental disorders, have demonstrated an important role for de novo mutations (DNMs) in their etiology[5]. In line with this, recurrent de novo chromosomal abnormalities play an important role in male infertility. Both azoospermia factor (AZF) deletions on the Y chromosome as well as an additional X chromosome, resulting in Klinefelter syndrome, occur de novo. Collectively, these de novo events explain up to 25% of all cases of nonobstructive azoospermia (NOA)[1,4]. Interestingly, in 1999 a DNM in the Y-chromosomal gene *USP9Y* was reported in a man with azoospermia[6]. Until now, however, a systematic analysis of the role of DNMs in male infertility had not been attempted, even though a pilot exome sequencing study in 13 infertile men and their parents was recently published[7]. This is partly explained by a lack of basic research in male reproductive health in general[4,8], but also by the practical challenges of collecting parental samples for this disorder, which is typically diagnosed in adults.

In this work, we address this lack of knowledge by analysing exome sequencing data of 185 infertile males and their parents and reporting on our findings of 29 DNM in these men which are likely causative for the infertility phenotype, based on variant and gene level evidence. We emphasize an enrichment for loss-of-function (LoF) DNM in LoF-intolerant genes and missense DNM in missense-intolerant genes. We identify a number of promising candidate genes for male infertility, including the mRNA splicing gene *RBM5*, which contains a possibly causative DNM in our trio cohort, and possibly causative heterozygous variants in six additional patients for which parental information is not available. This work suggests a potential role for DNM as a cause of severe male infertility and addresses the need for further investigation in larger patient–parent trio cohorts to solidify these results.

Results

Discovery of de novo mutations in infertile male trios. In this study, we investigated the role of DNMs in 185 unexplained cases of oligozoospermia (<5 million sperm cells/ml; $n = 74$) and azoospermia ($n = 111$) by performing whole exome sequencing (WES) in all patients and their parents (see Supplementary Figs. 1, 2, Supplementary Notes and Data for details on methodology and clinical descriptions). In total, we identified and validated 192 rare DNMs (MAF < 0.1%), including 145 protein-altering DNMs. All de novo point mutations were autosomal, except for one on chromosome X, and all occurred in different genes (Supplementary Data 1). Two rare de novo copy-number variations (CNVs) were also identified affecting a total of 7 genes (Supplementary Fig. 3). None of the 145 protein-altering DNMs occurred in a gene already known for its involvement in autosomal dominant human male infertility. This is not unexpected as only four autosomal dominant genes have so far been linked to isolated male infertility in humans[3,9].

Intolerance analysis of genes with de novo loss-of-function mutations. Broadly speaking, across genetic disorders, dominantly acting disease genes are usually intolerant to LoF mutations, as represented by a high pLI score[10] or a low LOEUF score[11]. In our cohort of infertile men, we detected a significant enrichment in the number of LoF-intolerant genes with a LoF DNM ($n = 17$). No such enrichment was identified in a cohort of 1,941 control cases from de novo-db v1.6.1[12] (median pLI in patients with male infertility = 0.80, median pLI in controls = 3.75×10^{-5}, p value = 1.00×10^{-5}, N simulations = 100,000) (Fig. 1a). Similar results were obtained using the LOEUF scores

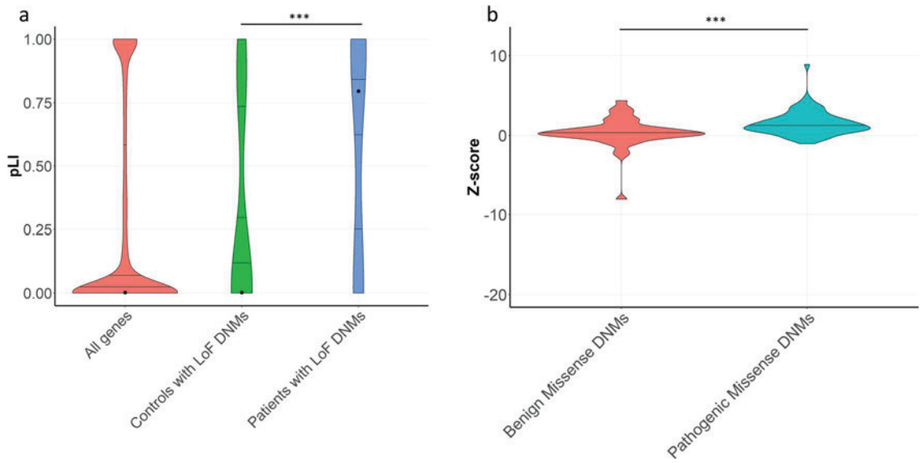


Fig. 1 Analysis of the intolerance to loss-of-function and missense variation in genes with de novo mutations. a Violin plot with quantile lines showing pLI scores in all genes in gnomAD (red), all genes affected by rare protein-altering loss-of-function (LoF) de novo mutations (DNMs) in a control population (http://de novo-db.gs.washington.edu/de novo-db/) (green) and in all genes with a rare protein-altering LoF DNM in our trio cohort (blue). Using the permutation-based, nonparametric test defined by Lelieveld et al. [64] a significant enrichment of LoF DNMs in LoF-intolerant genes in patient cohort was detected in comparison to the number of LoF in fertile control cohort (DNM LoF mutations in patients $n = 17$, median pLI in patients with male infertility = 0.80, DNM LoF mutations in controls $n = 21$, median pLI in controls = 3.75×10^{-5}, p value = 1.00×10^{-5}, N simulations = 100,000). The black dot indicates median pLI scores. **b** Violin plot with quantile lines showing the distribution of Z-scores for genes with predicted benign ($n = 59$) and pathogenic missense DNMs ($n = 63$) in infertile patients. A significant increase in predicated pathogenic DNMs in missense-intolerant genes was detected compared to benign missense DNM (Two-sided Mann–Whitney U test, p value of 3.44×10^{-4}). (***p value < 0.001).

(median LOEUF in patients with male infertility = 0.34, median LOEUF in controls = 0.59, p value = 1.00×10^{-5}, N simulations = 100,000) (Supplementary Fig. 4a). This observation indicates that LoF DNMs likely play an important role in male infertility, similar to what is known for developmental disorders and severe intellectual disability[13,14]. As an example, a heterozygous likely pathogenic frameshift DNM was observed in the LoF-intolerant gene *GREB1L* (pLI = 1) of Proband_076. Homozygous *Greb1l* knockout mice appear to be embryonic lethal, however, typical male infertility phenotypic features such as abnormal fetal testis morphology and decreased fetal testis volume are observed[15]. Interestingly, this patient has a reduced testis volume and severe oligozoospermia (Supplementary Notes Table 1). Nonsense and missense mutations in *GREB1L* in humans are known to cause renal agenesis[16] (OMIM: 617805), not known to be present in our patient. Of note, all previously reported damaging mutations in *GREB1L* causing renal agenesis are either maternally inherited or occurred de novo. This led the authors of one of these renal agenesis studies to speculate that disruption to *GREB1L* could cause infertility in males[15]. A recent WES study involving a cohort of 285 infertile men also noted several patients presenting with pathogenic mutations in genes with an associated systemic disease where male fertility is not always assessed[17].

We also assessed the damaging effects of the two rare de novo CNVs by looking at the pLI score of the genes involved. Proband_066 presented with a large 656 kb de novo deletion on chromosome 11, spanning 6 genes in total. This deletion partially overlapped with a deletion reported in 2014 in a patient with cryptorchidism and NOA[18]. Two genes affected in both patients, *QSER1* and *CSTF3*, are LoF-intolerant with pLI scores of 1 and 0.98, respectively. In particular, *CSTF3* is highly expressed within the testis and is known to be involved in pre-mRNA 3′-end cleavage and poylyadenylation[19].

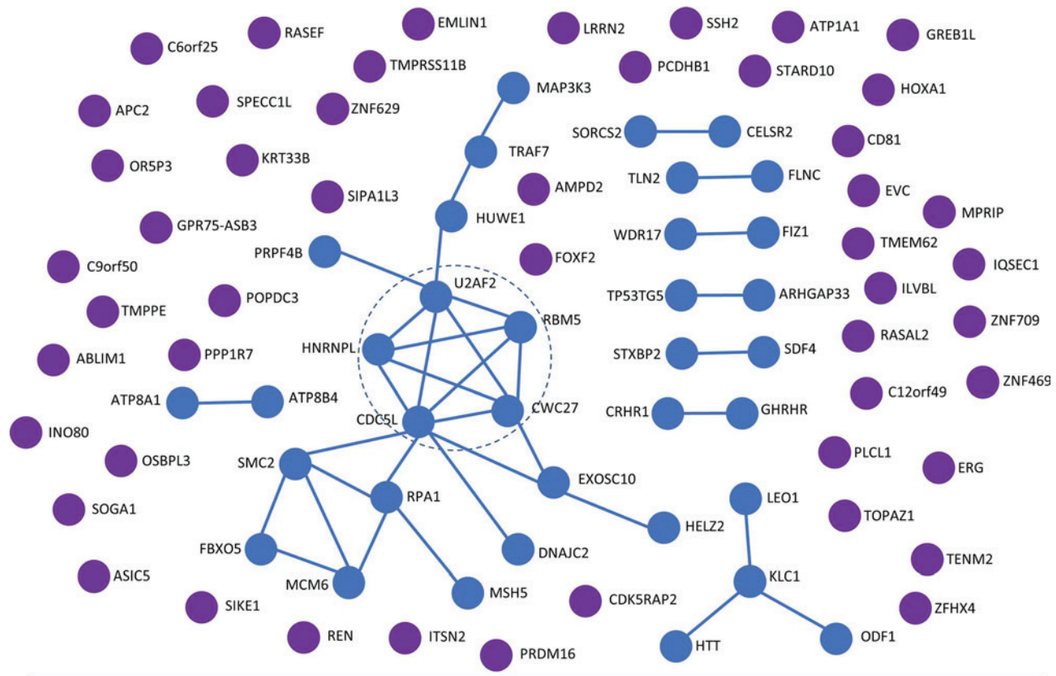
Missense intolerance in de novo mutation genes. To systematically evaluate and predict the likelihood of these DNMs causing male infertility and identify novel candidate disease genes, we assessed the predicted pathogenicity of all DNMs using three prediction methods based on SIFT[20], MutationTaster[21], and PolyPhen2[22] with a minimum of 2 of the 3 showing pathogenicity to define a variant as Pathogenic. Using this approach, 84 of 145 rare protein-altering DNM were predicted to be pathogenic, while the remaining 61 were predicted to be benign. To further analyse the impact of the variants on the genes affected, we looked at the missense Z-score of all 122 genes affected by a missense variant, which indicates the tolerance of genes to missense mutations[23]. We identified no significant enrichment in missense DNMs in missense-intolerant genes in our infertile cohort when compared to controls (median Z-score in male infertility patients = 0.83, median Z-score in controls = 1.04, p value = 1, N simulations = 100,000) (Supplementary Fig. 4b). Interestingly, however, we observed a significantly higher median missense Z-score in genes affected by a missense DNM predicted as pathogenic (median Z-score = 1.21, $n = 63$) when compared to genes affected by predicted benign (median Z-score = 0.98, $n = 59$) missense DNMs in our cohort (p value = 5.01×10^{-4}, Fig. 1b). It should be noted that the same analysis in controls showed no such significant difference (Supplementary Fig. 4c).

Protein–protein interactions reveal link to mRNA splicing. An analysis using the STRING database[24], revealed a significant enrichment of protein interactions amongst the 84 genes affected by a protein-altering DNM predicted to be pathogenic (PPI enrichment p value = 2.35×10^{-2}, Fig. 2). No such enrichment was observed for the genes highlighted as likely benign ($n = 61$, PPI enrichment p value = 0.206) or those affected by synonymous DNMs ($n = 35$, PPI enrichment p value = 0.992, Supplementary Fig. 5). This suggests that the proteins affected by predicted pathogenic DNMs share common biological functions.

The STRING network analysis also highlighted a central module of interconnected proteins with a significant enrichment of genes required for mRNA splicing (Supplementary Fig. 6). The genes *U2AF2*, *HNRNPL*, *CDC5L*, *CWC27*, and *RBM5* all contain predicted pathogenic DNMs and likely interact at a protein level during the mRNA splicing process. Pre-mRNA splicing allows gene functions to be expanded by creating alternative splice variants of gene products and is highly elaborated within the testis[25]. One of these genes, *RBM5* has been previously highlighted as an essential regulator of haploid male germ-cell pre-mRNA splicing and male fertility in mice[26]. Mice with a homozygous ENU-induced allele point mutation in *RBM5* present with azoospermia and germ cell development arrest at round spermatids. Whilst in mice, a homozygous mutation in *RBM5* is required to cause azoospermia, this may not be the case in humans as is well-documented for other genes[27], including the recently reported male infertility gene *SYCP2*[9]. Of note, *RBM5* is a tumor suppressor in the lung[28], with reduced expression affecting RNA splicing in patients with non-small cell lung cancer[29]. *HNRNPL* is another splicing factor affected by a possible pathogenic DNM in our study. One study implicated a role for *HNRNPL* in patients with Sertoli cell-only phenotype[30]. The remaining three mRNA splicing genes have not yet been implicated in human male infertility. However, mRNA for all three is expressed at medium to high levels in human germ cells and all are widely expressed during spermatogenesis[31]. Specifically, *CDC5L* is a component of the PRP19-CDC5L complex that forms an integral part of the spliceosome and is required for activating pre-mRNA splicing[32], as is *CWC27*[33]. *U2AF2* plays a role in pre-mRNA splicing and 3′-end processing[34]. Interestingly, *CSTF3*, one of the genes affected by a de novo CNV in Proband_066, affects the same mRNA pathway[18].

DNMs uncovering recessive disease and analysis of maternally inherited mutations. Whilst DNMs most often cause dominant disease, they can contribute to recessive disease, usually in combination with an inherited variant on the trans allele. In order to look for this, we analysed all DNM genes for the presence of inherited mutations on the other allele in the same patient. In Proband_060, who carried a DNM in Testis and Ovary Specific PAZ Domain Containing 1 (*TOPAZ1*) on the paternal allele, we did identify a maternally inherited variant predicted to be pathogenic (Supplementary Fig. 7). *TOPAZ1* is a germ cell-specific gene which is highly conserved in vertebrates[35]. Studies in mice revealed that *Topaz1* plays a crucial role in spermatocyte, but not oocyte, progression through meiosis[36]. In men, *TOPAZ1* is expressed in germ cells in both sexes[31,37,38]. Analysis of the testicular biopsy of this patient revealed a germ cell arrest in early spermiogenesis (Fig. 3).

Maternally inherited mutations can also result in dominant causes of male infertility if not affecting female fertility. We therefore studied all DNM genes for the presence of maternally inherited mutations in the entire cohort and compared this to the presence of paternally inherited mutations in the same genes. A total of 4 maternally inherited variants predicted to be pathogenic were identified in DNM genes (*TENM2* (2×), *CWC25*, and *EVC*). All of these variants, however, were also observed multiple times in an exome dataset from a cohort of 5784 fertile men suggesting that these maternally inherited variants are not causative of male infertility (Supplementary Data 2).



Number of nodes: 84	Average local clustering coefficient: 0.336
Number of edges: 36	Expected number of edges: 25
Average node degree: 0.857	PPI enrichment p-value: 0.0235

Fig. 2 Protein–protein interactions predicted for proteins affected by pathogenic de novo mutations. Significantly larger number of interactions were observed in proteins affected by de novo mutations than expected for a similar sized dataset of randomly selected proteins (PPI enrichment p value = 2.35×10^{-2}). The central module of the main interaction network (blue dashed circle) contains 5 proteins involved in mRNA splicing (Supplementary Fig. 6).

Further analysis in additional cohorts of infertile males. In addition to all systematic analyses described above, we evaluated the function of all DNM genes to give each a final pathogenicity classification (Table 1, details in Methods). Of all 192 DNMs, 29 affected genes were linked to male reproduction and classified as possibly causative, with a further 50 as unclear. For replication purposes, only one pilot study including 13 trios was recently published in male infertility[7]. None of the DNM genes reported in this study showed DNMs in our cohort. To further study the DNM genes identified in our cohort, we looked for the presence of rare predicted pathogenic mutations in these genes in exome datasets of infertile men ($n = 2{,}506$), in collaboration with members of the International Male Infertility Genomics Consortium and the Geisinger-Regeneron DiscovEHR collaboration[39]. For comparison, we included an exome dataset from a cohort of 11,587 fertile men and women from Radboudumc.

In the additional infertile cohorts, we identified 17 LoF mutations in our DNM LoF-intolerant genes (pLI ≥ 0.9), although we did not detect a statistical enrichment in the LoF mutations in these genes compared to fertile men (Two-tailed Fisher's Exact test with Bonferroni correction adjusted p values >0.05, Supplementary Data 3, 4). Next, we looked for an enrichment of rare predicted pathogenic missense mutations in these cohorts (Table 2 and Supplementary Data 5, 6). A total of 11 genes showed an enrichment of pathogenic missense mutations in infertile men compared to fertile men (Two-tailed Fisher's Exact test, p value < 0.05, Table 2). After applying the Bonferroni correction to counteract the effects of multiple testing, however, the only significant enrichment was observed in the *RBM5* gene (adjusted p value = 0.03). In this gene, six infertile men were found to carry a rare pathogenic missense mutation, in addition to the proband with a de novo missense mutation (Supplementary Fig. 8, Supplementary Data 7). Importantly, no such predicted pathogenic mutations were identified in men in the fertile cohort. In line with these results, *RBM5*, already highlighted above as an essential regulator of male germ cell pre-mRNA splicing and male infertility[26], is highly intolerant to missense mutations (missense Z-score 4.17).

In addition to the comparison between fertile and infertile men, we investigated whether there was any difference between the number of predicted pathogenic mutations carried in fertile men compared to fertile women. However, none of the DNM genes showed a significant difference between the sexes (Two-tailed Fisher's Exact test with Bonferroni correction adjusted p values = 1, Supplementary Data 3, 5).

Phasing of de novo mutations to identify parent of origin. Given the predicted impact of these DNMs on spermatogenesis, we were interested in investigating the parental origin of DNMs in our trio cohort. We were able to phase 29% ($n = 59$) of all our DNMs using a combination of short-read WES and targeted long-read sequencing (Supplementary Table 1). In agreement

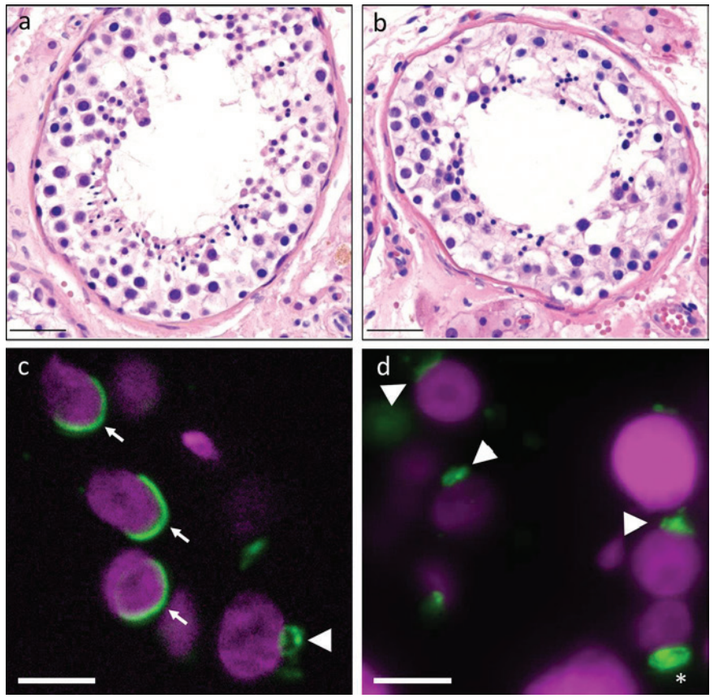


Fig. 3 Description of control and *TOPAZ1* proband testis histology and aberrant acrosome formation. a, **b** H&E stainings of (**a**) control and (**b**) Proband_060 with pathogenic mutations in *TOPAZ1* gene. The epithelium of the seminiferous tubules in the *TOPAZ1* proband show reduced numbers of germ cells and an absence of elongating spermatids based on the analysis of 150 seminiferous tubules in control and patient. **c**, **d** immunofluorescent labeling of DNA (magenta) and the acrosome (green) in control sections (**c**) and *TOPAZ1* proband sections (**d**). (**c**) The arrowhead indicates the acrosome in an early round spermatid and the arrows the acrosome in elongating spermatids. Spreading of the acrosome and nuclear elongation are hallmarks of spermatid maturation. (**d**) No acrosomal spreading (see arrowheads) or nuclear elongation is observed in the *TOPAZ1* proband. The asterisk indicates an example of progressive acrosome accumulation without spreading. Scale bar: 40 µm (**a**, **b**) and 5 µm (**c**, **d**).

Table 1 De novo mutation classification summary.

	Possibly causative	Unclear	Unlikely causative	Not causative	Total
Missense	21	38	50	13	122
Frameshift	4	8	1	0	13
Stop gained	1	3	0	0	4
In-frame indels	3	1	1	1	6
Splice site variant	0	0	0	11	11
Synonymous	0	0	0	36	36
TOTAL	29	50	52	61	192

Rare DNMs were classified based on pathogenicity prediction, ACMG classification, number of cases in gnomAD and presence of the exact mutation in verified fertile men of the control cohort, as well as functional data taking into account RNA expression in testis, RNA enrichment in the testis or involvement in spermatogenesis, protein expression in the testis, model organisms, the protein function in relation to spermatogenesis and interactions with known fertility genes.

with literature[40–43], 72% of all DNMs occurred on the paternal allele. Interestingly, phasing of 8 likely causative DNMs showed that 6 of these were of paternal origin (75%). This suggests that DNMs with a deleterious effect on the future germline can escape negative selection in the paternal germline. This may be possible because the DNM occurred after the developmental window in which the gene is active, or the DNM may have affected a gene in the gamete's genome that is critical for somatic cells supporting the (future) germline. Transmission of pathogenic DNMs may also be facilitated by the fact that from spermatogonia onwards, male germ cells form cysts and share mRNAs and proteins[44]. As such, the interconnectedness of male germ cells, which is essential for their survival[45], could mask detrimental effects of DNMs occurring during spermatogenesis.

Discussion

In 2010, we published a pilot study pointing to a de novo paradigm for mental retardation[46] (now more appropriately termed developmental disorders or intellectual disability). This work contributed to the widespread implementation of patient–parent WES studies in research and diagnostics for neurodevelopmental disorders[47], accelerating disease gene identification and increasing the diagnostic yield for these disorders. The data presented here suggest that a similar benefit could be achieved from trio-based exome sequencing in male infertility. In order to achieve this there is an urgent need to expand on this work as larger studies are essential to identify recurrently DNM genes and further demonstrate the exact contribution of DNMs to male infertility. Modeling studies recently done for developmental disorders showed that more than 350k trios may be required to have approximately 80% power to detect all haploinsufficient genes causing this disorder[48]. Evidently, these numbers can only be reached by implementing trio-based exome sequencing as a routine diagnostic test and by sharing these diagnostic data with the international research community. This research community

Table 2 Rare pathogenic missense mutations in exome data from various cohorts of infertile men and fertile control cohorts.

Gene	Missense Z-score	Total infertile men ($n = 2,506$)	Fertile Dutch men ($n = 5,784$)	Burden test infertile vs. fertile men	
				p value	Adjusted *p* value
RBM5	4.17	7	0	0.0002	0.03
HUWE1	8.87	6	0	0.001	0.12
REN	0.80	7	1	0.001	0.21
HIST1H1D	−8.06	10	5	0.004	0.59
ABLIM1	1.62	6	1	0.004	0.60
FUS	2.21	4	0	0.01	1
CNOT4	3.49	5	1	0.01	1
CDC5L	2.78	6	2	0.01	1
ZNF629	3.86	6	2	0.01	1
PCDHB1	1.02	11	8	0.01	1
AK3	−1.97	10	7	0.02	1

Genes affected by a rare missense DNM were investigated in additional cohorts of infertile patients and a cohort of verified fertile men to identify other individuals carrying rare missense mutations. A burden test was used to compare the total number of predicted pathogenic missense mutations observed in the infertile vs. fertile men. A two-tailed Fisher's Exact test was performed with and without Bonferroni correction applied to adjust p values for multiple testing of all 152 genes of interest. (Also see Supplementary Data 5).

will also have the enormous task of functionally validating the impact of these DNMs on spermatogenesis. Altogether, this will not only help to increase the diagnostic yield for men with infertility but will also enhance our fundamental biological understanding of human reproduction and natural selection. In addition, it will indicate whether male infertility follows a dominant inheritance pattern, and this has impact for disease transmission. Couples that seek treatment for male infertility should be counseled on the risk of transmitting this condition to their offspring, something that is now limited to couples receiving fertility treatment due to Y-chromosome deletions. Male infertility is also increasingly seen as the most visible symptom of a more complex disease with associated comorbidities[49]. Studying the long-term health of men with DNMs in specific genes should help in identifying genotype–phenotype correlations that may impact more than the fertility of these men.

Methods

Cohort of infertile patients and fertile parent trios. We enrolled a total of 185 patients who presented with unexplained (idiopathic) azoospermia ($N = 111$) or severe to extreme oligozoospermia (with or without asthenozoospermia $N = 74$) at the Radboudumc outpatient clinic between July 2007 and October 2017 ($N = 170$) and at the Newcastle upon Tyne Hospitals NHS Foundation Trust (Newcastle, UK) between January 2018 to January 2020 ($n = 15$). The reference values and semen nomenclature were used according to the WHO guidelines[50] (see Supplementary Note). Clinical evaluation did not lead to an etiologic diagnosis and all patients were negative for AZF deletions and chromosomal anomalies (see Supplementary Notes). The study protocol was approved by the respective Ethics Committees/Institutional Review Boards (Nijmegen: NL50495.091.14 version 5.0, Newcastle: REC ref. 18/NE/0089) and written informed consent from all patients and their parents was obtained prior to enrollment in the study. We used residual genomic DNA extracted from a blood sample taken at the time of evaluation and treatment at the fertility center. DNA from all proband's parents was obtained from saliva by using the Oragene OG-500 kit (DNA Genotek, Ottawa, Canada).

Immunofluorescence staining of human testis biopsies. Tissue sections were cut from formalin fixed paraffin embedded (FFPE) testicular biopsies. As staining controls testicular biopsies obtained from fertile men after a previous vasectomy was used. FFPE sections were prepared for staining following standard protocols. To detect RBM5, antibody HPA018011 from Atlas Antibodies was used in a 1:500 dilution. For detection, a donkey anti-rabbit Alexa488 antibody was used (A-21206, 1:1000 dilution), which was applied in combination with lectin coupled to Alexa568 (L32458, 1:1500 dilution) to detect the acrosome (both Thermo Scientific). Slides were counterstained with DAPI. Images were obtained with a Zeiss Axio Imager ZI fluorescence microscope equipped with the Zen software package.

Cohort of verified fertile Dutch parents. We used an anonymized exome dataset derived from 5784 Dutch men and 5803 Dutch women who had conceived at least one child as a control cohort for the frequency of rare variants in fertile men and fertile women. These men and women received routine exome sequencing at the Radboud diagnostics center as the healthy parent of a child with a severe illness. Although these men fathered a child with intellectual disability, their fertility is expected to be similar to an unselected sample of the male population.

Exome sequencing. WES samples were prepared and enriched following the manufacturer's protocols of either Illumina's Nextera DNA Exome Capture kit or Twist Bioscience's Twist Human Core Exome Kit. All sequencing was performed on the NovaSeq 6000 Sequencing System (Illumina) achieving comparable results covering more than 99% of all exonic regions using either kit (Supplementary Table 2) and an average depth of 72× (Illumina's Nextera Kit) and 99x (Twist Bioscience's Kit) (see Supplementary Fig. 9 and Supplementary Table 3). Sequenced reads were aligned to Human Reference Genome (GRCh37.p5/hg19) using BWA-Mem v0.7.17[51], Picard[52], and GATK v4.1.4.1[53]. The sex, ancestry and relatedness of each samples was calculated using peddy[54], samples found to have the incorrect sex or were unrelated to the correct samples were excluded from this study. Following best practice recommendations, single nucleotide variations and small indels were identified and quality-filtered using GATK's HaplotypeCaller obtaining comparable results independently of the kit or the origin of the DNA (see Supplementary Table 3). Afterwards, all variants were further analysed using a custom GATK4-based algorithm to identify and separate high- and low-confidence de novo variants from inherited variants. Briefly, posterior genotype probabilities (GQ) were recalculated for each sample at each variant site using Bayes' rule to take into account family and population priors[53,55]. Proband variants absent in parental samples with recalculated proband GQ >= 10 and allele count (AC) below 4 or allele frequency (AF) < 0.1% in all samples, whichever is more stringent, were classified as low-confidence DNMs. Variants with recalculated GQs ≥ 20 and the same AC/AF criterion were classified as high confidence DNMs. Afterwards, tagged variants with coverage <10, variant read percentage <15% and GATK quality scores <400 were removed to ensure only the most reliable variants were considered. Sanger sequencing was then used to validate DNMs calls. Ensembl's Variant Effect Predictor (VEP)[56] was used to fully annotate all de novo variants.

Variant filtration and interpretation. The primary stages in filtering of variants included removing all variants with an allele frequency of >0.1% in the gnomAD database to only include rare variants in our analysis. All variants then with <10 reads in the exome data and/or less than 15% of these reads containing the mutation were then removed. At this stage, any remaining variants lying outside the exonic regions were then removed. This provided the initial list of 192 rare de novo variants. All synonymous and non-protein-altering spice site variants were then removed, leaving a total of 145-protein-altering rare DNMs. Pathogenicity prediction was then based on SIFT[20], MutationTaster[21], and PolyPhen2[22] and all variants were classified according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 2015 guidelines[57]. All protein-altering variants predicted to be pathogenic by at least 2 out of 3 prediction models, absent from the fertile male cohort, present in <5 males in the gnomAD database were considered for further functional analysis ($n = 84$). Maternally inherited mutations present in genes identified as having a protein-altering DNM were identified in all patients and submitted to the exact same method of filtration and interpretation as described above.

Functional analysis was split into six different categories, each category provided a score of either 1 or 0 depending on whether they met the threshold for that category. These categories included: RNA expression of the gene in the testis, RNA enrichment in the testis or presence in spermatogenesis, protein expression in the testis, whether an infertile mouse model already exists for the given gene, the

protein function in relation to spermatogenesis and finally whether the given gene interacts with any known fertility genes. For expression levels retrieved for each gene of interest from the GTEx database (https://www.gtexportal.org/), an expression of medium (≥10 < 100 TPM) or high (>100 TPM) gave a score of 1 with low (>2 < 10 TPM) and no expression (<2 TPM) giving a score of 0. RNA enrichment was based on elevated expression (tissue enriched, group enriched, or tissue enhanced) in the Human Protein Atlas[58] or being among the genes up- or downregulated during spermatogenesis as found in a recent single cell RNA sequencing study[59]. Protein expression was retrieved from the Human Protein Atlas[58] and interaction with known infertility genes[3] was calculated using STRING version 11[24]. The final classification of the genes was then split into Not causative, Unlikely causative, Unclear and Possibly causative. These classifications were given based on the variant scores out of 6 with: [0 points + not expressed/not detected/ not present on several occasions = Unlikely causative], [0 points + "Unknown" on several occasions = Unclear], [1–2 points = Unclear] and [3–6 points = possibly causative].

CNV analysis. CNV calling was performed on our trio-based exome data with a custom GATK4-based pipeline. This workflow exploits the GATK4 sequence read depth normalization[60] and a custom R based segmentation and visualization[61]. Parental samples from the trios under examination were used as controls for the normalization step. The CNVs detected were annotated using AnnotSV (https://lbgi.fr/AnnotSV/)[62]. CNVs present in more than 1% of the samples of the Database of Genomic Variants present in more than 10% of the patients were excluded from the analysis. The remaining rare deletions and duplications were individually inspected through the genomic profiles and detailed Log2Ratio plots generated by the workflow. Only CNVs involving more than 2 exons were further considered to minimize the inclusion of false positives, and we selected 2 CNVs present in the probands but absent in their parents for further validation.

Variant validation. Validation of low-quality DNMs was performed using standard Sanger sequencing approach on an Applied Biosystems SeqStudio Genetic Analyzer (ThermoFisher, MA, USA) to confirm the presence of the mutation in probands and its absence in the parents. Primers for each SNV were designed using PrimerZ[63] (Supplementary Data 8) and PCR reactions were performed using AmpliTaq 360 DNA Polymerase (ThermoFisher, MA, USA) according to the manufacturer's protocol.

Validation of CNVs was performed with the whole genome Illumina Infinium CytoSNP-850K v1.1 microarray platform for the larger deletion on chromosome 11 and a gene-specific TaqMan Copy-Number assay designed for *NXT2* was exploited to validate the smaller CNV using the Applied Biosystems QuantStudio 7 Flex Real-Time PCR System (ThermoFisher, MA, USA).

Functional enrichment. To evaluate the intolerance of each gene for loss-of-function (LoF) mutations, we used the probability of LoF intolerance (pLI) score, based on data from the Genome Aggregation Database (gnomAD)[8] containing genetic data from 141,456 individuals. We computed the likelihood of the observed median pLI score of each gene (LoF in controls) set compared to the expected median pLI based on the method described in Lelieveld et al.[64]. In short, we simulated the expected number of recurrently mutated genes by redistributing the observed number of mutations at random over a determined set of genes based on their specific LoF and functional mutation rates, however, in contrast to Lelieveld et al.[64] and Samocha et al.[23] before them instead of using the complete set of 18,226 pLI annotated genes to obtain expected median pLI scores, we used a set of 2766 coding DNMs in 1941 control individuals, downloaded from the de novo-db version 1.6.1 (http://de novo-db.gs.washington.edu/de novo-db/)[12], to correct for the gene-specific mutation rate. The empirical *P* value was calculated by comparing the observed median pLI to the expected pLI following 100,000 random sampling simulations. Case and fertile controls were processed using the exact same filtration and annotation parameters as described above so that each variant detected was evaluated in a comparable manner. The same method was then repeated using the Loss-of-function observed/expected upper bound fraction or LOEUF score, which also is an indicator of LoF intolerance. To evaluate the impact of the de novo missense mutations to each gene, we used missense Z-scores calculated by gnomAD[10,23] to predict the tolerance of each gene to variation in place of the pLI scores when applying the Lelieveld et al.[64] methodology described above following 100,000 simulations. The presence of missense mutations in intolerant genes was compared between predicted pathogenic and benign using a two-tailed Mann–Whitney *U* test in our samples and in controls independently. To predict the affected protein function and the potential role in disease, we evaluated the interactions between the genes with a DNM using STRING version 11[24].

Additional cohorts of infertile men. The strongest candidate genes with DNMs were further investigated in exome data from four additional cohorts of infertile men. For the Italian cohort of 48 patients with NOA, exome sequencing was carried out as a service by Macrogen Inc. (Republic of Korea) utilizing the Agilent SureSelect_V6 enrichment and a NovaSeq 6000. The German Male Reproductive Genomics (MERGE) study comprised exome data of 887 men with azoo-, crypto-, or severe oligozoospermia. Known causes for male infertility like chromosomal aberrations and microdeletions of the AZF region were excluded in advance. WES was performed as previously described[65]. The 88 patients diagnosed with male infertility participating in the Geisinger-Regeneron DiscovEHR collaboration were selected from deidentified EHR information using the ICD-10CM code N46 which refers to "Male Infertility" including oligospermia, azoospermia, other male infertility and male infertility unspecified. All patients were sequenced at the Regeneron Genetics Center (RGC) as previously described[39]. In brief, 1ug of genomic DNA per sample was used for targeted exome capture using the NimbleGen VCRome 2.1 or the IDT XGen reagents. Captured libraries were sequenced on the Illumina HiSeq 2500 platform with v4 chemistry using paired-end 75 bp reads. Exome sequencing was performed such that >85% of the bases were covered at 20× or greater. Raw sequence reads were mapped and aligned to the GRCh38/hg38 human genome reference assembly using BWA-mem[51], single nucleotide and indel variants were called using GATK's HaplotypeCaller[53]. The Genetics of Male Infertility INitiative (GEMINI) is a multicenter study funded by the United States NIH. The GEMINI project performed whole-exome sequencing on 1,011 unrelated men diagnosed with spermatogenic failure, the vast majority with unexplained NOA. Sequencing of genomic DNA was performed at the McDonnell Genome Institute of Washington University in St. Louis, MO, USA, using an in-house exome targeting reagent capturing 39.1 Mb of exome and 2 × 150 bp paired-end sequencing on Illumina HiSeq 4000. Following sample QC, a final cohort of 924 men were analysed as part of the current study.

Genetic variants identified within the 152 candidate genes were extracted from each exome dataset. Consistent with our filtering method described above variants with <10 reads and/or <15% reads containing the mutation were discarded. To minimize discrepancies between genomic positions and annotation, genomic coordinates were recalculated to the GCRh37/hg19 where necessary and fully reannotated with VEP[56]. Following annotation variants from each of the additional case and control cohorts were filtered and processed in an identical manner as previously described. Shortly, variants with allele frequency >1% in gnomAD were discarded to focus only on rare variants: Pathogenicity predictions based on SIFT[20], MutationTaster[21] and PolyPhen[22] were then used to exclude benign variants, all remaining variants were classified according to ACMG guidelines[56]. Like before, all protein-altering variants were considered pathogenic if predicted to be so by at least 2 out of 3 prediction models, absent from the fertile cohorts and present in <5 males in the gnomAD database. A similar analysis was done for all variants obtained in the control cohorts. However, just to be clear, for the male control cohort we did not exclude variants as pathogenic if they were present in this cohort itself.

Burden testing. Having identified several likely pathogenic rare loss-of-function and missense mutations in these 152 genes we performed a gene-based burden test to compare the combined data in all cohorts of infertile men with the control cohort of fertile fathers. The proportion of individuals with pathogenic variants in each of the 152 genes was statistically evaluated using two-tailed Fisher's Exact tests, individual *p* values were corrected using the Bonferroni method corrections to adjust for performing 152 consecutive statistical tests and reduced the risk of Type I errors. Similarly, a gene-based burden test was performed to compare fertile fathers with fertile mothers from the control cohort of verified fertile parents to investigate whether any of the sexes predominantly carried a greater number of rare pathogenic mutations.

Phasing analysis to determine parent-of-origin. The origin of DNMs identified in the exomes of patients was first investigated in the short-read exome data by performing phasing analysis on those variants that contained a parental informative SNP (iSNP) within 150 bp from the DNM. As a next step, all DNMs were target-enriched with long-range PCR and sequenced using the Oxford Nanopore's MinION sequencer (Oxford Nanopore technologies, Oxford Science Park, UK). Target regions were designed to encapsulate both the DNM and a parentally informative SNP, from which parent-of-origin, and allele frequencies (percentage read counts associated to a given allele) could be ascertained and DNM pre-/post-zygosity could be determined.

Primers were designed using Primer3[66] (version 2.3.6) and GRCh37.p5 based in-house GUI-wrapped pipeline. All expected fragment sizes were limited to a maximum of 12 kb for quality control and enrichment success rate. For those DNMs with no exome supported iSNPs within a 10 kb distance, primers were designed to cover approximately 2.5 kb on either side of the DNM with the expectation of finding additional iSNPs in the intronic regions. Long-range PCR target enrichment was carried out using our optimized running conditions of 3 separate supermixes/enzymes (see Supplementary Table 4). Sample fragment sizes were confirmed using gel electrophoresis, and quantities were measured with the Qubit dsDNA HS kit (ThermoFisher Scientific, Waltham, MA, USA), with the best quality supermix enrichment for each given sample/target selected for sequencing, where quality was assessed by cleanest banding in gel electrophoresis and greatest concentration.

The long-range PCR target enrichments of >20 ng were prepared for sequencing with the ONT ligation sequencing kit (SQK-LSK109) following the manufacturer's protocol, with adjustments for sample type and yield. Individual sample libraries were concentrated where necessary at given bead clean-up steps and pooled based on fragment size. Fragment size-based pools were combined prior to flowcell loading. Prepared samples were sequenced on the MinION using the FLO-MIN106 version 9.4 flowcell platform. Flowcells were run until complete pore exhaustion, with minimal refuel of flowcells performed whenever active pore percentages dropped below 70%, achieving an average of 30 billion basecall yields per flowcell and coverage depth per sample of >5000×.

The sequence signal data in multi-fast5 format were basecalled using Guppy[67] (version 3.4.4, https://nanoporetech.com/), resulting fastq outputs were adapter trimmed and low-quality reads discarded using cutadapt (version 2.5)[68]. Cleaned fastq files were mapped against Human Reference Genome (GRCh37.p5/hg19) using BWA-Mem[51] (version 0.7.17), and sample targets were extracted from the resulting BAM file using SAMtools (version 0.1.19)[69]. Aligned ONT reads were phased using an in-house tool, with frequencies and pre/post-zygosity calls affirmed via IGV and principal component analysis using the available exome sequence data for probands and parents to support the ONT data.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Sequencing data has been deposited in the European Genome-phenome Archive(EGA) under the accession code EGAS00001005417 and will be made available upon reasonable request for academic use and within the limitations of the provided informed consent by the corresponding author upon acceptance. Every request will be reviewed by the Newcastle University Male Infertility Genomics Data Access Committee; the researcher will need to sign a data access agreement after approval.

Code availability

The code for the integrated pipeline used to process sequencing data to detect and call rare germline copy-number variants (CNVs) is available at https://github.com/AnetaMikulasova/CNVRobot.

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Author contributions

This study was designed by M.S.O., L.E.L.M.V., L.R. and J.A.V. R.M.S., J.G., H.T. and G.W.v.d.H. provided all clinical data and performed the TESE histology and cytology analysis under supervision of L.R., D.D.M.B., E.S., K.F., K.D.H. and K.M. J.C. performed the exome sequencing with support from B.A. and bioinformatics support was provided by M.J.X., G.A., C.G. and S.C. Sanger sequencing was performed by P.F.d.V., H.I., H.E.S., L.E.B. and B.K.S.A. M.S.O. and H.E.S. performed the SNV analyses with support from M.J.X., F.K.M. performed CNV analysis with support from A.M. and M.S.K. and G.S.H. and L.E.B. performed the phasing. D.J.E., H.S., B.J.H. and M.K.O.B. provided support on the functional interpretation of mutations. D.F.C., L.N., C.F., S.K., F.T., K.I.A., A.R.E., C.K. and C.G.-J. were involved in the replication study. The first draft of the paper was prepared by M.S.O., H.E.S., R.M.S., M.J.X., G.W.v.d.H. and J.A.V.. All authors contributed to the final paper.

Competing interests

The authors declare no competing interests.

Additional information

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FOCUS ON COVID-19, PART IV

ANDROLOGY WILEY

Prospective two-arm study of the testicular function in patients with COVID-19

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Abstract

Background: The COVID-19 pandemic has led the international community to conduct extensive research into potential negative effects of the disease on multiple organs and systems in the human body. One of the most discussed areas is potential of the virus to compromise the testicular function. However, the lack of prospective studies on this topic makes it impossible to draw reliable conclusions on whether the disease affects the male reproductive system and, if so, to what extent.

Objectives: The current trial is aimed at investigating the effect of SARS-CoV-2 on the testicular function, hormone levels and determining the extent of impact on spermatogenesis and damage to testicular tissue.

Materials and methods: This prospective study included healthy controls and cases of patients suffering from viral pneumonia based on chest computed tomography (CT) and a positive SARS-CoV-2 throat swab exhibited moderate symptoms (World Health Organization (WHO) classification). Epidemiological, clinical, laboratory and ultrasound data were collected. A semen analysis was performed in cases during their hospital stay and 3 months after the discharge home. We also assessed the testicles obtained during autopsies of patients who died of COVID-19 ($n = 20$).

Results: A total of 88 participants were included (44 controls and 44 cases). Blood testosterone levels were significantly decreased in 27.3% of the cases (12/44). The mean level (7.3±2.7 nmol/L) was lower than that in the healthy controls (13.5±5.2 nmol/L, $p < 0.001$). An increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) was also detected compared to the healthy controls ($p = 0.04$ and $p = 0.002$). The semen analysis revealed decreased motility in COVID-19 patients ($p = 0.001$), and a higher number of immobile sperm (during COVID-19: 58.8% and at 3 months 47.4%, $p = 0.005$). All parameters returned to normal at 3 months after discharge. Direct mixed agglutination reaction (MAR) test at 3 months showed an increase of Ig A ($p = 0.03$). In the majority of autopsies (18/20), structural disorders of the testicular tissue, with signs of damage to germ cells were observed.

Discussion and conclusion: COVID-19 and its management strategies significantly affect male hormone levels and sperm quality at the onset of the disease. Postmortem examination of testicular tissue confirmed inflammation and viral infiltration of the testicles. However, in patients with moderate to severe disease, the studied parameters of the testicular function returned to normal values within 3 months.

KEYWORDS
COVID-19, male fertility, SARS-CoV-2, testes

1 | INTRODUCTION

Research into SARS-CoV-2-associated syndromes and disorders is an active field of research. COVID-19 is associated with inflammatory syndrome targeting a multitude of human organs. One of them was described in the early days of the pandemic by Zou et al. who reported that non-respiratory symptoms may be explained by the binding of the virus to angiotensin convertase Type-2 (ACE-2) in other organs.[1] Previous studies assessed the possible effects of COVID-19 at several organs sites as kidneys, intestines, etc.[–4] Shen and Wang found ACE-2 expression in testicular cells (namely spermatogonia, Leydig cells, and Sertoli cells) which makes them potential targets for the virus.[5] In fact, there are reports of orchitis and epididymitis in patients diagnosed with COVID-19,[6] which may suggest that SARS-CoV-2 is able to directly damage testicular tissue potentially compromising male fertility and hormone function.

To date, there has not been a focused study of hormonal levels and inflammatory markers in the semen and testicular tissues. It has been suggested that COVID-19 can have a potentially negative effect on male fertility through direct damage to the testes. The systematic reviews by Fathi et al. and Khalil et al. summarized available data which show that the COVID-19 infection often leads to a decrease in testosterone levels and may affect semen quality.[7,8] However, the small size and retrospective nature of the previous studies render any conclusive statements impossible for now. Moreover, a large percentage of the available research separately assessed a limited number of parameters in isolation—such as hormone levels, sperm quality, testicular pathology, without adequate controls.

There is ultimately too little information to draw reliable conclusions regarding the effects of the virus on male reproduction. Published reports are limited by small study groups, lack of the control group, and the absence of follow-up examinations during recovery warranting further research and in-depth exploration of the topic.[9]

The current prospective series is aimed at investigating the effect of SARS-CoV-2 on the testicular function and determining the extent of damage to testicular cells.

2 | MATERIALS AND METHODS

After Institutional Review Board approval and registration (clinicaltrials.gov ID NCT04716179), we prospectively recruited male patients aged 18–65 years. The study included both healthy participants with no history of COVID-19 or vaccination (controls) and those during the acute stage of the disease (pneumonia as identified by chest computed tomography (CT) and confirmed with nucleic acid detection of SARS-CoV-2 from throat swab samples using reverse transcription-polymerase chain reaction, RT-PCR). Only patients with recent disease onset (the onset was defined as the date when symptoms appeared) and who had undergone no prior antiviral therapy were included. At the time of inclusion, all patients experienced moderate to severe symptoms in accordance with the World Health Organization (WHO) classification.[12] It is important to emphasize that while all the patients collected material for semen analysis during hospital stay, the analysis was only conducted after improvement in their general condition. The exclusion criteria were inability to collect semen for analysis, history of congenital anomalies, hypogonadism, testicular dysfunction, infertility, and severe varicocele. All the COVID-19 participants were recruited at a single center (COVID-19 Hospital of Sechenov University, Moscow, Russia). The controls were males with no known disorders of fertility in past medical history. It is necessary to emphasize that all the controls volunteered to join the study, with no specific urological or andrological conditions (the controls received assessment and semen analysis results which motivated them to join). They were recruited separately from the COVID-19 cohort (at the Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia) and represent a similar geographical cohort. None of the controls had received vaccination or had a history of COVID-19. All those had negative RT-PCR test to SARS-CoV-2 prior to inclusion to the control group. The exclusion criteria were identical to those in the COVID-19 cohort.

The trial was powered to detect changes in semen analysis (sperm motility, morphology, and count). The sample size calculation was based on the finding that decreased semen quality could be found in almost 50% of otherwise healthy males.[10] According to the available data,

ΥΠΟΦΥΣΗ

ΚΩΝΣΤΑΝΤΙΝΟΣ ΤΟΥΛΗΣ

ΣΤΡΑΤΙΩΤΙΚΟΣ ΙΑΤΡΟΣ,
ΔΙΔΑΚΤΩΡ ΙΑΤΡΙΚΗΣ Α.Π.Θ.

ABSTRACTS ON GROWTH HORMONE DEFICIENCY

Long-term Safety of Growth Hormone in Adults With Growth Hormone Deficiency: Overview of 15, 809 GH-Treated Patients

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Abstract
Context
Data on long-term safety of growth hormone (GH) replacement in adults with GH deficiency (GHD) are needed.
Objective
We aimed to evaluate the safety of GH in the full KIMS (Pfizer International Metabolic Database) cohort.
Methods
The worldwide, observational KIMS study included adults and adolescents with confirmed GHD. Patients were treated with GH (Genotropin [somatropin]; Pfizer, NY) and followed through routine clinical practice. Adverse events (AEs) and clinical characteristics (eg, lipid profile, glucose) were collected.
Results
A cohort of 15 809 GH-treated patients were analyzed (mean follow-up of 5.3 years). AEs were reported in 51.2% of patients (treatment-related in 18.8%). Crude AE rate was higher in patients who were older, had GHD due to pituitary/hypothalamic tumors, or adult-onset GHD. AE rate analysis adjusted for age, gender, etiology, and follow-up time showed no correlation with GH dose. A total of 606 deaths (3.8%) were reported (146 by neoplasms, 71 by cardiac/vascular disorders, 48 by cerebrovascular disorders). Overall, de novo

cancer incidence was comparable to that in the general population (standard incidence ratio 0.92; 95% CI, 0.83-1.01). De novo cancer risk was significantly lower in patients with idiopathic/congenital GHD (0.64; 0.43-0.91), but similar in those with pituitary/hypothalamic tumors or other etiologies versus the general population. Neither adult-onset nor childhood-onset GHD was associated with increased de novo cancer risks. Neutral effects were observed in lipids/fasting blood glucose levels.

Conclusion

These final KIMS cohort data support the safety of long-term GH replacement in adults with GHD as prescribed in routine clinical practice.

Safety of growth hormone replacement in survivors of cancer and intracranial and pituitary tumours: a consensus statement

Margaret C S Boguszewski, Cesar L Boguszewski, Wassim Chemaitilly, Laurie E Cohen, Judith Gebauer, Claire Higham, Andrew R Hoffman, Michel Polak, Kevin C J Yuen, Nathalie Alos ... Show more

European Journal of Endocrinology

Volume 186, Issue 6, Jun 2022, Pages P35–P52, https://doi.org/10.1530/EJE-21-1186

Published:21 April 2022

Abstract

Growth hormone (GH) has been used for over 35 years, and its safety and efficacy has been studied extensively. Experimental studies showing the permissive role of GH/insulin-like growth factor 1 (IGF-I) in carcinogenesis have raised concerns regarding the safety of GH replacement in children and adults who have received treatment for cancer and those with intracranial and pituitary tumours. A consensus statement was produced to guide decision-making on GH replacement in children and adult survivors of cancer, in those treated for intracranial and pituitary tumours and in patients with increased cancer risk. With the support of the European Society of Endocrinology, the Growth Hormone Research Society convened a Workshop, where 55 international key opinion leaders representing 10 professional societies were invited to participate. This consensus statement utilized: (1) a critical review

paper produced before the Workshop, (2) five plenary talks, (3) evidence-based comments from four breakout groups, and (4) discussions during report-back sessions. Current evidence reviewed from the proceedings from the Workshop does not support an association between GH replacement and primary tumour or cancer recurrence. The effect of GH replacement on secondary neoplasia risk is minor compared to host- and tumour treatment-related factors. There is no evidence for an association between GH replacement and increased mortality from cancer amongst GH-deficient childhood cancer survivors. Patients with pituitary tumour or craniopharyngioma remnants receiving GH replacement do not need to be treated or monitored differently than those not receiving GH. GH replacement might be considered in GH-deficient adult cancer survivors in remission after careful individual risk/benefit analysis. In children with cancer predisposition syndromes, GH treatment is generally contraindicated but may be considered cautiously in select patients.

Efficacy and Safety of Weekly Somatrogon vs Daily Somatropin in Children With Growth Hormone Deficiency: A Phase 3 Study

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Carl L Roland, Carrie Turich Taylor, Srinivas Rao Valluri, Michael P Wajnrajch, Aleksandra Pastrak, Bradley S Miller

The Journal of Clinical Endocrinology & Metabolism

Volume 107, Issue 7, July 2022, Pages e2717–e2728, https://doi.org/10.1210/clinem/dgac220

Published:11 April 2022

Abstract

Context

Somatrogon is a long-acting recombinant human growth hormone (rhGH) in development for once-weekly treatment of children with growth hormone deficiency (GHD).

Objective

We aimed to compare the efficacy and safety of once-weekly somatrogon with once-daily somatropin in prepubertal children with GHD.

Methods

In this 12-month, open-label, randomized, active-controlled, parallel-group, phase 3 study, participants were randomized 1:1 to receive once-weekly somatrogon (0.66 mg/kg/week) or once-daily somatropin (0.24 mg/kg/week) for 12 months. A total of 228 prepubertal children (boys aged 3-11 years, girls aged 3-10 years) with GHD, impaired height and height velocity (HV), and no prior rhGH treatment were randomized and 224 received ≥1 dose of study treatment (somatrogon: 109; somatropin: 115). The primary endpoint was annualized HV at month 12.

Results

HV at month 12 was 10.10 cm/year for somatrogon-treated subjects and 9.78 cm/year for somatropin-treated subjects, with a treatment difference (somatrogon-somatropin) of 0.33 (95% CI: −0.24, 0.89). The lower bound of the 2-sided 95% CI was higher than the prespecified noninferiority margin (−1.8 cm/year), demonstrating noninferiority of once-weekly somatrogon vs daily somatropin. HV at month 6 and change in height standard deviation score at months 6 and 12 were similar between both treatment groups. Both treatments were well tolerated, with a similar percentage of subjects experiencing mild to moderate treatment-emergent adverse events in both groups (somatrogon: 78.9%, somatropin: 79.1%).

Conclusion

The efficacy of once-weekly somatrogon was noninferior to once-daily somatropin, with similar safety and tolerability profiles. (ClinicalTrials.gov no. NCT02968004).

ABSTRACTS ON ACROMEGALY

Predictive Factors of Somatostatin Receptor Ligand Response in Acromegaly—A Prospective Study

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The Journal of Clinical Endocrinology & Metabolism
Volume 107, Issue 11, November 2022, Pages 2982–2991, https://doi.org/10.1210/clinem/dgac512
Published:22 September 2022

Abstract

Context

Somatostatin receptor ligands (SRLs) are the cornerstone medical treatments for acromegaly; however, many patients remain unresponsive to SRLs. Well-established predictive markers of response are needed.

Objective

We aimed to explore the relationship between responsiveness to SRLs relative to somatostatin (SST)2A and 5 receptor expression, adenoma granularity, and T2-weighted magnetic resonance imaging (MRI) signal intensity (T2WSI).

Methods

We conducted a multicentric, prospective, observational cohort study, in France. Forty-nine naïve patients (ie, patients without preoperative SRL treatment) with active acromegaly following surgery were treated with octreotide (group 1; n = 47), or pasireotide if uncontrolled under first-generation SRLs (group 2; n = 9). Data were collected at baseline and months 3 and 6. Biochemical measurements, immunohistochemistry studies, and MRI readings were centralized.

Results

In group 1, IGF-I decrease from baseline to month 6 positively correlated with SST2A immunoreactive score (IRS), *P* = 0.01. Densely granulated/intermediate adenomas had a greater IGF-I and GH decrease

under octreotide compared with sparsely granulated adenomas (P = 0.02 and P = 0.006, respectively), and expressed greater levels of SST2A (P < 0.001), coupled with lower levels of SST5 (P = 0.004). T2WSI changed between preoperative MRI and month 6 MRI in one-half of the patients. Finally, SST5 IRS was higher in preoperative hyperintense compared with preoperative hypointense adenomas (P = 0.04), and most sparsely granulated and most hyperintense adenomas expressed high SST5 levels.

Conclusion

We prospectively confirm that SST2A and adenoma granularity are good predictors of response to octreotide. We propose the IRS for scoring system harmonization. MRI sequences must be optimized to be able to use the T2WSI as a predictor of treatment response.

Maintenance of response to oral octreotide compared with injectable somatostatin receptor ligands in patients with acromegaly: a phase 3, multicentre, randomised controlled trial

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Lancet Diabetes and Endocrinology
2022 Feb;10(2):102-111.

Background

Despite biochemically responding to injectable somatostatin receptor ligands (iSRLs), many patients with acromegaly experience treatment burdens. We aimed to assess maintenance of biochemical response and symptomatic control with oral octreotide capsules versus iSRLs in patients with acromegaly who previously tolerated and responded to both.

Methods

This global, open-label, randomised controlled phase 3 trial was done in 29 clinical sites in Austria, France, Germany, Hungary, Italy, Lithuania, Russia, Serbia, Spain, and the USA. Eligible patients were adults aged 18–75 years with acromegaly who were receiving iSRLs (long-acting octreotide or lanreotide autogel) for at least 6 months before baseline with a stable dose for at least 4 months, and were deemed to be biochemically responding (insulin-like growth factor I [IGF-I] <1·3 × upper limit of normal [ULN] and mean integrated growth hormone <2·5 ng/mL). In the 26-week run-in phase, all patients received oral octreotide (40 mg a day, optional titration to 60 or 80 mg a day). Eligibility for the randomised treatment phase was completion of the run-in phase as a biochemical responder (IGF-I <1·3 × ULN and mean integrated growth hormone <2·5 ng/mL at week 24) and investigator assessment of acromegaly being adequately controlled. Patients were randomly assigned (3:2) to oral octreotide capsules or iSRL at the same dose and interval as before enrolment. Randomisation and drug dispensing were conducted through a qualified randomisation service provider (eg, interactive web or voice response system). The primary endpoint was a non-inferiority assessment (margin −20 percentage points) of proportion of participants maintaining biochemical response throughout the randomised treatment phase (IGF-I <1·3 × ULN using time-weighted average; assessed by comparing the lower bound of the 2-sided 95% CI for the difference in biochemical response between groups). IGF-I was assessed once a month during the run-in and randomised treatment phases (single sample). Efficacy and safety assessments were performed on the randomised population. This trial is registered with ClinicalTrials.gov, NCT02685709.

Findings

Between Feb 11, 2016, and Aug 20, 2020, 218 patients were assessed for eligibility. 72 patients were excluded, and 146 participants were enrolled into the run-in phase. 116 patients completed the run-in phase and 30 participants discontinued treatment. 92 participants were randomly assigned to oral octreotide (n=55) or iSRL (n=37). 50 (91%) of 55 participants who received oral octreotide (95% CI 44–53) and 37 (100%) of 37 participants who received iSRLs (34–37) maintained biochemical response. The lower bound of the 2-sided 95% CI for the adjusted difference in proportions between the two treatment groups achieved the prespecified non-inferiority criterion of −20% (95% CI −19·9 to 0·5). 19 (35%) of 55 participants in the oral octreotide group and 15 (41%) of 37 participants in the iSRL group had treatment-related adverse events; the most common of which in both groups were gastrointestinal.

Interpretation

Oral octreotide was non-inferior to iSRL treatment, and might be a favourable alternative to iSRLs for many patients with acromegaly.

ACROBAT Edge: Safety and Efficacy of Switching Injected SRLs to Oral Paltusotine in Patients With Acromegaly

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Ajay Madan, Christine Ferrara-Cook, R Scott Struthers, Alan Krasner

The Journal of Clinical Endocrinology & Metabolism
dgac643, https://doi.org/10.1210/clinem/dgac643
Published:10 November 2022

Abstract

Context

Paltusotine is a once-daily, oral, nonpeptide small-molecule somatostatin receptor type 2 (SST2) agonist in clinical development for treatment of acromegaly.

Objective

This work aimed to evaluate change in insulin-like growth factor I (IGF-I) levels in patients switched from octreotide long-acting release or lanreotide depot monotherapy to paltusotine.

Methods

A phase 2, open-label, prospective, multicenter, multinational, nonrandomized, single-arm exploratory study was conducted in which dosage uptitrations were performed in a double-blinded manner. At 26 global sites, patients with acromegaly switched to paltusotine from injected somatostatin receptor ligand (SRL)-based therapy. Patients received 13-week treatment with once-daily oral paltusotine (10-40 mg/d). The primary end point was change from baseline to week 13 in IGF-I for patients who switched from long-acting octreotide or lanreotide depot monotherapy to paltusotine (group 1). All patients underwent a 4-week paltusotine washout at end of treatment period (wk 13-17). IGF-I, growth hormone (GH), patient-reported outcome, and safety data were collected.

Results

Forty-seven patients enrolled. In group 1 (n = 25), IGF-I and GH showed no significant change between SRL baseline and end of paltusotine treatment at week 13 (median change in IGF-I = −0.03×upper limit of normal [ULN]; *P* = .6285; GH = −0.05 ng/mL; *P* = .6285). IGF-I and GH rose significantly in the 4 weeks after withdrawing paltusotine (median change in IGF-I = 0.55×ULN; *P* < .0001 [median increase 39%]; GH = 0.72 ng/mL; *P* < .0001 [109.1% increase]). No patients discontinued because of adverse events (AE); no treatment-related serious AEs were reported.

Conclusion

These results suggest once-daily oral paltusotine was effective in maintaining IGF-I values in patients with acromegaly who switched from injected SRLs. Paltusotine was well tolerated with a safety profile consistent with other SRLs.

High Prevalence of Vertebral Fractures Associated With Preoperative GH Levels in Patients With Recent Diagnosis of Acromegaly

Stefano Frara, Meliha Melin Uygur, Luigi di Filippo, Mauro Doga, Marco Losa, Simona Santoro, Pietro Mortini, Andrea Giustina
Author Notes

The Journal of Clinical Endocrinology & Metabolism
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Published:29 March 2022

Abstract

Context

Osteopathy and morphometric vertebral fractures (VFs) are emerging complications in acromegaly. However, the prediction of VFs in this clinical setting is still a matter of uncertainty, and it is debated whether they are an early event in the natural history of the disease.

Objective

We aimed to evaluate the prevalence and determinants of morphometric VFs in patients with recently diagnosed acromegaly.

Methods

We enrolled 92 patients (43 men/49 women) on admission to the neurosurgery unit before transsphenoidal surgery, and compared them with control individuals without secondary forms of osteoporosis and pituitary disorders. We performed a VF assessment on preoperative chest x-ray images and collected biochemical, demographic, and clinical data.

Results

We detected a significantly higher prevalence of VFs (33.7%) in patients with acromegaly than in controls (*P* = .001). Among the patients with acromegaly and VFs, 12 (38.7%) showed multiple VFs, and 5 (16.1%) showed moderate/severe VFs. Patients with VFs had higher random serum growth hormone (GH) levels than those with no VFs (*P* = .03), but there was no difference in insulin-like growth factor-1 (IGF-1) (*P* = .07) and IGF-1/Upper Normal Limit ratio (*P* = .08). Free 3,5,3′-triiodothyronine was slightly lower in patients with acromegaly and VFs than in those without VFs (*P* = .05). In multiple logistic analysis, GH was independently associated with risk for VFs (*P* = .003). The preoperative serum GH cutoff value that predicted VFs was 12 ng/mL.

Conclusion

For the first time, high prevalence of radiological VFs is reported in patients with recent diagnosis of acromegaly. Therefore, we can hypothesize that VFs are an early phenomenon of acromegaly and related to GH levels. VF assessment should be included in the workup at the diagnosis of acromegaly.

ABSTRACTS ON CUSHING'S DISEASE

Randomized Trial of Osilodrostat for the Treatment of Cushing Disease

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Chih Hao Chen Ku, Davide Carvalho, Michael Roughton, Judi Wojna, Alberto M Pedroncelli, Peter J Snyder

The Journal of Clinical Endocrinology & Metabolism
Volume 107, Issue 7, July 2022, Pages e2882–e2895, https://doi.org/10.1210/clinem/dgac178
Published:23 March 2022

Abstract

Context

Cushing disease, a chronic hypercortisolism disorder, is associated with considerable morbidity and mortality. Normalizing cortisol production is the primary treatment goal.

Objective

We aimed to evaluate the safety and efficacy of osilodrostat, a potent, orally available 11βhydroxylase inhibitor, compared with placebo in patients with Cushing disease.

Methods

LINC 4 was a phase III, multicenter trial comprising an initial 12-week, randomized, double-blind, placebo-controlled (osilodrostat:placebo, 2:1) period followed by a 36-week, open-label treatment period (NCT02697734). Adult patients (aged 18-75 years) with confirmed Cushing disease and mean urinary free cortisol (mUFC) excretion ≥ 1.3 times the upper limit of normal (ULN) were eligible. The primary endpoint was the proportion of randomized patients with mUFC ≤ ULN at week 12. The key secondary endpoint was the proportion achieving mUFC ≤ ULN at week 36 (after 24 weeks' open-label osilodrostat).

Results

Seventy-three patients (median age, 39 years [range, 19-67]; mean/median mUFC, 3.1 × ULN/2.5 × ULN) received randomized treatment with osilodrostat

(n = 48) or placebo (n = 25). At week 12, significantly more osilodrostat (77%) than placebo (8%) patients achieved mUFC ≤ ULN (odds ratio 43.4; 95% CI 7.1, 343.2; *P* < 0.0001). Response was maintained at week 36, when 81% (95% CI 69.9, 89.1) of all patients achieved mUFC ≤ ULN. The most common adverse events during the placebo-controlled period (osilodrostat vs placebo) were decreased appetite (37.5% vs 16.0%), arthralgia (35.4% vs 8.0%), and nausea (31.3% vs 12.0%).

Conclusion

Osilodrostat rapidly normalized mUFC excretion in most patients with Cushing disease and maintained this effect throughout the study. The safety profile was favorable.

Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension

Maria Fleseriu, John Newell-Price, Rosario Pivonello, Akira Shimatsu, Richard J Auchus, Carla Scaroni, Zhanna Belaya, Richard A Feelders, Greisa Vila, Ghislaine Houde
Rama Walia, Miguel Izquierdo, Michael Roughton, Alberto M Pedroncelli, Beverly M K Biller

European Journal of Endocrinology
Volume 187, Issue 4, Oct 2022, Pages 531–541, https://doi.org/10.1530/EJE-22-0317
Published:16 September 2022

Abstract

Objective

To investigate the long-term efficacy and tolerability of osilodrostat, a potent oral 11β-hydroxylase inhibitor, for treating Cushing's disease (CD).

Design/methods

A total of 137 adults with CD and mean 24-h urinary free cortisol (mUFC) > 1.5 × upper limit of normal (ULN) received osilodrostat (starting dose 2 mg bid; maximum 30 mg bid) during the prospective, Phase III, 48-week LINC 3 (NCT02180217) core study. Patients benefiting from osilodrostat at week 48 could enter the optional extension (ending when all patients had received ≥ 72 weeks of treatment or discontinued). Efficacy and safety were assessed for all enrolled patients from the core study baseline.

Results

Median osilodrostat exposure from the core study baseline to study end was 130 weeks (range 1–245) and median average dose was 7.4 mg/day (range 0.8–46.6). The reduction in mean mUFC achieved during the core was maintained during the extension and remained ≤ ULN. Of 106 patients, 86 (81%) patients who entered the extension had mUFC ≤ ULN at week 72. Improvements in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism (fat pads, central obesity, rubor, striae, and hirsutism in females), and quality of life in the core study were also maintained or improved further during the extension. No new safety signals were reported; 15/137 (10.9%) and 12/106 (11.3%) patients discontinued for adverse events during the core and extension, respectively. Mean testosterone in females decreased towards baseline levels during the extension.

Conclusions

Data from this large, multicentre trial show that long-term treatment with osilodrostat sustains cortisol normalisation alongside clinical benefits in most patients with CD and is well tolerated.

Copeptin Levels Before and After Transsphenoidal Surgery for Cushing Disease: A Potential Early Marker of Remission

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Journal of the Endocrine Society
Volume 6, Issue 6, June 2022, bvac053, https://doi.org/10.1210/jendso/bvac053

Published:06 April 2022

Abstract

Context

Arginine-vasopressin and CRH act synergistically to stimulate secretion of ACTH. There is evidence that glucocorticoids act via negative feedback to suppress arginine-vasopressin secretion.

Objective

Our hypothesis was that a postoperative increase in plasma copeptin may serve as a marker of remission of Cushing disease (CD).

Design

Plasma copeptin was obtained in patients with CD before and daily on postoperative days 1 through 8 after transsphenoidal surgery. Peak postoperative copeptin levels and Δcopeptin values were compared among those in remission vs no remission.

Results

Forty-four patients (64% female, aged 7-55 years) were included, and 19 developed neither diabetes insipidus (DI) or syndrome of inappropriate anti-diuresis (SIADH). Thirty-three had follow-up at least 3 months postoperatively. There was no difference in peak postoperative copeptin in remission (6.1 pmol/L [4.3-12.1]) vs no remission (7.3 pmol/L [5.4-8.4], *P* = 0.88). Excluding those who developed DI or SIADH, there was no difference in peak postoperative copeptin in remission (10.2 pmol/L [6.9-21.0]) vs no remission (5.4 pmol/L [4.6-7.3], *P* = 0.20). However, a higher peak postoperative copeptin level was found in those in remission (14.6 pmol/L [±10.9] vs 5.8 (±1.4), *P* = 0.03]) with parametric testing. There was no difference in the Δcopeptin by remission status.

Conclusions

A difference in peak postoperative plasma copeptin as an early marker to predict remission of CD was not consistently present, although the data point to the need for a larger sample size to further evaluate this. However, the utility of this test may be limited to those who develop neither DI nor SIADH postoperatively.

ABSTRACTS ON PITUITARY TUMOURS AND THEIR TREATMENT

Aggressive pituitary tumours and carcinomas, characteristics and management of 171 patients

Pia Burman, Jacqueline Trouillas, Marco Losa, Ann McCormack, Stephan Petersenn, Vera Popovic, Marily Theodoropoulou, Gerald Raverot, Olaf M Dekkers, Agathe Guenego ... Show more

Author Notes

European Journal of Endocrinology

Volume 187, Issue 4, Oct 2022, Pages 593–605, https://doi.org/10.1530/EJE-22-0440

Published:19 September 2022

Abstract

Objective

To describe clinical and pathological characteristics and treatment outcomes in a large cohort of aggressive pituitary tumours (APT)/pituitary carcinomas (PC).

Design

Electronic survey August 2020–May 2021.

Results

96% of 171 (121 APT, 50 PC), initially presented as macro/giant tumours, 6 were microadenomas (5 corticotroph). Ninety-seven tumours, initially considered clinically benign, demonstrated aggressive behaviour after 5.5 years (IQR: 2.8–12). Of the patients, 63% were men. Adrenocorticotrophic hormone (ACTH)-secreting tumours constituted 30% of the APT/PC, and the gonadotroph subtypes were under-represented. Five out of 13 silent corticotroph tumours and 2/6 silent somatotroph tumours became secreting. Metastases were observed after median 6.3 years (IQR 3.7–12.1) from diagnosis. At the first surgery, the Ki67 index was ≥3% in 74/93 (80%) and ≥10% in 38/93 (41%) tumours. An absolute increase of Ki67 ≥ 10% after median of 6 years from the first surgery occurred in 18/49 examined tumours. Tumours with an aggressive course from outset had higher Ki67, mitotic counts, and p53. Temozolomide treatment in 156/171 patients resulted in complete response in 9.6%, partial response in 30.1%, stable disease in

28.1%, and progressive disease in 32.2% of the patients. Treatment with bevacizumab, immune checkpoint inhibitors, and peptide receptor radionuclide therapy resulted in partial regression in 1/10, 1/6, and 3/11, respectively. Median survival in APT and PC was 17.2 and 11.3 years, respectively. Tumours with Ki67 ≥ 10% and ACTH-secretion were associated with worse prognosis.

Conclusion

APT/PCs exhibit a wide and challenging spectrum of behaviour. Temozolomide is the first-line chemotherapy, and other oncological therapies are emerging. Treatment response continues to be difficult to predict with currently studied biomarkers.

Risk of **second brain tumour** after **radiotherapy** for **pituitary adenoma** or **craniopharyngioma**: a **retrospective**, **multicentre**, **cohort study** of **3679 patients** with **long-term imaging surveillance**.

Hamblin R, Vardon A, Akpalu J, Tampourlou M, Spiliotis I, Sbardella E, Lynch J, Shankaran V, Mavilakandy A, Gagliardi I, Meade S, Hobbs C, Cameron A, Levy MJ, Ayuk J, Grossman A, Ambrosio MR, Zatelli MC, Reddy N, Bradley K, Murray RD, Pal A, Karavitaki N.

Lancet Diabetes Endocrinol.
2022 Aug;10(8):581-588. doi: 10.1016/S2213-8587(22)00160-7. Epub 2022 Jul 1.

Summary

Background

Radiotherapy is a valuable treatment in the management algorithm of pituitary adenomas and craniopharyngiomas. However, the risk of second brain tumour following radiotherapy is a major concern. We assessed this risk using non-irradiated patients with the same primary pathology and imaging surveillance as controls.

Methods

In this multicentre, retrospective cohort study, 4292 patients with pituitary adenoma or craniopharyngioma were identified from departmental registries at six adult endocrine centres (Birmingham, Oxford, Leeds, Leicester, and Bristol, UK and Ferrara, Italy). Patients with insufficient clinical data, known genetic predisposition to or history of brain tumour before study entry (n=532), and recipients of proton beam or stereotactic radiotherapy (n=81) were excluded. Data were analysed for 996 patients exposed to 2-dimensional radiotherapy, 3-dimensional conformal radiotherapy, or intensity-modulated radiotherapy, and compared with 2683 controls.

Findings

Over 45 246 patient-years, second brain tumours were reported in 61 patients (seven malignant [five radiotherapy, two controls], 54 benign [25 radiotherapy, 29 controls]). Radiotherapy exposure and older age at pituitary tumour detection were associated with increased risk of second brain tumour. Rate ratio for irradiated patients was 2·18 (95% CI 1·31–3·62, p<0·0001). Cumulative probability of second brain tumour was 4% for the irradiated and 2·1% for the controls at 20 years.

Interpretation

Irradiated adults with pituitary adenoma or craniopharyngioma are at increased risk of second brain tumours, although this risk is considerably lower than previously reported in studies using general population controls with no imaging surveillance. Our data clarify an important clinical question and guide clinicians when counselling patients with pituitary adenoma or craniopharyngioma on the risks and benefits of radiotherapy.

Safety of Withholding Perioperative Hydrocortisone for Patients With Pituitary Adenomas With an Intact Hypothalamus-Pituitary-Adrenal Axis A Randomized Clinical Trial

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JAMA Netw Open.
2022;5(11):e2242221. doi:10.1001/jamanetworkopen.2022.42221

Key Points

Question Is withholding hydrocortisone during the perioperative period of pituitary adenoma surgery noninferior to the conventional regimen of hydrocortisone supplementation for patients with an intact hypothalamus-pituitary-adrenal (HPA) axis, who account for more than half of patients with pituitary adenomas?

Findings In this parallel-group, triple-masked, noninferiority randomized clinical trial that included 436 patients with pituitary adenomas who had an intact HPA axis, withholding perioperative hydrocortisone protocol was noninferior to conventional care with respect to the incidence of postoperative new-onset adrenal insufficiency.

Meaning The results support the withholding of perioperative hydrocortisone for patients with pituitary adenomas with sufficient baseline HPA axis function.

Abstract

Importance Pituitary adenoma is the second most common primary brain tumor. Perioperative hydrocortisone has been used for decades to avoid postoperative adrenal insufficiency. Recent studies suggest that withholding perioperative hydrocortisone may be safe for patients with an intact hypothalamus-pituitary-adrenal (HPA) axis.

Objective To assess the safety of withholding hydrocortisone during the perioperative period of pituitary adenoma surgery for patients with an intact HPA axis.

Design, Setting, and Participants A parallel-group, triple-masked, noninferiority randomized clinical trial was conducted at Peking Union Medical College Hospital from November 1, 2020, to January 31, 2022, among 436 patients aged 18 to 70 years with an intact HPA axis undergoing surgery for pituitary adenomas.

Interventions Hydrocortisone supplementation protocol (intravenous and subsequent oral hydrocortisone, using a taper program) or no-hydrocortisone protocol.

Main Outcomes and Measures The primary outcome was the incidence of new-onset adrenal insufficiency (morning cortisol level, <5 μg/dL with adrenal insufficiency–related symptoms) during the perioperative period (on the day of operation and the following 2 days). The secondary outcome was the incidence of adrenal insufficiency in postoperative month 3. Analysis was on an intention-to-treat basis.

Results Of the 436 eligible patients, 218 were randomly assigned to the hydrocortisone group (136 women [62.4%]; mean [SD] age, 45.4 [13.0] years) and 218 to the no-hydrocortisone group (128 women [58.7%]; mean [SD] age, 44.5 [13.8] years). All patients completed 3-month postoperative follow-up. The incidence of new-onset adrenal insufficiency during the perioperative period was 11.0% (24 of 218; 95% CI, 6.9%-15.2%) in the no-hydrocortisone group and 6.4% (14 of 218; 95% CI, 3.2%-9.7%) in the hydrocortisone group, with a difference of 4.6% (95% CI, −0.7% to 9.9%), meeting the prespecified noninferiority margin of 10 percentage points. The incidence of adrenal insufficiency at the 3-month follow-up was 3.7% (8 of 218) in the no-hydrocortisone group and 3.2% (7 of 218) in the hydrocortisone group (difference, 0.5%; 95% CI, −3.0% to 3.9%). Incidences of new-onset diabetes mellitus (1 of 218 [0.5%] vs 9 of 218 [4.1%]), hypernatremia (9 of 218 [4.1%] vs 21 of 218 [9.6%]), hypokalemia (23 of 218 [10.6%] vs 34 of 218 [15.6%]), and hypocalcemia (6 of 218 [2.8%] vs 19 of 218 [8.7%]) were lower in the no-hydrocortisone group than in the hydrocortisone group. Lower preoperative morning cortisol levels were associated with higher risks of the primary event (<9.3 μg/dL; odds ratio, 3.0; 95% CI, 1.5-5.9) and the secondary event (<8.8 μg/dL; odds ratio, 7.8; 95% CI, 2.6-23.4) events.

Conclusions and Relevance This study found that withholding hydrocortisone was safe and demonstrated noninferiority to the conventional hydrocortisone supplementation regimen regarding the incidence of new-onset adrenal insufficiency among patients with an intact HPA axis undergoing pituitary adenomectomy.

ABSTRACTS ON POSTERIOR PITUITARY

COMPLETE ARTICLE ON CHANGING THE NAME OF DIABETES INSIPIDUS

Changing the Name of Diabetes Insipidus: A Position Statement of the Working Group for Renaming Diabetes Insipidus

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Abstract

'*What's in a name? That which we call a rose/By any other name would smell as sweet'* (Juliet, from *Romeo and Juliet* by William Shakespeare). Shakespeare's implication is that a name is nothing but a word, and it therefore represents a convention with no intrinsic meaning. While this may

be relevant to romantic literature, disease names do have real meanings, and consequences, in medicine. Hence, there must be a very good rationale for changing the name of a disease that has a centuries-old historical context. A working group of representatives from national and international endocrinology, and pediatric endocrine societies now proposes changing the name of ‘diabetes insipidus’ to ‘arginine vasopressin deficiency (AVP-D)’ for central etiologies, and ‘arginine vasopressin resistance (AVP-R)’ for nephrogenic etiologies. This article provides both the historical context and the rationale for this proposed name change.

Reasons for changing a disease name

Understanding of disease processes is a dynamic field, with rapidly evolving concepts of pathophysiology based on emerging molecular and genetic data. Consequently, newer understanding of pathophysiology is one of the major reasons for renaming diseases. In endocrinology, appreciation of hyperprolactinemia as the common pathophysiology underlying many different clinical situations causing galactorrhea and amenorrhea led to the effective abandonment of many previous eponymous names for these conditions, such as Chiari–Frommel syndrome, Forbes–Albright syndrome and Ahumada–del Castillo syndrome (1). A second reason is based on historical discoveries that a previous eponymous name for a syndrome was inappropriately attributed to an individual who was not the first or even the most significant person involved in the description of the syndrome (2). A third reason is later appreciation of medically unethical behaviors of individuals with diseases eponymously named for them, as characterized by the renaming of Reiter’s syndrome to ‘reactive arthritis’ and Wegener’s granulomatosis to ‘granulomatosis with polyangiitis’, because of the association of the eponymous physicians with Nazi antihumanitarian crimes (3, 4). The first three of these reasons for changing disease names make a strong case for detaching eponyms from disease processes whenever possible (5). However, endocrinologists would be loathe to abandon the eponyms of Addison, Cushing, Hashimoto and others for their unique and seminal contributions to our understanding of endocrine disease processes. However, yet a fourth reason for renaming diseases is when traditional disease names lead to confusion between pathophysiologically different processes, leading to treatment errors and consequent adverse outcomes for patients. This last reason represents the major impetus to change the name of diabetes insipidus at this time.

Historical context

Before explaining the rationale for the name change, it is instructive to review the historical context for the name of diabetes insipidus. The polyuria and polydipsia of diabetes were first described by Demetrius of Apameia (1st–2nd century BC), who used the term ‘diabetes’, meaning ‘passing water like a siphon’ to describe the polyuria characteristic of this condition. Araetus of Cappadocia (81–138 AD) further defined the clinical characteristics of this disease (6). Although observations that the urine was sweet were alluded to in both Greek and Indian history, the first documented report of the sweet character of diabetic urine was published by the English physician Sir Thomas Willis in 1674 (*The Diabetes or Pissing Evil*). However, the differentiation

between the saccharine urine of glucosuria and the non-saccharine urine of other forms of polyuria is attributed to the Scottish physician William Cullen, who appended the Latin word ‘mellitus’ (sweet) to the Greek term ‘diabetes’ to distinguish between these two types of polyuria (7). In 1794, Johann Peter Frank first introduced the term ‘diabetes insipidus’ to differentiate these patients from those with diabetes mellitus (7). These terms persisted as valid clinical descriptions without known pathophysiology until the vasopressor and antidiuretic actions of posterior pituitary extracts were discovered in the late 19th and early 20th centuries, including the use of posterior pituitary extracts to treat diabetes insipidus. In the mid-20th century, arginine vasopressin (AVP) was synthesized and identified as the antidiuretic hormone, and the distinct central and nephrogenic etiologies of diabetes insipidus were recognized and characterized (8). Despite new knowledge of the underlying pathophysiology of the different etiologies of diabetes insipidus by the late 20th century, no attempts were made to rename diabetes insipidus according to the known causes of the disorder, namely, deficiency of AVP or resistance to the receptor-mediated actions of AVP.

Rationale for changing the name of diabetes insipidus

There are multiple reasons for changing the name of diabetes insipidus at this time. First and foremost, although the terms ‘mellitus’ and ‘insipidus’ do differentiate between the clinical characteristics of these two very different causes of polyuria, and clearly are not eponyms, the use of the common term ‘diabetes’ in both has unfortunately led to confusion for both patients and their caretakers. This confusion with diabetes mellitus has been to the detriment of patients with diabetes insipidus when they are under the care of non-endocrine specialists. Some physicians and nurses do not appreciate the difference between these two very different disorders. In several patients with central diabetes insipidus, desmopressin treatment was withheld with serious adverse outcomes, including death (9). This has led to high-profile litigation cases and coroners’ inquests involving the police, with wide media coverage. Subsequent to these unfortunate but avoidable cases, national safety alerts, surveys among endocrinologists, and a global taskforce consisting of a wide range of senior clinicians involved with the care of patients with diabetes insipidus, have led to a strong impetus to change the name of the condition. Secondly, patients with diabetes insipidus strongly support changing the name to eliminate ‘diabetes’. In a survey of >1000 patients with central diabetes insipidus recently published in *The Lancet Diabetes & Endocrinology* (10), 85% preferred the name to be changed, mainly because of experiences with insufficient understanding of the disease by health professionals who confused this disorder with diabetes mellitus. Eighty-seven percent of patients felt that this lack of knowledge and the resulting clinical confusion affected the management of their condition, for example, repeated blood sugar measurements or prescription of medication for diabetes mellitus during hospitalization. Finally, we believe the names of medical disorders should, ideally, reflect the underlying pathophysiology, which in the case of diabetes insipidus is now well known to be deficient secretion and/or end-organ effects of the hormone AVP. Hence, for all the above reasons, the

working group proposes that the name diabetes insipidus should be changed to ‘arginine vasopressin deficiency (AVP-D)’ for central etiologies and ‘arginine vasopressin resistance (AVP-R)’ for nephrogenic etiologies, and this proposal has been endorsed by the following societies represented by the working group members: Endocrine Society, European Society of Endocrinology, Pituitary Society, Society for Endocrinology, European Society for Paediatric Endocrinology, Endocrine Society of Australia, Brazilian Endocrine Society, and Japan Endocrine Society, and is under review at several other societies.

Implementation of the name change for diabetes insipidus

In order to ease the transition in terms of online searches and to avoid confusion in the literature, we propose that for several years, we keep the previous name in parentheses. Therefore, we will begin using the terms ‘AVP deficiency (cranial diabetes insipidus) and AVP resistance (nephrogenic diabetes insipidus)’ in manuscripts and chapters. Once the transition is complete, it is likely that the parenthetic term will be lost, albeit people can still use it if they wish. In addition, we have initiated a request to the ICD (International Statistical Classification of Diseases and Related Health Problems) Coordination and Maintenance Committee to have the ICD-11 coding changed to reflect the new names.

We fully recognize that changing a name for a long-standing disease is never easy. However, just as the rheumatologists who proposed the name change of granulomatosis with polyangiitis (Wegener’s granulomatosis) (4), we hope our medical colleagues will recognize and accept the above rationale for making this change, not only in the interest of scientific accuracy, but more so for the benefit and safety of our mutual patients with diabetes insipidus, so that their disease and its treatment will no longer be confused with diabetes mellitus.

Serum copeptin levels at day two after pituitary surgery and ratio to baseline predict postoperative central diabetes insipidus

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Pituitary
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Abstract

Purpose: Central diabetes insipidus is a complication that may occur after pituitary surgery and has been difficult to predict. This study aimed to identify the cutoff levels of serum copeptin and its optimal timing for predicting the occurrence of central diabetes insipidus in patients who underwent transsphenoidal surgery.

Methods: This was a prospective observational study of patients who underwent transsphenoidal surgery for pituitary gland or stalk lesions. Copeptin levels were measured before surgery, 1 h after extubation, and on postoperative days 1, 2, 7, and 90.

Results: Among 73 patients, 14 (19.2%) and 13 (17.8%) patients developed transient and permanent central diabetes insipidus, respectively. There was no significant difference in copeptin levels before surgery and 1 h after extubation; copeptin levels on postoperative days 1, 2, 7, and 90 were significantly lower in patients with permanent central diabetes insipidus than in those without central diabetes insipidus. Copeptin measurement on postoperative day 2 exhibited the highest performance for predicting permanent central diabetes insipidus among postoperative days 1, 2, and 7 (area under the curve [95% confidence interval] = 0.754 [0.632-0.876]). Serum copeptin level at postoperative day 2(< 3.1 pmol/L) showed a sensitivity of 92.3% and a negative predictive value of 97.1%. The ratio of copeptin at postoperative day 2 to baseline (< 0.94) presented a sensitivity of 84.6% and a negative predictive value of 94.9%. The copeptin levels > 3.4 and 7.5 pmol/L at postoperative day 2 and 7 may have ruled out the occurrence of CDI with a negative predictive value of 100%.

Conclusion: The copeptin level at postoperative day 2 and its ratio to baseline can predict the occurrence of permanent central diabetes insipidus after pituitary surgery.

Post-pituitary surgery copeptin analysis as a ‘rule-out’ test for post-operative diabetes insipidus

- Hussam Rostom, Sean Noronha, Bahram Jafar-Mohammadi,

Endocrine2022

Abstract

Background

Diabetes insipidus (DI) is a recognised complication of pituitary surgery, with diagnosis requiring clinical observation aided by plasma and urine electrolytes and osmolalities. Copeptin is a stable surrogate marker of AVP release and has potential to facilitate prompt diagnosis of post-operative DI. This assay has been shown to accurately predict which patients are likely to develop DI following pituitary surgery.

Objective

To determine whether copeptin analysis can be used to predict which patients are at risk of developing DI following trans-sphenoidal surgery (TSS).

Methods

Seventy-eight patients undergoing TSS had samples taken for copeptin pre-operatively and at day 1 post-TSS. The majority of patients also had samples from day 2, day 8, and week 6 post-TSS. Results from patients who developed post-operative DI (based on clinical assessment, urine and plasma biochemistry and the need for treatment with DDAVP) were compared to those who did not. Patients with any evidence of pre-operative DI were excluded.

Results

Of 78 patients assessed, 11 were clinically determined to have developed DI. Differences were observed between patients with DI and those without in post-operative samples. Of note, there was a significant difference in plasma copeptin at day 1 post-operation ($p = 0.010$ on Kruskal–Wallis test), with copeptin levels greater than 3.4 pmol/l helping to rule out DI (91% sensitivity, 55% specificity at this cut off).

Conclusion

In the post-TSS setting, copeptin is a useful rule-out test in patients with values above a defined threshold, which may facilitate earlier decision making and shorter hospital stays.

ABSTRACT ON SIADH

Treatment Effect of the SGLT2 Inhibitor Empagliflozin on Chronic Syndrome of Inappropriate Antidiuresis: Results of a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Background

The syndrome of inappropriate antidiuresis (SIAD) is characterized by a reduction of free water excretion with consecutive hypotonic hyponatremia and is therefore challenging to treat. The sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin promotes osmotic diuresis *via* urinary glucose excretion, likely leading to increased electrolyte free water clearance.

Methods

In this randomized, double-blind, placebo-controlled, crossover trial, we compared 4-week treatment with empagliflozin 25 mg/d to placebo in outpatients with chronic SIAD-induced hyponatremia. At baseline and after both treatment cycles, patients underwent different assessments including neurocognitive testing (Montreal Cognitive Assessment [MoCA]). The primary end point was the difference in serum sodium levels between treatments.

Results

Fourteen patients, 50% female, with a median age of 72 years (interquartile range [IQR], 65–77), completed the trial. Median serum sodium level at baseline was 131 mmol/L (IQR, 130–132). After treatment with empagliflozin, median serum sodium level rose to 134 mmol/L (IQR, 132–136), whereas no increase was seen with placebo (130 mmol/L; IQR, 128–132), corresponding to a serum sodium increase of 4.1 mmol/L (95% confidence interval [CI], 1.7 to 6.5; P =0.004). Exploratory analyses showed that treatment with empagliflozin led to improved neurocognitive function with an increase of 1.16 (95% CI, 0.05 to 2.26) in the MoCA score. Treatment was well tolerated; no serious adverse events were reported.

Conclusion

The SGLT2 inhibitor empagliflozin is a promising new treatment option for chronic SIAD-induced hyponatremia, possibly improving neurocognitive function. Larger studies are needed to confirm the observed treatment effects.

ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ

ΝΙΚΟΛΑΟΣ ΒΑΛΒΗΣ

ΕΙΔΙΚΟΣ ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ - ΔΙΑΒΗΤΟΛΟΓΟΣ

Randomized Controlled Trial
Lancet Diabetes Endocrinol
2022 Oct;10(10):720-731.
doi: 10.1016/S2213-8587(22)00212-1. Epub 2022 Sep 1.

Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study

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Affiliations expand

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- DOI: 10.1016/S2213-8587(22)00212-1

Abstract

Background: Adults with type 1 diabetes who are treated with multiple daily injections of insulin plus intermittently scanned continuous glucose monitoring (isCGM) can have suboptimal glucose control. We aimed to assess the efficacy of an advanced hybrid closed loop (AHCL) system compared with such therapy in this population.

Methods: The Advanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes (ADAPT) trial is a prospective, multicentre, open-label, randomised controlled trial that involved 14 centres in three European countries (France, Germany, and the UK). We enrolled patients who were at least 18 years of age, had a type 1 diabetes duration of at least 2 years, HbA_{1c} of at least 8% (64 mmol/mol), and were using multiple daily injections of insulin plus isCGM (cohort A) or real time continuous glucose monitoring (cohort B) for at least 3 months. Here, only results for cohort A are reported. Participants were randomly allocated 1:1 to AHCL therapy or continuation of multiple daily injections of insulin plus continuous glucose monitoring for 6 months with an investigator-blinded block randomisation procedure. Participants and treating clinicians could not be masked to the arm assignment. The primary endpoint was the between-group difference in mean HbA_{1c} change from baseline to 6 months in the intention-to-treat population using AHCL therapy and those using multiple daily injections of insulin plus isCGM. The primary endpoint was analysed using a repeated measures random-effects model with the study arm and period as factors. Safety

endpoints included the number of device deficiencies, severe hypoglycaemic events, diabetic ketoacidosis, and serious adverse events. This study is registered with ClinicalTrials.gov, NCT04235504.

Findings: Between July 13, 2020, and March 12, 2021, 105 people were screened and 82 randomly assigned to treatment (41 in each arm). At 6 months, mean HbA_{1c} had decreased by 1·54% (SD 0·73), from 9·00% to 7·32% in the AHCL group and 0·20% (0·80) in the multiple daily injections of insulin plus isCGM from 9·07% to 8·91% (model-based difference -1·42%, 95% CI -1·74 to -1·10; p<0·0001). No diabetic ketoacidosis, severe hypoglycaemia, or serious adverse events related to study devices occurred in either group; two severe hypoglycaemic events occurred in the run-in phase. 15 device-related non-serious adverse events occurred in the AHCL group, compared with three in the multiple daily injections of insulin plus isCGM group. Two serious adverse events occurred (one in each group), these were breast cancer (in one patient in the AHCL group) and intravitreous haemorrhage (in one patient in the multiple daily injections of insulin plus isCGM group).

Interpretation: In people with type 1 diabetes using multiple daily injections of insulin plus isCGM and with HbA_{1c} of at least 8%, the use of AHCL confers benefits in terms of glycaemic control beyond those that can be achieved with multiple daily injections of insulin plus isCGM. These data support wider access to AHCL in people with type 1 diabetes not at target glucose levels.

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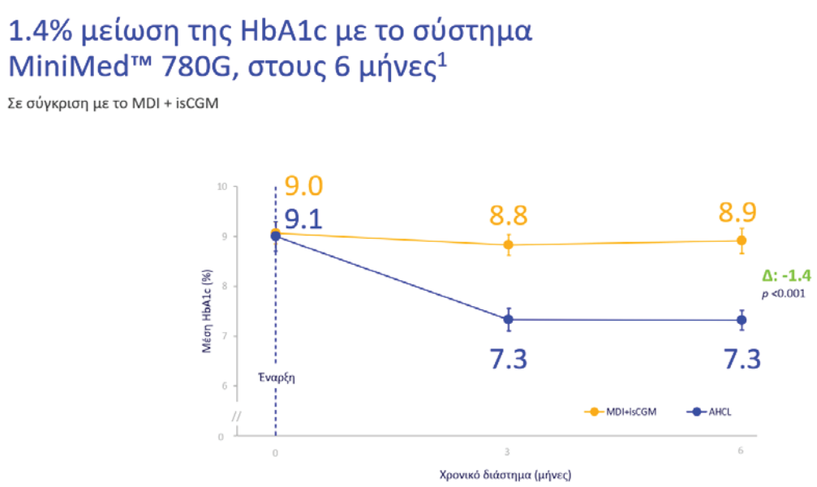

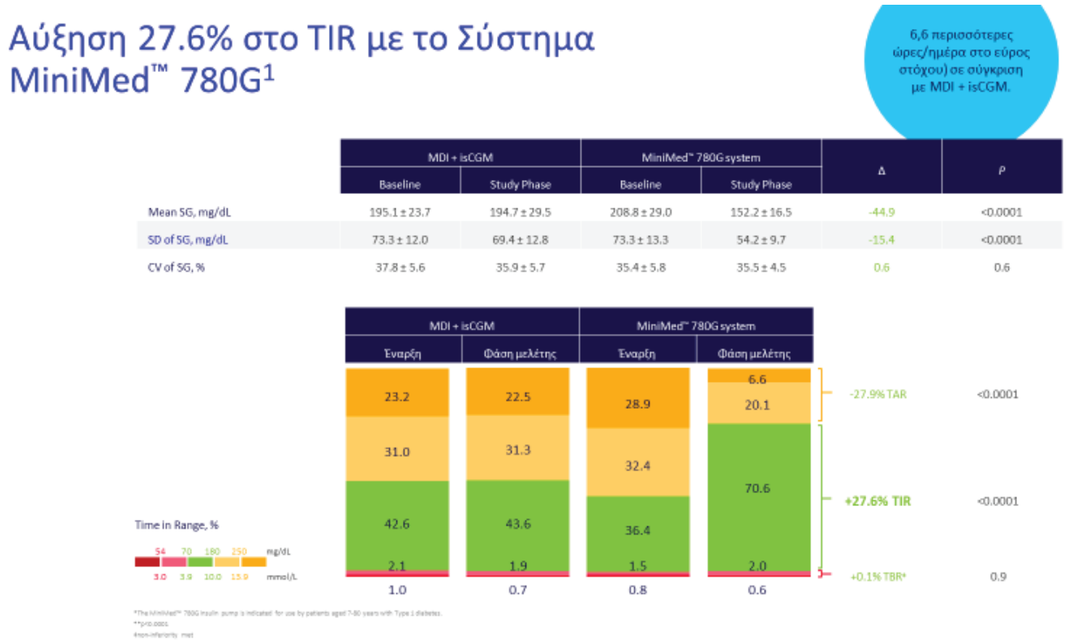

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Open-Source Automated Insulin Delivery in Type 1 Diabetes

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ABSTRACT

BACKGROUND

Open-source automated insulin delivery (AID) systems are used by many patients with type 1 diabetes. Data are needed on the efficacy and safety of an open-source AID system.

METHODS

In this multicenter, open-label, randomized, controlled trial, we assigned patients with type 1 diabetes in a 1:1 ratio to use an open-source AID system or a sensor-augmented insulin pump (control). The patients included both children (defined as 7 to 15 years of age) and adults (defined as 16 to 70 years of age). The AID system was a modified version of AndroidAPS 2.8 (with a standard OpenAPS 0.7.0 algorithm) paired with a preproduction DANA-i insulin pump and Dexcom G6 CGM, which has an Android smartphone application as the user interface. The primary outcome was the percentage of time in the target glucose range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) between days 155 and 168 (the final 2 weeks of the trial).

RESULTS

A total of 97 patients (48 children and 49 adults) underwent randomization (44 to open-source AID and 53 to the control group). At 24 weeks, the mean (±SD) time in the target range increased from 61.2±12.3% to 71.2±12.1% in the AID group and decreased from 57.7±14.3% to 54.5±16.0% in the control group (adjusted difference, 14 percentage points; 95% confidence interval, 9.2 to 18.8; P<0.001), with no treatment effect according to age (P=0.56). Patients in the AID group spent 3 hours 21 minutes more in the target range per day than those in the control group. No severe hypoglycemia or diabetic ketoacidosis occurred in either group. Two patients in the AID group withdrew from the trial owing to connectivity issues.

CONCLUSIONS

In children and adults with type 1 diabetes, the use of an open-source AID system resulted in a significantly higher percentage of time in the target glucose range than the use of a sensor-augmented insulin pump at 24 weeks. (Supported by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12620000034932.)

From the Departments of Pediatrics (M.J.B., R.A.M., O.J.S., M.I.B.) and Population Health (J.A.W.), University of Otago, and the Department of Pediatrics, Canterbury District Health Board (M.J.B., O.J.S., M.I.B.), Christchurch, Te Huataki Waiora School of Health, Sport and Human Performance, University of Waikato (H.R.C.), and Waikato Regional Diabetes Service, Waikato District Health Board (R.G.P., C.S.L., S.K.J.P.), Hamilton, the Department of Pediatric Endocrinology, Starship Children's Health, Auckland District Health Board (C.A.J., A.M.F., C.L.), and the Liggins Institute, University of Auckland (C.A.J.), Auckland, the Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago (C.M.F., S.D.J., B.J.W.), and the Pediatric Department, Southern District Health Board (B.J.W.), Dunedin, and Nightscout New Zealand, Hamilton (T.C.G.) — all in New Zealand; and OpenAPS, Seattle (D.M.L.). Dr. de Bock can be contacted at martin.debock@otago.ac.nz or at the Department of Pediatrics, University of Otago, 4 Oxford Terrace, Christchurch 8011, New Zealand.

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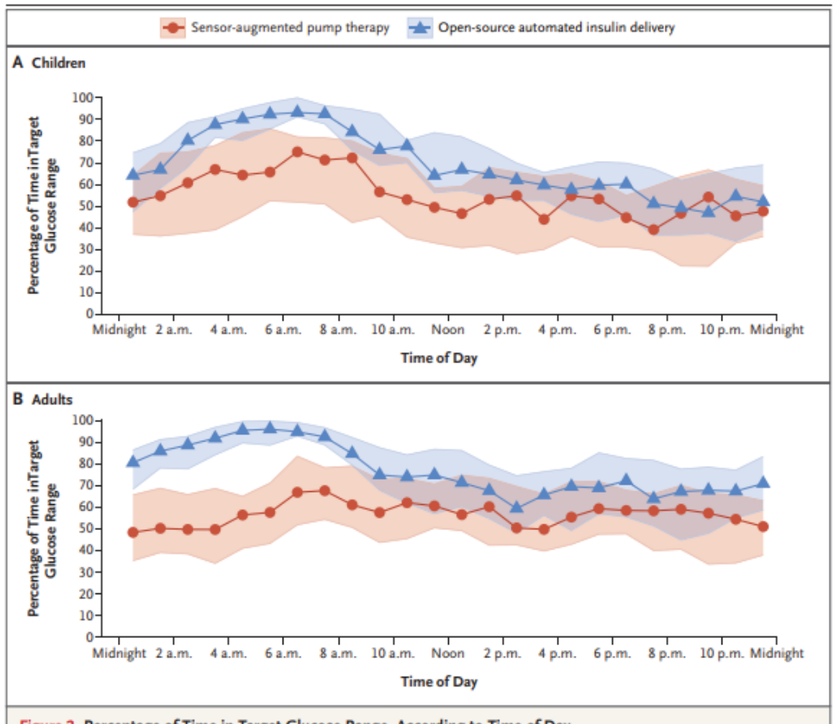

Figure 2. Percentage of Time in Target Glucose Range, According to Time of Day.
Envelope plots show the percentage of time that children and adults in the two trial groups were in the target glucose range, as measured by continuous glucose monitoring during weeks 22 and 23 after randomization. Symbols represent hourly group median values, and shaded regions indicate the 25th and 75th percentiles.

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doi: 10.2337/dc21-2004.

Continuous Glucose Monitoring Initiation Within First Year of Type 1 Diabetes Diagnosis Is Associated With Improved Glycemic Outcomes: 7-Year Follow-Up Study

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PMID: 35018417

DOI: 10.2337/dc21-2004

Abstract

Objective: To evaluate long-term glycemic outcomes of continuous glucose monitoring (CGM) initiation within the first year of type 1 diabetes diagnosis.

Research design and methods: Patients with type 1 diabetes (N = 396) were divided into three groups: 1) CGM (CGM use within 1 year of diabetes diagnosis and continued through the study), 2) no-CGM (no CGM use throughout the study), and 3) new-CGM (CGM use after 3 years since diabetes diagnosis). Patients were followed up to 7 years.

Results: A1c was significantly lower in the CGM compared with the no-CGM group throughout 7 years of follow-up (least squares mean A1c values: 6 months, 7.3% vs. 8.1%; 1 year, 7.4% vs. 8.6%; 2 years, 7.7% vs. 9.1%; 3 years, 7.6% vs. 9.3%; 4 years, 7.4% vs. 9.6%; 5 years, 7.6% vs. 9.7%; 6 years, 7.5% vs. 10.0%; and 7 years, 7.6% vs. 9.8%; for all, P < 0.001) adjusting for age at diagnosis, sex, and insulin delivery method.

Conclusions: CGM initiation within first year of type 1 diabetes diagnosis results in long-term improvement in A1c.

ORIGINAL ARTICLE

Intermittently Scanned Continuous Glucose Monitoring for Type 1 Diabetes

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ABSTRACT

BACKGROUND

In persons with type 1 diabetes and high glycated hemoglobin levels, the benefits of intermittently scanned continuous glucose monitoring with optional alarms for high and low blood glucose levels are uncertain.

METHODS

In a parallel-group, multicenter, randomized, controlled trial involving participants with type 1 diabetes and glycated hemoglobin levels between 7.5% and 11.0%, we investigated the efficacy of intermittently scanned continuous glucose monitoring as compared with participant monitoring of blood glucose levels with fingerstick testing. The primary outcome was the glycated hemoglobin level at 24 weeks, analyzed in accordance with the intention-to-treat principle. Key secondary outcomes included sensor data, participant-reported outcome measures, and safety.

RESULTS

A total of 156 participants were randomly assigned, in a 1:1 ratio, to undergo intermittently scanned continuous glucose monitoring (the intervention group, 78 participants) or to monitor their own blood glucose levels with fingerstick testing (the usual-care group, 78 participants). At baseline, the mean (±SD) age of the participants was 44±15 years, and the mean duration of diabetes was 21±13 years; 44% of the participants were women. The mean baseline glycated hemoglobin level was 8.7±0.9% in the intervention group and 8.5±0.8% in the usual-care group; these levels decreased to 7.9±0.8% and 8.3±0.9%, respectively, at 24 weeks (adjusted mean between-group difference, −0.5 percentage points; 95% confidence interval [CI], −0.7 to −0.3; P<0.001). The time per day that the glucose level was in the target range was 9.0 percentage points (95% CI, 4.7 to 13.3) higher or 130 minutes (95% CI, 68 to 192) longer in the intervention group than in the usual-care group, and the time spent in a hypoglycemic state (blood glucose level, <70 mg per deciliter [<3.9 mmol per liter]) was 3.0 percentage points (95% CI, 1.4 to 4.5) lower or 43 minutes (95% CI, 20 to 65) shorter in the intervention group. Two participants in the usual-care group had an episode of severe hypoglycemia, and 1 participant in the intervention group had a skin reaction to the sensor.

CONCLUSIONS

Among participants with type 1 diabetes and high glycated hemoglobin levels, the use of intermittently scanned continuous glucose monitoring with optional alarms for high and low blood glucose levels resulted in significantly lower glycated hemoglobin levels than levels monitored by fingerstick testing. (Funded by Diabetes UK and others; FLASH-UK ClinicalTrials.gov number, NCT03815006.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Leelarathna can be contacted at lalantha.leelarathna@manchester.ac.uk or at the Diabetes, Endocrinology, and Metabolism Centre, Peter Mount Bldg., Manchester Royal Infirmary, Oxford Rd., Manchester M13 9WL, United Kingdom.

*The members of the FLASH-UK Trial Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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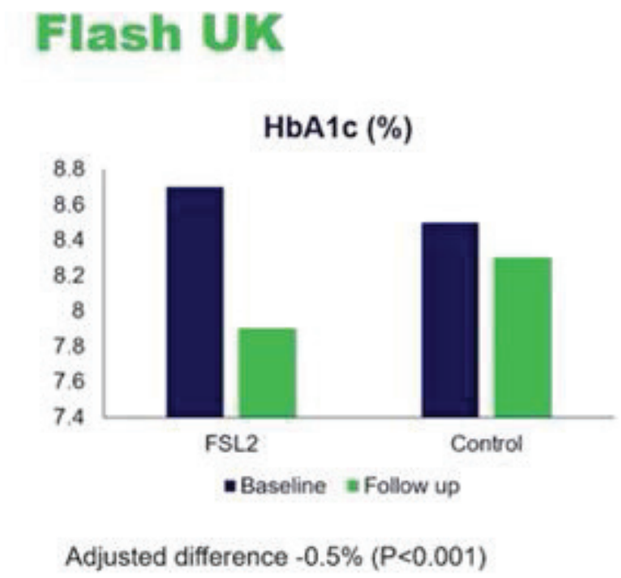
DOI: 10.1056/NEJMoa2205650



Βάλβης 5

JOURNAL ARTICLE

Relationship Between Time in Range, Glycemic Variability, HbA1c, and Complications in Adults With Type 1 Diabetes Mellitus

Anass El Malahi, Michiel Van Elsen, Sara Charleer, Eveline Dirinck, Kristien Ledeganck, Bart Keymeulen, Laurent Crenier, Régis Radermecker, Youri Taes, Chris Vercammen ... Show more

The Journal of Clinical Endocrinology & Metabolism, Volume 107, Issue 2, February 2022, Pages e570–e581, https://doi.org/10.1210/clinem/dgab688
Published:
17 September 2021

Abstract

Purpose

Real-time continuous glucose monitoring (RT-CGM) provides information on glycemic variability (GV), time in range (TIR), and guidance to avoid hypoglycemia, thereby complimenting HbA1c for diabetes management. We investigated whether GV and TIR were independently associated with chronic and acute diabetes complications.

Methods

Between September 2014 and January 2017, 515 subjects with type 1 diabetes using sensor-augmented pump therapy were followed for 24 months. The link between baseline HbA1c and CGM-derived glucometrics (TIR [70-180 mg/dL], coefficient of variation [CV], and SD) obtained from the first 2 weeks of RT-CGM use and the presence of complications was investigated. Complications were defined as: composite microvascular complications (presence of neuropathy, retinopathy, or nephropathy), macrovascular complications, and hospitalization for hypoglycemia and/or ketoacidosis.

Results

Individuals with microvascular complications were older ($P < 0.001$), had a longer diabetes duration ($P < 0.001$), a higher HbA1c (7.8 ± 0.9 vs 7.5 ± 0.9%, $P < 0.001$), and spent less time in range (60.4 ± 12.2 vs 63.9 ± 13.8%, $P = 0.022$) compared with those without microvascular complication. Diabetes duration (odds ratio [OR] = 1.12

[1.09-1.15], *P* < 0.001) and TIR (OR = 0.97 [0.95-0.99], *P* = 0.005) were independent risk factors for composite microvascular complications, whereas SD and CV were not. Age (OR = 1.08 [1.03-1.14], *P* = 0.003) and HbA1c (OR = 1.80 [1.02-3.14], *P* = 0.044) were risk factors for macrovascular complications. TIR (OR = 0.97 [0.95-0.99], *P* = 0.021) was the only independent risk factor for hospitalizations for hypoglycemia or ketoacidosis.

Conclusions

Lower TIR was associated with the presence of composite microvascular complications and with hospitalization for hypoglycemia or ketoacidosis. TIR, SD, and CV were not associated with macrovascular complications.

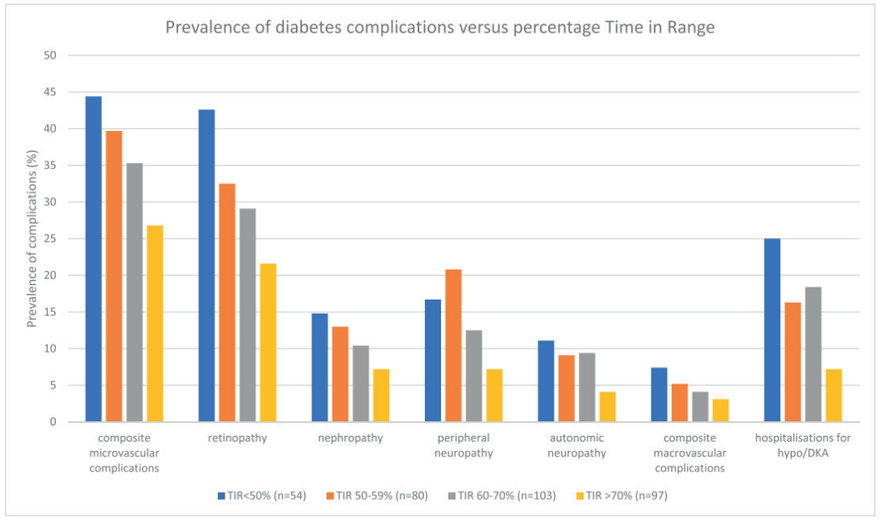


Figure 2. Prevalence of complications versus percentage of time spent in optimal range (70-180 mg/dL or 3.9-10.0 mmol/L).

Βάλβης 6

Diabetes Care
2022 Feb 1;45(2):365-371.
doi: 10.2337/dc21-0602.

CGM Metrics Predict Imminent Progression to Type 1 Diabetes: Autoimmunity Screening for Kids (ASK) Study

Andrea K Steck, Fran Dong, Cristy Geno Rasmussen, Kimberly Bautista, Flor Sepulveda, Judith Baxter, Liping Yu, Brigitte I Frohnert, Marian J Rewers; ASK Study Group.; Marian Rewers, Aaron Barbour, Kimberly Bautista, Judith Baxter, Daniel Felipe-Morales, Fran Dong, Paul Dormond-Brooks, Kimberly Driscoll, Brigitte Frohnert, Cristy Geno Rasmussen, Patricia Gesualdo, Michelle Hoffman, Rachel Karban, Flor Sepulveda, Hanan Shorrosh, Kimberly Simmons, Andrea Steck, Iman Taki, Kathleen Waugh, Liping Yu, Edwin Liu, Marisa Gallant, R Brett McQueen, Jill M Norris

- PMID: 34880069
- DOI: 10.2337/dc21-0602

Abstract

Objective: Children identified with stage 1 type 1 diabetes are at high risk for progressing to stage 3 (clinical) diabetes and require accurate monitoring. Our aim was to establish continuous glucose monitoring (CGM) metrics that could predict imminent progression to diabetes.

Research design and methods: In the Autoimmunity Screening for Kids study, 91 children who were persistently islet autoantibody positive (median age 11.5 years; 48% non-Hispanic White; 57% female) with a baseline CGM were followed for development of diabetes for a median of 6 (range 0.2-34) months. Of these, 16 (18%) progressed to clinical diabetes in a median of 4.5 (range 0.4-29) months.

Results: Compared with children who did not progress to clinical diabetes (nonprogressors), those who did (progressors) had significantly higher average sensor glucose levels (119 vs. 105 mg/dL, P < 0.001) and increased glycemic variability (SD 27 vs. 16, coefficient of variation, 21 vs. 15, mean of daily differences 24 vs. 16, and mean amplitude of glycemic excursions 43 vs. 26, all P < 0.001). For progressors, 21% of the time was spent with glucose levels >140 mg/dL (TA140) and 8% of time >160 mg/dL, compared with 3% and 1%, respectively, for nonprogressors. In survival analyses, the risk of progression to diabetes in 1 year was 80% in those with TA140 >10%; in contrast, it was only 5% in the other participants. Performance of prediction by receiver operating curve analyses showed area under the curve of ≥0.89 for both individual and combined CGM metric models.

Conclusions: TA140 >10% is associated with a high risk of progression to clinical diabetes within the next year in autoantibody-positive children. CGM should be included in the ongoing monitoring of high-risk children and could be used as potential entry criterion for prevention trials.

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01805-3

Check for updates

Empagliflozin add-on therapy to closed-loop insulin delivery in type 1 diabetes: a 2 × 2 factorial randomized crossover trial

Ahmad Haidar[1,2,3], Leif Erik Lovblom[4], Nancy Cardinez[4], Nikita Gouchie-Provencher[2], Andrej Orszag[4], Michael A. Tsoukas[2,3], C. Marcelo Falappa[4], Adnan Jafar[1], Milad Ghanbari[1], Devrim Eldelekli[4], Joanna Rutkowski[1], Jean-François Yale[2,3] and Bruce A. Perkins[4,5] ✉

There is a need to optimize closed-loop automated insulin delivery in type 1 diabetes. We assessed the glycemic efficacy and safety of empagliflozin 25 mg d^{-1} as add-on therapy to insulin delivery with a closed-loop system. We performed a 2 × 2 factorial randomized, placebo-controlled, crossover two-center trial in adults, assessing 4 weeks of closed-loop delivery versus sensor-augmented pump (SAP) therapy and empagliflozin versus placebo. The primary outcome was time spent in the glucose target range (3.9–10.0 mmol l^{-1}). Primary comparisons were empagliflozin versus placebo in each of closed-loop or SAP therapy; the remaining comparisons were conditional on its significance. Twenty-four of 27 randomized participants were included in the final analysis. Compared to placebo, empagliflozin improved time in target range with closed-loop therapy by 7.2% and in SAP therapy by 11.4%. Closed-loop therapy plus empagliflozin improved time in target range compared to SAP therapy plus empagliflozin by 6.1% but by 17.5% for the combination of closed-loop therapy and empagliflozin compared to SAP therapy plus placebo. While no diabetic ketoacidosis or severe hypoglycemia occurred during any intervention, uncomplicated ketosis events were more common on empagliflozin. Empagliflozin 25 mg d^{-1} added to automated insulin delivery improves glycemic control but increases ketone concentration and ketosis compared to placebo.

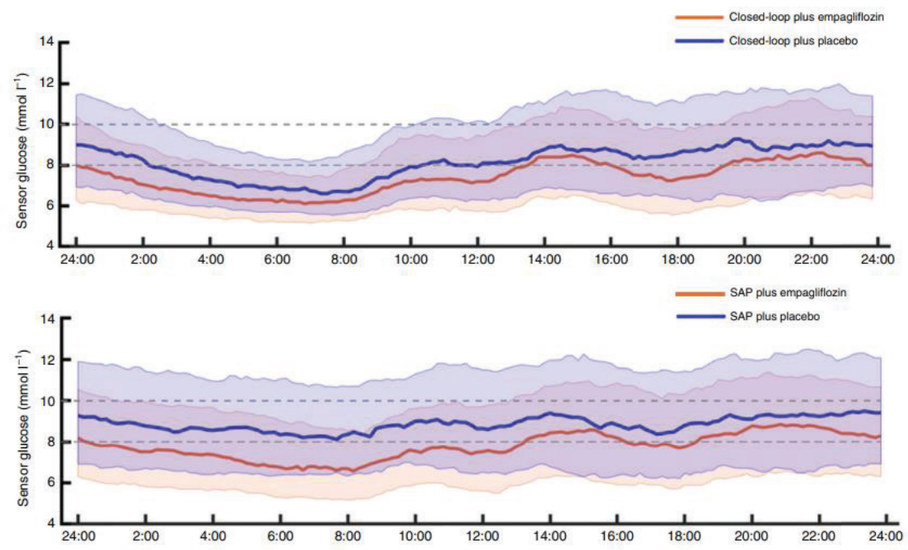


Fig. 2 | The median (IQR) profiles of glucose levels during the interventions from midnight to midnight. $n = 24$ independent participants in each of the four settings. Median values according to time of day are represented by the bold blue and red lines. Interquartile ranges by time of day are represented by the shaded light blue and light red areas. The dashed lines indicate the upper threshold levels for the target ranges analyzed as outcomes, specifically 3.9 to 10.0 mmol l^{-1} and 3.9 to 7.8 mmol l^{-1}.

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DOI: 10.1111/dom.14898

ORIGINAL ARTICLE

WILEY

Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial

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Funding information
Sanofi

Abstract

Aim: To use continuous glucose monitoring (CGM)-based time-in-range (TIR) as a primary efficacy endpoint to compare the second-generation basal insulin (BI) analogues insulin glargine 300 U/ml (Gla-300) and insulin degludec 100 U/ml (IDeg-100) in adults with type 1 diabetes (T1D).

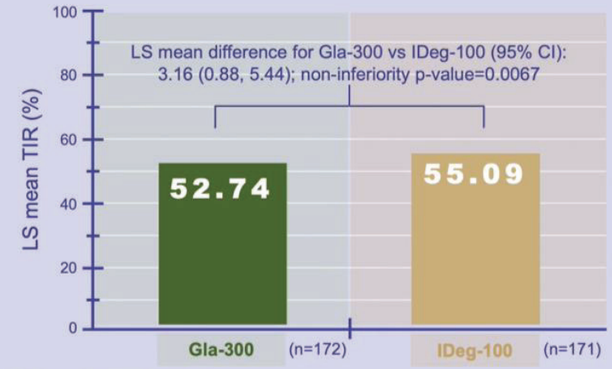
Materials and Methods: InRange was a 12-week, multicentre, randomized, active-controlled, parallel-group, open-label study comparing glucose TIR and variability between Gla-300 and IDeg-100 using blinded 20-day CGM profiles. The inclusion criteria consisted of adults with T1D treated with multiple daily injections, using BI once daily and rapid-acting insulin analogues for at least 1 year, with an HbA1c of 7% or higher and of 10% or less at screening.

Results: Overall, 343 participants were randomized: 172 received Gla-300 and 171 IDeg-100. Non-inferiority (10% relative margin) of Gla-300 versus IDeg-100 was shown for the primary endpoint (percentage TIR ≥ 70 to ≤ 180 mg/dl): least squares (LS) mean (95% confidence interval) 52.74% (51.06%, 54.42%) for Gla-300 and 55.09% (53.34%, 56.84%) for IDeg-100; LS mean difference (non-inferiority): 3.16% (0.88%, 5.44%) (non-inferiority $P = .0067$). Non-inferiority was shown on glucose total coefficient of variation (main secondary endpoint): LS mean 39.91% (39.20%, 40.61%) and 41.22% (40.49%, 41.95%), respectively; LS mean difference (non-inferiority) −5.44% (−6.50%, −4.38%) (non-inferiority $P < .0001$). Superiority of Gla-300 over IDeg-100 was not shown on TIR. Occurrences of self-measured and CGM-derived hypoglycaemia were comparable between treatment groups. Safety profiles were consistent with known profiles, with no unexpected findings.

Conclusions: Using clinically relevant CGM metrics, InRange shows that Gla-300 is non-inferior to IDeg-100 in people with T1D, with comparable hypoglycaemia and safety profiles.

The primary endpoint of the InRange study was met:

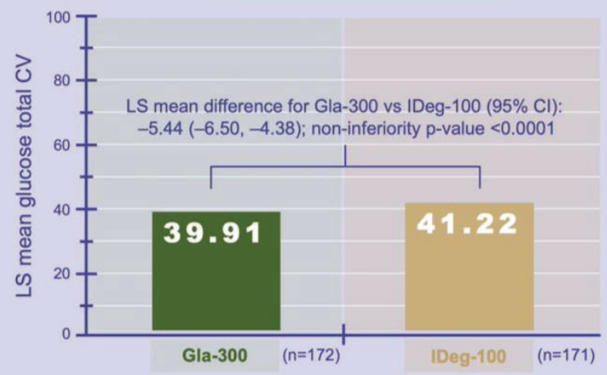
Gla-300 was non-inferior to **IDeg-100** for **% TIR 70–180 mg/dL (3.9–10.0 mmol/L)**



Relative non-inferiority margin 10%, difference Gla-300 – 0.9*IDeg-100
CI, confidence interval; LS, least squares

The main secondary endpoint of glucose total CV was also met:

Gla-300 was non-inferior to **IDeg-100** for **glucose total CV**



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ORIGINAL ARTICLE

WILEY

Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: The PRONTO-Peds trial

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Funding information
Eli Lilly and Company

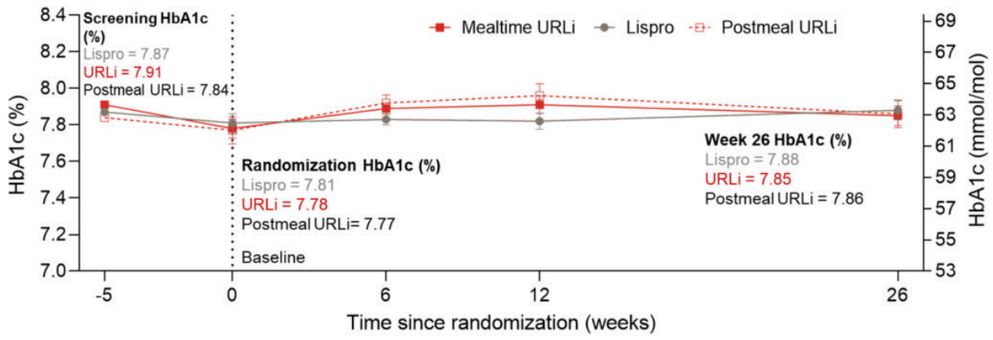
Abstract

Aims: To evaluate the efficacy and safety of ultra-rapid lispro (URLi) versus lispro in a paediatric population with type 1 diabetes (T1D) in a Phase 3, treat-to-target study.

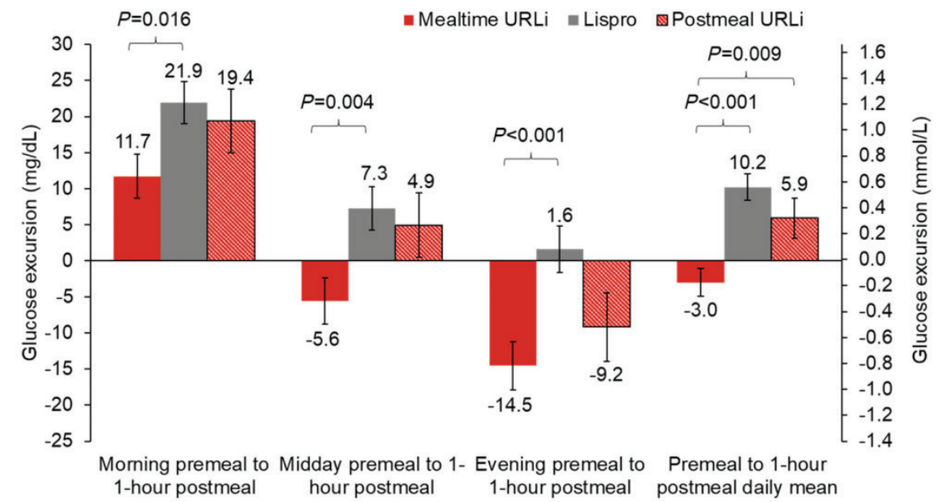
Materials and Methods: After a 4-week lead-in to optimize basal insulin, participants were randomized to double-blind URLi ($n = 280$) or lispro ($n = 298$) injected 0 to 2 minutes prior to meals (mealtime), or open-label URLi ($n = 138$) injected up to 20 minutes after start of meals (postmeal). Participants remained on pre-study basal insulin (degludec, detemir or glargine). The primary endpoint was glycated haemoglobin (HbA1c) change from baseline after 26 weeks (noninferiority margin 4.4 mmol/mol [0.4%]).

Results: Both mealtime and postmeal URLi demonstrated noninferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi −0.23 mmol/mol (95% confidence interval [CI] −1.84, 1.39) and postmeal URLi −0.17 mmol/mol (95% CI −2.15, 1.81). Mealtime URLi reduced 1-hour postprandial glucose (PPG) daily mean ($P = 0.001$) and premeal to 1 hour postmeal PPG excursion daily mean ($P < 0.001$) versus lispro. The rate and incidence of severe, nocturnal or documented hypoglycaemia (<3.0 mmol/L [54 mg/dL]) were similar for all treatments. With mealtime URLi versus lispro, the rate of postdose hypoglycaemia (<3.0 mmol/L) was higher at ≤2 hours ($P = 0.034$). The incidence of treatment-emergent adverse events was similar for all treatments. More participants reported an injection site reaction with mealtime URLi (7.9%) versus postmeal URLi (2.9%) and lispro (2.7%).

Conclusions: In children and adolescents with T1D, URLi demonstrated good glycaemic control, and noninferiority to lispro in HbA1c change for mealtime and postmeal URLi. When dosed at the beginning of meals, URLi reduced 1-hour PPG and PPG excursions versus lispro.



Mean glycated haemoglobin (HbA1c) from study entry to Week 26. Data are mean at screening and least squares mean ± standard error at all other timepoints and based on the mixed-effects model for repeated measurements analysis in the efficacy estimand. Abbreviations: HbA1c, glycated haemoglobin haemoglobin; URLi, ultra-rapid lispro



Postprandial glucose excursions at week 26. Data are least squares mean ± standard error. Abbreviation: URLi, ultra-rapid lispro

JAMA Network Open

Research Letter | Infectious Diseases

Association of SARS-CoV-2 Infection With New-Onset Type 1 Diabetes Among Pediatric Patients From 2020 to 2021

Ellen K. Kendall, BA; Veronica R. Olaker, BS; David C. Kaelber, MD, PhD; Rong Xu, PhD; Pamela B. Davis, MD, PhD

Introduction

Incidence of new-onset type 1 diabetes (T1D) increased during the COVID-19 pandemic,[1] and this increase has been associated with SARS-CoV-2 infection.[2] The US Centers for Disease Control and Prevention reported that pediatric patients with COVID-19 were more likely to be diagnosed with diabetes after infection, although types 1 and 2 were not separated.[3] Therefore, whether COVID-19 was associated with new-onset T1D among youths remains unclear. This cohort study assessed whether there was an increase in new diagnoses of T1D among pediatric patients after COVID-19.

Discussion

In this study, new T1D diagnoses were more likely to occur among pediatric patients with prior COVID-19 than among those with other respiratory infections (or with other encounters with health systems). Respiratory infections have previously been associated with onset of T1D,[6] but this risk was even higher among those with COVID-19 in our study, raising concern for long-term, post–COVID-19 autoimmune complications among youths. Study limitations include potential biases owing to the observational and retrospective design of the electronic health record analysis, including the possibility of misclassification of diabetes as type 1 vs type 2, and the possibility that additional unidentified factors accounted for the association. Results should be confirmed in other populations. The increased risk of new-onset T1D after COVID-19 adds an important consideration for risk-benefit discussions for prevention and treatment of SARS-CoV-2 infection in pediatric populations.

Diabetologia (2022) 65:1473–1482
https://doi.org/10.1007/s00125-022-05722-5

ARTICLE

Obesity in late adolescence and incident type 1 diabetes in young adulthood

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Received: 30 November 2021 / Accepted: 8 March 2022 / Published online: 5 June 2022

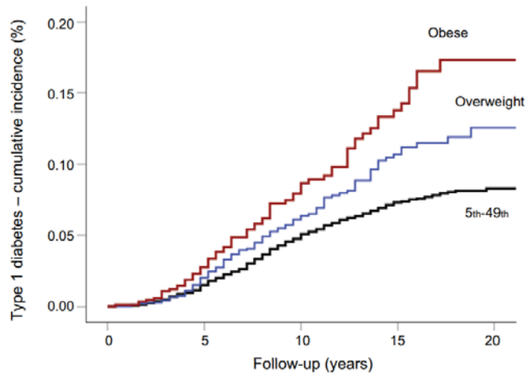
Abstract

Aims/hypothesis Studies in children have reported an association between increased BMI and risk for developing type 1 diabetes, but evidence in late adolescence is limited. We studied the association between BMI in late adolescence and incident type 1 diabetes in young adulthood.

Methods All Israeli adolescents, ages 16–19 years, undergoing medical evaluation in preparation for mandatory military conscription between January 1996 and December 2016 were included for analysis unless they had a history of dysglycaemia. Data were linked with information about adult onset of type 1 diabetes in the Israeli National Diabetes Registry. Weight and height were measured at study entry. Cox proportional models were applied, with BMI being analysed both as a categorical and as a continuous variable.

Results There were 777 incident cases of type 1 diabetes during 15,819,750 person-years (mean age at diagnosis 25.2 ±3.9 years). BMI was associated with incident type 1 diabetes. In a multivariable model adjusted for age, sex and socio-demographic variables, the HRs for type 1 diabetes were 1.05 (95% CI 0.87, 1.27) for the 50th–74th BMI percentiles, 1.41 (95% CI 1.11, 1.78) for the 75th–84th BMI percentiles, 1.54 (95% CI 1.23, 1.94) for adolescents who were overweight (85th–94th percentiles), and 2.05 (95% CI 1.58, 2.66) for adolescents with obesity (≥95th percentile) (reference group: 5th–49th BMI percentiles). One increment in BMI SD was associated with a 25% greater risk for incidence of type 1 diabetes (HR 1.25, 95% CI 1.17, 1.32).

Conclusions Excessively high BMI in otherwise healthy adolescents is associated with increased risk for incident type 1 diabetes in early adulthood.



Kaplan–Meier survival analysis of the association between adolescent obesity and incident type 1 diabetes in young adulthood stratified by BMI categories (5th–49th percentiles, overweight and obese).

Continuous glucose monitoring and metrics for clinical trials: an international consensus statement

Tadej Battelino, Charles M Alexander, Stephanie A Amiel, Guillermo Arreaza-Rubin, Roy W Beck, Richard M Bergenstal, Bruce A Buckingham, James Carroll, Antonio Ceriello, Elaine Chow, Pratik Choudhary, Kelly Close, Thomas Danne, Sanjoy Dutta, Robert Gabbay, Satish Garg, Julie Heverly, Irl B Hirsch, Tina Kader, Julia Kenney, Boris Kovatchev, Lori Laffel, David Maahs, Chantal Mathieu, Dídac Mauricio, Revital Nimri, Rimei Nishimura, Mauro Scharf, Stefano Del Prato, Eric Renard, Julio Rosenstock, Banshi Saboo, Kohjiro Ueki, Guillermo E Umpierrez, Stuart A Weinzimer, Moshe Phillip

Lancet Diabetes Endocrinol 2023; 11: 42–57

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Randomised controlled trials and other prospective clinical studies for novel medical interventions in people with diabetes have traditionally reported HbA_{1c} as the measure of average blood glucose levels for the 3 months preceding the HbA_{1c} test date. The use of this measure highlights the long-established correlation between HbA_{1c} and relative risk of diabetes complications; the change in the measure, before and after the therapeutic intervention, is used by regulators for the approval of medications for diabetes. However, with the increasing use of continuous glucose monitoring (CGM) in clinical practice, prospective clinical studies are also increasingly using CGM devices to collect data and evaluate glucose profiles among study participants, complementing HbA_{1c} findings, and further assess the effects of therapeutic interventions on HbA_{1c}. Data is collected by CGM devices at 1–5 min intervals, which obtains data on glycaemic excursions and periods of asymptomatic hypoglycaemia or hyperglycaemia (ie, details of glycaemic control that are not provided by HbA_{1c} concentrations alone that are measured continuously and can be analysed in daily, weekly, or monthly timeframes). These CGM-derived metrics are the subject of standardised, internationally agreed reporting formats and should, therefore, be considered for use in all clinical studies in diabetes. The purpose of this consensus statement is to recommend the ways CGM data might be used in prospective clinical studies, either as a specified study endpoint or as supportive complementary glucose metrics, to provide clinical information that can be considered by investigators, regulators, companies, clinicians, and individuals with diabetes who are stakeholders in trial outcomes. In this consensus statement, we provide recommendations on how to optimise CGM-derived glucose data collection in clinical studies, including the specific glucose metrics and specific glucose metrics that should be evaluated. These recommendations have been endorsed by the American Association of Clinical Endocrinologists, the American Diabetes Association, the Association of Diabetes Care and Education Specialists, DiabetesIndia, the European Association for the Study of Diabetes, the International Society for Pediatric and Adolescent Diabetes, the Japanese Diabetes Society, and the Juvenile Diabetes Research Foundation. A standardised approach to CGM data collection and reporting in clinical trials will encourage the use of these metrics and enhance the interpretability of CGM data, which could provide useful information other than HbA_{1c} for informing therapeutic and treatment decisions, particularly related to hypoglycaemia, postprandial hyperglycaemia, and glucose variability.

ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ

ΧΑΡΑΛΑΜΠΟΣ ΜΗΛΙΩΝΗΣ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ,
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ARTICLE

The impact of population-level HbA_{1c} screening on reducing diabetes diagnostic delay in middle-aged adults: a UK Biobank analysis

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Abstract

Aims/hypothesis Screening programmes can detect cases of undiagnosed diabetes earlier than symptomatic or incidental diagnosis. However, the improvement in time to diagnosis achieved by screening programmes compared with routine clinical care is unclear. We aimed to use the UK Biobank population-based study to provide the first population-based estimate of the reduction in time to diabetes diagnosis that could be achieved by HbA_{1c}-based screening in middle-aged adults.

Methods We studied UK Biobank participants aged 40–70 years with HbA_{1c} measured at enrolment (but not fed back to participants/clinicians) and linked primary and secondary healthcare data (n=179,923) and identified those with a pre-existing diabetes diagnosis (n=13,077, 7.3%). Among the remaining participants (n=166,846) without a diabetes diagnosis, we used an elevated enrolment HbA_{1c} level (≥48 mmol/mol [≥6.5%]) to identify those with undiagnosed diabetes. For this group, we used Kaplan–Meier analysis to assess the time between enrolment HbA_{1c} measurement and subsequent clinical diabetes diagnosis up to 10 years, and Cox regression to identify clinical factors associated with delayed diabetes diagnosis.

Results In total, 1.0% (1703/166,846) of participants without a diabetes diagnosis had undiagnosed diabetes based on calibrated HbA_{1c} levels at UK Biobank enrolment, with a median HbA_{1c} level of 51.3 mmol/mol (IQR 49.1–57.2) (6.8% [6.6–7.4]). These participants represented an additional 13.0% of diabetes cases in the study population relative to the 13,077 participants with a diabetes diagnosis. The median time to clinical diagnosis for those with undiagnosed diabetes was 2.2 years, with a median HbA_{1c} at clinical diagnosis of 58.2 mmol/mol (IQR 51.0–80.0) (7.5% [6.8–9.5]). Female participants with lower HbA_{1c} and BMI measurements at enrolment experienced the longest delay to clinical diagnosis.

Conclusions/interpretation Our population-based study shows that HbA_{1c} screening in adults aged 40–70 years can reduce the time to diabetes diagnosis by a median of 2.2 years compared with routine clinical care. The findings support the use of HbA_{1c} screening to reduce the time for which individuals are living with undiagnosed diabetes.

Keywords Diabetes · HbA_{1c} · Public health · Screening · UK Biobank

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Abbreviations

ADA-RTS	ADA Risk Test Score
FINDRISC	Finnish Diabetes Risk Score
IMD	Index of Multiple Deprivation
LRS	Leicester Risk Score
NNS	Number needed to screen
NSC	National Screening Committee
UKPDS	UK Prospective Diabetes Study

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nutrients

MDPI

Article

Differential Glycemic Effects of Low- versus High-Glycemic Index Mediterranean-Style Eating Patterns in Adults at Risk for Type 2 Diabetes: The MEDGI-Carb Randomized Controlled Trial

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Abstract: A Mediterranean-style healthy eating pattern (MED-HEP) supports metabolic health, but the utility of including low-glycemic index (GI) foods to minimize postprandial glucose excursions remain unclear. Therefore, we investigated the relative contribution of GI towards improvements in postprandial glycemia and glycemic variability after adopting a MED-HEP. We conducted a randomized, controlled dietary intervention, comparing high- versus low-GI diets in a multi-national (Italy, Sweden, and the United States) sample of adults at risk for type 2 diabetes. For 12 weeks, participants consumed either a low-GI or high-GI MED-HEP. We assessed postprandial plasma glucose and insulin responses to high- or low-GI meals, and daily glycemic variability via continuous glucose monitoring at baseline and post-intervention. One hundred sixty adults (86 females, 74 males; aged 55 ± 11 y, BMI 31 ± 3 kg/m^2, mean ± SD) with ≥two metabolic syndrome traits completed the intervention. Postprandial insulin concentrations were greater after the high-GI versus the low-GI test meals at baseline ($p = 0.004$), but not post-intervention ($p = 0.17$). Postprandial glucose after the high-GI test meal increased post-intervention, being significantly higher than that after the low-GI test meal (35%, $p < 0.001$). Average daily glucose concentrations decreased in both groups post-intervention. Indices of 24-h glycemic variability were reduced in the low-GI group as compared to baseline and the high-GI intervention group. These findings suggest that low-GI foods may be an important feature within a MED-HEP.

Keywords: Mediterranean diet; metabolic syndrome; metabolic health; impaired glycemic control; metabolic risk factors; insulinemia; glycemic variability; continuous glucose monitoring; oral glucose tolerance test; meal glucose tolerance test

1. Introduction

Type 2 diabetes is a dire metabolic condition that has a profound impact on the estimated ~400 million individuals afflicted worldwide [1]. Without a rapid and robust response, type 2 diabetes is projected to continue along this course of precipitous increases in cases during the upcoming decades [1,2]. The deleterious effects of type 2 diabetes are further magnified when its contributions towards cardiovascular disease, the leading cause of mortality in Western nations, are considered [3,4]. Given the societal burden, research

ASN EST. 1928

Effect of a ketogenic diet versus Mediterranean diet on glycated hemoglobin in individuals with prediabetes and type 2 diabetes mellitus: The interventional Keto-Med randomized crossover trial

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Abstract

Background: Consensus has not been reached on what constitutes an optimal diet in individuals with prediabetes and type 2 diabetes mellitus (T2DM), especially between low-carbohydrate options.

Objectives: We compared 2 low-carbohydrate diets with 3 key similarities (incorporating nonstarchy vegetables and avoiding added sugars and refined grains) and 3 key differences (incorporating compared with avoiding legumes, fruits, and whole, intact grains) for their effects on glucose control and cardiometabolic risk factors in individuals with prediabetes and T2DM.

Methods: Keto-Med was a randomized, crossover, interventional trial. Forty participants aged ≥18 years with prediabetes or T2DM followed the well-formulated ketogenic diet (WFKD) and the Mediterranean-plus diet (Med-Plus) for 12 weeks each, in random order. The diets shared the 3 key similarities noted above. The Med-Plus incorporated legumes, fruits, and whole, intact grains, while the WFKD avoided them. The primary outcome was the percentage change in glycated hemoglobin (HbA1c) after 12 weeks on each diet. Secondary and exploratory outcomes included percentage changes in body weight, fasting insulin, glucose, and blood lipids; average glucose from continuous glucose monitor (CGM), and nutrient intake.

Results: The primary analysis was of 33 participants with complete data. The HbA1c values did not differ between diets at 12 weeks. Triglycerides decreased more for the WFKD [percentage changes, −16% (SEM, 4%) compared with −5% (SEM, 6%) for the Med-Plus; $P = 0.02$] and LDL cholesterol was higher for the WFKD [percentage changes, +10% (SEM, 4%) compared with −5% (SEM, 5%) for the Med-Plus; $P = 0.01$]. Weight decreased 8% (SEM, 1%) compared with 7% (SEM, 1%) and HDL cholesterol increased 11% (SEM, 2%) compared with 7% (SEM, 3%) for the WFKD compared with the Med-Plus, respectively; however, there was a significant interaction of diet × order for both. Participants had lower intakes of fiber and 3 nutrients on the WFKD compared with the Med-Plus. Twelve-week follow-up data suggest the Med-Plus is more sustainable.

Conclusions: HbA1c values were not different between diet phases after 12 weeks, but improved from baseline on both diets, likely due to several shared dietary aspects. The WFKD led to a greater decrease in triglycerides, but also had potential untoward risks from elevated LDL cholesterol and lower nutrient intakes from avoiding legumes, fruits, and whole, intact grains, as well as being less sustainable. This trial was registered at clinicaltrials.gov as NCT03810378. *Am J Clin Nutr* 2022;116:640–652.

Keywords: Mediterranean, ketogenic, diet, diabetes, prediabetes, HbA1c, metabolomic, intervention, human

All authors report no conflicts of interest.

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Supplemental Methods, Supplemental Tables 1–20, and Supplemental Figures 1–8 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ADA, American Diabetes Association; ALT, alanine aminotransferase; ASD, absolute standardized difference; CGM, continuous glucose monitoring; COVID-19, coronavirus disease 2019; CTRU, Clinical and Translational Research Unit; HbA1c, glycated hemoglobin; low-carb, low carbohydrate; Med-Plus, Mediterranean-plus diet; NDS-R, Nutrition Data System for Research; T2DM, type 2 diabetes mellitus; TIR, time-in-range; WFKD, well-formulated ketogenic diet.

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Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes

The GRADE Study Research Group*

ABSTRACT

BACKGROUND

The comparative effectiveness of glucose-lowering medications for use with metformin to maintain target glycated hemoglobin levels in persons with type 2 diabetes is uncertain.

METHODS

In this trial involving participants with type 2 diabetes of less than 10 years' duration who were receiving metformin and had glycated hemoglobin levels of 6.8 to 8.5%, we compared the effectiveness of four commonly used glucose-lowering medications. We randomly assigned participants to receive insulin glargine U-100 (hereafter, glargine), the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or sitagliptin, a dipeptidyl peptidase 4 inhibitor. The primary metabolic outcome was a glycated hemoglobin level, measured quarterly, of 7.0% or higher that was subsequently confirmed, and the secondary metabolic outcome was a confirmed glycated hemoglobin level greater than 7.5%.

RESULTS

A total of 5047 participants (19.8% Black and 18.6% Hispanic or Latinx) who had received metformin for type 2 diabetes were followed for a mean of 5.0 years. The cumulative incidence of a glycated hemoglobin level of 7.0% or higher (the primary metabolic outcome) differed significantly among the four groups (P<0.001 for a global test of differences across groups); the rates with glargine (26.5 per 100 participant-years) and liraglutide (26.1) were similar and lower than those with glimepiride (30.4) and sitagliptin (38.1). The differences among the groups with respect to a glycated hemoglobin level greater than 7.5% (the secondary outcome) paralleled those of the primary outcome. There were no material differences with respect to the primary outcome across prespecified subgroups defined according to sex, age, or race or ethnic group; however, among participants with higher baseline glycated hemoglobin levels there appeared to be an even greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin. Severe hypoglycemia was rare but significantly more frequent with glimepiride (in 2.2% of the participants) than with glargine (1.3%), liraglutide (1.0%), or sitagliptin (0.7%). Participants who received liraglutide reported more frequent gastrointestinal side effects and lost more weight than those in the other treatment groups.

CONCLUSIONS

All four medications, when added to metformin, decreased glycated hemoglobin levels. However, glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining target glycated hemoglobin levels. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143.)

The members of the writing committee (David M. Nathan, M.D., John M. Lachin, Sc.D., Ashok Balasubramanyam, M.D., Henry B. Burch, M.D., John B. Buse, M.D., Nicole M. Butera, Ph.D., Robert M. Cohen, M.D., Jill P. Crandall, M.D., Steven E. Kahn, M.B., Ch.B., Heidi Krause-Steinrauf, M.S., Mary E. Larkin, R.N., Neda Rasouli, M.D., Margaret Tiktin, D.N.P., Deborah J. Wexler, M.D., and Naji Younes, Ph.D.) assume responsibility for the overall content and integrity of this article.

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*The members of the GRADE Study Research Group are listed in the Supplementary Appendix, available at NEJM.org.

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CME at NEJM.org

Full title: **Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists and their combination in type 2 diabetes**

Short running title: MACCE & heart failure risk with antidiabetics

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Abstract

Objective: To assess associations between current use of SGLT2i, GLP-1RA and their combination and risk for MACCE and heart failure (HF) in people with type 2 diabetes.

Research Design and Methods: In three nested case-control studies involving people with type 2 diabetes in England and Wales (primary care data from CPRD and SAIL Databank with linkage to hospital and mortality records), we matched each patient experiencing an event with up to 20 controls. Adjusted odds ratios for MACCE and HF among patients receiving SGLT2i or GLP-1RA regimens vs other combinations were estimated using conditional logistic regression and pooled using random-effects meta-analysis.

Results: Among 336,334 people with type 2 diabetes and without cardiovascular disease, 18,531 (5.5%) experienced a MACCE. 17,451 (4.2%) experienced a HF event in a cohort of 411,206 with type 2 diabetes and without HF. Compared with other combination regimens, the adjusted pooled odds ratio and 95% confidence interval (CI) for MACCE associated with SGLT2i regimens was 0.82 (95% CI 0.73-0.92); with GLP-1RA regimens 0.93 (95% CI 0.81-1.06), and with the SGLT2i/GLP-1RA combination 0.70 (95% CI 0.50-0.98). Corresponding data for HF were: SGLT2i, 0.49 (95% CI 0.42-0.58); GLP-1RA, 0.82 (95% CI 0.71-0.95); and SGLT2i/GLP-1RA combination, 0.43 (95% CI 0.28-0.64).

Conclusions: SGLT2i and SGLT2i/GLP-1RA combination regimens may be beneficial in primary prevention of MACCE and heart failure and GLP-1RA for heart failure. These data call for primary prevention trials using these agents and their combination.

ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΧΑΡΑΛΑΜΠΟΣ ΜΗΛΙΩΝΗΣ

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ORIGINAL ARTICLE

WILEY

Efficacy and safety of a basal insulin + 2-3 oral antihyperglycaemic drugs regimen versus a twice-daily premixed insulin + metformin regimen after short-term intensive insulin therapy in individuals with type 2 diabetes: The multicentre, open-label, randomized controlled BEYOND-V trial

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Abstract

Aim: To compare the efficacy and safety of basal insulin glargine 100 units/ml (Gla) + 2-3 oral antihyperglycaemic drugs (OADs) with twice-daily premixed insulin aspart 70/30 (Asp30) + metformin (MET) after short-term intensive insulin therapy in adults with type 2 diabetes in China.

Materials and Methods: This open-label trial enrolled insulin-naïve adults with type 2 diabetes and an HbA1c of 7.5%-11.0% (58-97 mmol/mol) despite treatment with 2-3 OADs. All participants stopped previous OADs except MET, then received short-term intensive insulin therapy during the run-in period, when those with a fasting plasma glucose of less than 7.0 mmol/L and 2-hour postprandial glucose of less than 10.0 mmol/L were randomized to Gla + MET + a dipeptidyl peptidase-4 inhibitor or twice-daily Asp30 + MET. If HbA1c was more than 7.0% (>53 mmol/mol) at week 12, participants in the Gla group were added repaglinide or acarbose, at the physician's discretion, and participants in the Asp30 group continued to titrate insulin dose. The change in HbA1c from baseline to week 24 was assessed in the per protocol (PP) population (primary endpoint).

Results: There were 384 enrollees (192 each to Gla and Asp30); 367 were included in the PP analysis. The threshold for non-inferiority of Gla + OADs versus Asp30 + MET was met, with a least squares mean change from baseline in HbA1c of −1.72% and −1.70% (−42.2 and −42.1 mmol/mol), respectively (estimated difference −0.01%; 95% CI −0.20%, 0.17% [−0.1 mmol/mol; 95% CI −2.2, 1.9]). Achievement of

PATHOPHYSIOLOGY/COMPLICATIONS

Advanced Glycation End Products Predict Loss of Renal Function and High-Risk Chronic Kidney Disease in Type 2 Diabetes

Juraj Koska,[1] Hertzel C. Gerstein,[2] Paul J. Beisswenger,[3] and Peter D. Reaven[1,2]

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OBJECTIVE

To evaluate the association of a multicomponent advanced glycation end product (AGE) panel with decline in kidney function and its utility in predicting renal function loss (RFL) when added to routine clinical measures in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Carboxymethyl and carboxyethyl lysine and methylglyoxal, 3-deoxyglucosone, and glyoxal hydroimidazolones were measured in baseline serum and plasma samples, respectively, from Action to Control Cardiovascular Risk in Diabetes (ACCORD) (n = 1,150) and Veterans Affairs Diabetes Trial (VADT) (n = 447) participants. A composite AGE score was calculated from individual AGE z scores. The primary outcome was a sustained 30% decline in estimated glomerular filtration rate (eGFR) (30% RFL in both cohorts). Secondary outcomes (in ACCORD) were 40% RFL, macroalbuminuria, and high-risk chronic kidney disease (hrCKD).

RESULTS

After adjustment for baseline and follow-up HbA_{1c} and other risk factors in ACCORD, the AGE score was associated with reduction in eGFR (β-estimate −0.66 mL/min · 1.73 m^2 per year; P = 0.001), 30% RFL (hazard ratio 1.42 [95% CI 1.13–1.78]; P = 0.003), 40% RFL (1.40 [1.13–1.74]; P = 0.003), macroalbuminuria (1.53 [1.13–2.06]; P = 0.006), and hrCKD (1.88 [1.37–2.57]; P < 0.0001). AGE score improved net reclassification (NRI) and relative integrated discrimination (IDI) for 30% RFL (NRI 23%; P = 0.02) (relative IDI 7%; P = 0.009). In VADT, the AGE score calculated by the ACCORD-derived coefficients was associated with 30% RFL (1.37 [1.03–1.82]; P = 0.03) and improved NRI (24%; P = 0.03) but not IDI (P = 0.18).

CONCLUSIONS

These data provide further support for a causal role of AGEs in diabetic nephropathy independently of glycemic control and suggest utility of the composite AGE panel in predicting long-term decline in renal function.

Diabetic kidney disease (DKD) is a major complication of diabetes and increases risk for end-stage renal disease and mortality. DKD risk is related to chronic

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EXTENDED OBSERVATIONS FROM THE TODAY STUDY

Pregnancy Outcomes in Young Women With Youth-Onset Type 2 Diabetes Followed in the TODAY Study

*TODAY Study Group**

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OBJECTIVE

To assess pregnancy outcomes in young women with youth-onset type 2 diabetes followed in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study.

RESEARCH DESIGN AND METHODS

Pregnancy information (outcome and any maternal or fetal complications) was obtained from the female participants by self-report. Additionally, medical records for the pregnancy and the child's neonatal course were obtained with data abstracted into standardized forms.

RESULTS

Over a maximum of 15 years, 260 pregnancies were reported by 141 women (aged 21.5 ± 3.2 years, BMI 35.6 ± 7.2 kg/m^2, and diabetes duration 8.1 ± 3.2 years). Contraception use prior to pregnancy was reported by 13.5% of the women. Complications were reported by 65% of the women during their pregnancy. Pregnancy loss was observed in 25.3% and preterm birth in 32.6% of pregnancies. HbA_{1c} ≥8% was observed in 31.9% of the pregnancies, and 35% of the pregnancies were complicated by chronic hypertension. Nephropathy prior to pregnancy was observed in 25% of the women. In the offspring, 7.8% were classified as small for gestational age, 26.8% large for gestational age, and 17.9% in the macrosomic range.

CONCLUSIONS

Based on observations from the TODAY cohort, young women with pregestational, youth-onset type 2 diabetes had very high rates of maternal complications stemming from significant socioeconomic disadvantage. The substantial maternal and infant complications seen in these young moms could potentially be avoided with improved contraception rates and reproductive planning.

With the increase in youth-onset type 2 diabetes (1), the number of pregnancies in women complicated by preexisting type 2 diabetes is increasing (2). From 2000 to 2010, the prevalence of pregestational diabetes (including type 2 diabetes) increased by 37% (3). According to the most recent report by the Centers for Disease Control and Prevention (CDC) in 2016, the national prevalence of

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This article is featured in a podcast available at diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

**Members of the TODAY Study Group Writing Committee are listed in the APPENDIX. A complete list of the TODAY Study Group members can be found in the supplementary material online.*

This article is part of a special article collection available at diabetesjournals.org/journals/collection/268/Serious-Later-Risks-Associated.

See accompanying articles, pp. 1046, 1049, 1056, 1065, and 1073.

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ORIGINAL RESEARCH
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Determinants of Diabetic Peripheral Neuropathy and Their Clinical Significance: A Retrospective Cohort Study

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Background: In this study, we investigated the epidemiological characteristics and predictors of diabetic peripheral neuropathy (DPN) in adult patients with type 2 diabetes mellitus (DM).

Methods: The study was designed as a retrospective cohort trial at the First Affiliated Hospital of Wenzhou Medical University. From January 2017 to December 2020, a total of 1,262 patients with DM were enrolled to assess the risk factors for DPN. The patients were divided into two groups (DPN group and non-DPN group). The Mann–Whitney *U* test or *t*-test, receiver operating characteristic (ROC) analyses, univariate chi-square analyses, and multiple logistic regression analyses were used to analyze the adjusted predictors of DPN.

Results: The overall prevalence of DPN in DM patients was 72.7% (n = 793/1,091). Multivariate analysis revealed that age > 66 years (odds ratio [OR], 2.647; 95% confidence interval [CI] 1.469–4.770; $p = 0.002$), history of hypertension (OR, 1.829; 95% CI 1.146–2.920; $p = 0.011$), neutrophil (NE) levels exceeding 4.0×10^9/L (OR 0.256; 95% CI 0.162–0.405; $p = 0.001$), lymphocyte (LY) levels over 3.0×10^9/L (OR 7.173; 95% CI 4.258–12.086; $p = 0.000$), HbA1c > 7.7% (OR 3.151; 95% CI 1.959–5.068; $p = 0.000$), and FT3 > 4.4 pmol/L (OR 0.417; 95% CI 0.263–0.662; $p = 0.000$) were six significant predictive factors for the prevalence of DPN.

Conclusions: High levels of LY, HbA1c, history of hypertension, and > 66 years of age increase the risk of DPN in adult patients with DM, while high levels of NE and FT3 were protective factors of DPN. Thus, the prediction of DPN can significantly be improved by identifying older patients over the age of 66 and history of hypertension, as well as establishing the biochemical cutoff values of NE, LY, HbA1c, and FT3.

Keywords: type-2 diabetes mellitus, diabetic peripheral neuropathy, determinants, clinical significance, prevalence, risk factor

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Continuous Glucose Monitoring–Guided Insulin Administration in Hospitalized Patients With Diabetes: A Randomized Clinical Trial

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OBJECTIVE

The efficacy and safety of continuous glucose monitoring (CGM) in adjusting inpatient insulin therapy have not been evaluated.

RESEARCH DESIGN AND METHODS

This randomized trial included 185 general medicine and surgery patients with type 1 and type 2 diabetes treated with a basal-bolus insulin regimen. All subjects underwent point-of-care (POC) capillary glucose testing before meals and bedtime. Patients in the standard of care (POC group) wore a blinded Dexcom G6 CGM with insulin dose adjusted based on POC results, while in the CGM group, insulin adjustment was based on daily CGM profile. Primary end points were differences in time in range (TIR; 70–180 mg/dL) and hypoglycemia (<70 mg/dL and <54 mg/dL).

RESULTS

There were no significant differences in TIR (54.51% ± 27.72 vs. 48.64% ± 24.25; *P* = 0.14), mean daily glucose (183.2 ± 40 vs. 186.8 ± 39 mg/dL; *P* = 0.36), or percent of patients with CGM values <70 mg/dL (36% vs. 39%; *P* = 0.68) or <54 mg/dL (14 vs. 24%; *P* = 0.12) between the CGM-guided and POC groups. Among patients with one or more hypoglycemic events, compared with POC, the CGM group experienced a significant reduction in hypoglycemia reoccurrence (1.80 ± 1.54 vs. 2.94 ± 2.76 events/patient; *P* = 0.03), lower percentage of time below range <70 mg/dL (1.89% ± 3.27 vs. 5.47% ± 8.49; *P* = 0.02), and lower incidence rate ratio <70 mg/dL (0.53 [95% CI 0.31–0.92]) and <54 mg/dL (0.37 [95% CI 0.17–0.83]).

CONCLUSIONS

The inpatient use of real-time Dexcom G6 CGM is safe and effective in guiding insulin therapy, resulting in a similar improvement in glycemic control and a significant reduction of recurrent hypoglycemic events compared with POC-guided insulin adjustment.

Diabetes is reported in 20–34% of hospitalized adult patients in general medicine and surgery units (1,2). Dysglycemia, defined as hyperglycemia, hypoglycemia, and increased glucose variability in hospitalized patients with diabetes, has been associated with adverse outcomes, such as prolonged length of stay and increased risk of

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Research Article

A Randomized, Controlled Trial Exploring Collaborative Nursing Intervention on Self-Care Ability and Blood Glucose of Patients with Type 2 Diabetes Mellitus

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Objective. For determining the impacts of collaborative nursing intervention (CNI) on self-care ability and blood glucose (BG) of patients with type 2 diabetes mellitus (T2DM). *Methods*. The study enrolled 72 T2DM patients, who are referred to our hospital between April 2017 and September 2019. Of them, 35 cases given routine nursing were set as the control group (CG) and 37 cases given CNI were set as the research group (RG). The Exercise of Self-Care Agency (ESCA) scale scores and the levels of fasting plasma glucose (FPG) as well as glycosylated hemoglobin (HbAlc) were observed pre- and postintervention. The scores of SAS and HAMD and Morisky pre- and postnursing intervention as well as postnursing SF-36 scores and patients' satisfaction toward the nursing content were recorded. *Results*. After intervention, RG presented notably lower serum HbAlc and FPG levels than CG ($P < 0.05$); RG presented evidently lower SAS and HAMD scores while distinctly higher Morisky, SF-36, and ESCA scores than CG ($P < 0.05$); the nursing satisfaction in RG and CG was 97.30% and 51.43%, respectively. *Conclusions*. In view of the fact that CNI can decrease HbAlc and FPG levels in patients with T2DM and enhance their self-care ability, it is worth popularizing in the clinic.

1. Introduction

Diabetes mellitus (DM) is a ubiquitous metabolic dysregulation with a terribly high incidence across the globe [1]. It is a set of metabolic diseases featured with hyperglycemia due to insulin secretion deficiency or insulin action or the two. Chronic hyperglycemia of diabetes is bound up with long-run injury, dysfunction, and organ failure, especially the nerves, kidneys, eyes, and heart as well as blood vessels [2]. DM is currently the illness with the highest incidence worldwide, and society advancement and improvement of people's living standards are driving the increasing incidence of DM [3]. According to research statistics, the proportion of diabetes worldwide reached 25.6% in 2015 [4]. DM can predispose people to complications like nervous system diseases and kidney diseases. Once the disease deteriorates because of the absence of timely therapy, it will lead to malignant tumours directly. DM, defined by elevated blood glucose (BG) markers, is a primary risk factor for cardiovascular illnesses, which bears the major responsibility for death in diabetic patients [5]. The treatment of diabetes is still a challenge. Clinically, efforts have been made to find a way to effectively prevent and treat diabetes, but no significant breakthrough has been made so far [6]. Hence, early screening and diagnosis are of utmost importance.

Patients with DM need long-time medication, and some also require insulin injections to control their BG. And during treatment, patients' compliance and awareness of the disease directly affect their BG status and mental health. Today, the major obstacle that stands in the way of nursing work is how to make patients face diabetes actively and rationally and receive professional and systematic treatment [7–9]. The concept of collaborative nursing intervention (CNI) mode is to give full play to patients' self-care ability

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RESEARCH Open Access

A randomized trial of comparing video telecare education vs. in-person education on dietary regimen compliance in patients with type 2 diabetes mellitus: a support for clinical telehealth Providers

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Abstract

Background: Compliance to dietary recommendations by patients is the most difficult part of diabetes management. The nature of any educational method is to increase patients' awareness. But the question is, what is the effect of each method and for this purpose a comparative method should be considered. Therefore, this study was conducted to compare the effects of in-person education versus video tele-education on dietary regimen compliance in patients with T2DM.

Methods: In this trial, 378 patients with type 2 diabetes mellitus (T2DM) were random allocated into video tele-education, in-person education and control groups. The patients' weight and biochemical parameters were measured before educational programs and three-month later.

Results: The mean changes of patients' weight, glycemic parameters, and Lipid profiles decreased more in the two educational groups than the control group in a three-month period. There were no significant differences in the all study variables between the in-person and video education groups in post interventions except Total Cholesterol (TC). The pre- and post-intervention changes in the weight, TC, hemoglobin A1c, Triglyceride, and Very Low-density Lipoprotein Cholesterol were significant in both in-person group and video group. None of the educational programs had a significant impact on the Fasting blood sugar, Low-Density Lipoprotein Cholesterol, and High-Density Lipoprotein Cholesterol.

Discussion: Video tele-education was just as effective as in-person educational method on dietary regimen compliance among patients with T2DM in a three-month period. Therefore, it is recommended to use video tele-education in combination with or as an alternative to the in-person education method. This study provides support for diabetes educator.

Trial registration: This investigation was registered in the Iranian Registry of Clinical Trials Center (IRCT20150302021307N4).

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ORIGINAL ARTICLE

Clinical Trials Study

Effectiveness and safety of human umbilical cord-mesenchymal stem cells for treating type 2 diabetes mellitus

Xiao-Fen Lian, Dong-Hui Lu, Hong-Li Liu, Yan-Jing Liu, Xiu-Qun Han, Yang Yang, Yuan Lin, Qing-Xiang Zeng, Zheng-Jie Huang, Feng Xie, Cai-Hao Huang, Hong-Mei Wu, Ai-Mei Long, Ling-Ping Deng, Fan Zhang

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Abstract

BACKGROUND
Progressive pancreatic β-cell dysfunction is a fundamental part of the pathology of type 2 diabetes mellitus (T2DM). Cellular therapies offer novel opportunities for the treatment of T2DM to improve the function of islet β-cells.

AIM
To evaluate the effectiveness and safety of human umbilical cord-mesenchymal stem cell (hUC-MSC) infusion in T2DM treatment.

METHODS
Sixteen patients were enrolled and received 1 × 10^6 cells/kg per week for 3 wk as intravenous hUC-MSC infusion. The effectiveness was evaluated by assessing fasting blood glucose, C-peptide, normal glycosylated hemoglobin A1c (HbA1c), insulin resistance index (homeostatic model assessment for insulin resistance), and islet β-cell function (homeostasis model assessment of β-cell function). The dosage of hypoglycemic agents and safety were evaluated by monitoring the occurrence of any adverse events (AEs).

RESULTS

During the entire intervention period, the fasting plasma glucose level was significantly reduced [baseline: 9.3400 (8.3575, 11.7725), day 14 ± 3: 6.5200 (5.2200, 8.6900); $P < 0.01$]. The HbA1c level was significantly reduced on day 84 ± 3 [baseline: 7.8000 (7.5250, 8.6750), day 84 ± 3: 7.150 (6.600, 7.925); $P < 0.01$]. The patients' islet β-cell function was significantly improved on day 28 ± 3 of intervention [baseline: 29.90 (16.43, 37.40), day 28 ± 3: 40.97 (19.27, 56.36); $P < 0.01$]. The dosage of hypoglycemic agents was reduced in all patients, of whom 6 (50%) had a decrement of more than 50% and 1 (6.25%) discontinued the hypoglycemic agents. Four patients had transient fever, which occurred within 24 h after the second or third infusion. One patient (2.08%) had asymptomatic nocturnal hypoglycemia after infusion on day 28 ± 3. No liver damage or other side effects were reported.

CONCLUSION
The results of this study suggest that hUC-MSC infusion can improve glycemia, restore islet β-cell function, and reduce the dosage of hypoglycemic agents without serious AEs. Thus, hUC-MSC infusion may be a novel option for the treatment of T2DM.

Key Words: Type 2 diabetes; Human umbilical cord mesenchymal stem cells; Blood glucose; Homeostasis model assessment of β-cell function; Hypoglycemic agents

Core Tip: Our article focused on the effectiveness and safety of human umbilical cord mesenchymal stem cell (hUC-MSC) infusion for treating type 2 diabetes. The results suggest that hUC-MSC infusion can improve glycemia, restore islet βcell function, and reduce the dosage of hypoglycemic agents without serious adverse events.

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INTRODUCTION

Diabetes has been a major public health problem worldwide in recent decades. Data from the International Diabetes Federation shows that the prevalence of diabetes among adults is 463 million globally. The estimated prevalence of diabetes and prediabetes among adults in China is 10.9% and 35.7% respectively[1], of which type 2 diabetes mellitus (T2DM) accounts for more than 90% of cases. In China, only 5.6% of T2DM patients achieved glycemic control in 2017[2].

T2DM is regarded as a chronic, progressive disease that arises from an impairment in the insulin-sensing mechanisms and culminates in insulin resistance (IR). Initially, the IR is compensated by increased insulin production; however, as the T2DM progresses over time, the general pancreatic dysfunction leads to increasingly lower insulin production. As glucose continues to accumulate in the bloodstream, chronic hyperglycemia promotes a chronic vicious cycle of metabolic decline[3]. In the first 10 years of T2DM, the β-cell function reduces by ~10%, but this is followed by a period of much more rapid decrease, of an additional ~10% every 2 years, until it eventually results in insulin-dependent diabetes[4].

Current treatments for diabetes include diet control, physical exercise, oral antidiabetic agents, and insulin therapy. Although novel medications and diet therapies continue to be developed, none has provided full protection against deterioration of β-cell function[5,6]. Islet/pancreas transplantation is an efficient way to restore islet β-cell function, but its clinical application is greatly restricted by the limited resource of donor tissues or organs, the immune rejection response, and the high cost and side effects of immunosuppressive drugs[7]. Therefore, the need for an effective and safe strategy to restore β-cell function in T2DM patients remains unmet.

In recent years, mesenchymal stem cell (MSC) therapy for diabetic patients has been extensively studied[8-10] as a novel therapeutic option for diabetes. MSCs are a population of multipotent stem cells from the mesoderm. Human umbilical cord-MSCs (hUC-MSCs) have been an important resource in clinical applications with many advantages including convenient material obtainability, less ethical controversy, great differentiation potential, robust multiplication capacity, low immunogenicity, and

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ARTICLE

Genetic risk of type 2 diabetes modifies the effects of a lifestyle intervention aimed at the prevention of gestational and postpartum diabetes

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Abstract

Aims/hypothesis The aim of this study was to assess the interaction between genetic risk and lifestyle intervention on the occurrence of gestational diabetes mellitus (GDM) and postpartum diabetes.

Methods The RADIEL study is an RCT aimed at prevention of GDM and postpartum diabetes through lifestyle intervention. Participants with a BMI ≥30 kg/m^2 and/or prior GDM were allocated to intervention and control groups before pregnancy or in early pregnancy. The study visits took place every 3 months before pregnancy, once in each trimester, and at 6 weeks and 6 and 12 months postpartum. We calculated a polygenic risk score (PRS) based on 50 risk variants for type 2 diabetes.

Results Altogether, 516 participants provided genetic and GDM data. The PRS was associated with higher glycaemic levels (fasting glucose and/or HbA_{1c}) and a lower insulin secretion index in the second and third trimesters and at 12 months postpartum, as well as with a higher occurrence of GDM and glycaemic abnormalities at 12 months postpartum ($n = 356$). There was an interaction between the PRS and lifestyle intervention (p=0.016 during pregnancy and p=0.024 postpartum) when analysing participants who did not have GDM at the first study visit during pregnancy (n = 386). When analysing women in tertiles according to the PRS, the intervention was effective in reducing the age-adjusted occurrence of GDM only among those with the highest genetic risk (OR 0.37; 95% CI 0.17, 0.82). The risk of glycaemic abnormalities at 12 months postpartum was reduced in the same group after adjusting additionally for BMI, parity, smoking and education (OR 0.35; 95% CI 0.13, 0.97).

Conclusions/interpretation Genetic predisposition to diabetes modifies the response to a lifestyle intervention aimed at prevention of GDM and postpartum diabetes. This suggests that lifestyle intervention may benefit from being tailored according to genetic risk.

Clinical trial registration ClinicalTrials.gov identifier: NCT01698385

Hannele Laivuori and Saila B. Koivusalo contributed equally to this study.

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Stem Cell Research & Therapy

RESEARCH Open Access

Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial

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Abstract

Background: To determine the efficacy and safety of umbilical cord-derived mesenchymal stem cells (UC-MSCs) in Chinese adults with type 2 diabetes mellitus (T2DM).

Methods: In this single-center, double-blinded, randomized, placebo-controlled phase II trial, 91 patients were randomly assigned to receive intravenous infusion of UC-MSCs ($n = 45$) or placebo ($n = 46$) three times with 4-week intervals and followed up for 48 weeks from October 2015 to December 2018. The primary endpoint was the percentage of patients with glycated hemoglobin (HbA1c) levels of < 7.0% and daily insulin reduction of ≥ 50% at 48 weeks. Additional endpoints were changes of metabolic control, islet β-cell function, insulin resistance, and safety.

Results: At 48 weeks, 20% of the patients in the UC-MSCs group and 4.55% in the placebo group reached the primary endpoint ($p < 0.05$, 95% confidence interval (CI) 2.25–28.66%). The percentage of insulin reduction of the UC-MSCs group was significantly higher than that of the placebo group (27.78% versus 15.62%, $p < 0.05$). The levels of HbA1c decreased 1.31% (9.02 ± 1.27% to 7.52 ± 1.07%, $p < 0.01$) in the UC-MSCs group, and only 0.63% in the placebo group (8.89 ± 1.11% to 8.19 ± 1.02%, $p > 0.05$; $p = 0.0081$ between both groups). The glucose infusion rate (GIR) increased significantly in the UC-MSCs group (from 3.12 to 4.76 mg/min/kg, $p < 0.01$), whereas no significant change was observed in the placebo group (from 3.26 to 3.60 mg/min/kg, $p > 0.05$; $p < 0.01$ between both groups). There was no improvement in islet β-cell function in both groups. No major UC-MSCs transplantation-related adverse events occurred.

Conclusions: UC-MSCs transplantation could be a potential therapeutic approach for Chinese adults with T2DM.

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Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

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ABSTRACT

BACKGROUND

Treatment of gestational diabetes improves maternal and infant health, although diagnostic criteria remain unclear.

METHODS

We randomly assigned women at 24 to 32 weeks' gestation in a 1:1 ratio to be evaluated for gestational diabetes with the use of lower or higher glycemic criteria for diagnosis. The lower glycemic criterion was a fasting plasma glucose level of at least 92 mg per deciliter (≥5.1 mmol per liter), a 1-hour level of at least 180 mg per deciliter (≥10.0 mmol per liter), or a 2-hour level of at least 153 mg per deciliter (≥8.5 mmol per liter). The higher glycemic criterion was a fasting plasma glucose level of at least 99 mg per deciliter (≥5.5 mmol per liter) or a 2-hour level of at least 162 mg per deciliter (≥9.0 mmol per liter). The primary outcome was the birth of an infant who was large for gestational age (defined as a birth weight above the 90th percentile according to Fenton–World Health Organization standards). Secondary outcomes were maternal and infant health.

RESULTS

A total of 4061 women underwent randomization. Gestational diabetes was diagnosed in 310 of 2022 women (15.3%) in the lower-glycemic-criteria group and in 124 of 2039 women (6.1%) in the higher-glycemic-criteria group. Among 2019 infants born to women in the lower-glycemic-criteria group, 178 (8.8%) were large for gestational age, and among 2031 infants born to women in the higher-glycemic-criteria group, 181 (8.9%) were large for gestational age (adjusted relative risk, 0.98; 95% confidence interval, 0.80 to 1.19; P=0.82). Induction of labor, use of health services, use of pharmacologic agents, and neonatal hypoglycemia were more common in the lower-glycemic-criteria group than in the higher-glycemic-criteria group. The results for the other secondary outcomes were similar in the two trial groups, and there were no substantial between-group differences in adverse events. Among the women in both groups who had glucose test results that fell between the lower and higher glycemic criteria, those who were treated for gestational diabetes (195 women), as compared with those who were not (178 women), had maternal and infant health benefits, including fewer large-for-gestational-age infants.

CONCLUSIONS

The use of lower glycemic criteria for the diagnosis of gestational diabetes did not result in a lower risk of a large-for-gestational-age infant than the use of higher glycemic criteria. (Funded by the Health Research Council of New Zealand and others; GEMS Australian New Zealand Clinical Trials Registry number, ACTRN12615000290594.)

From the Liggins Institute (C.A.C., D.S., C.J.M.), the Department of Obstetrics and Gynaecology (L.M.E.M.), and the School of Population Health (R.E.), University of Auckland, Auckland, New Zealand; and Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney (T.T.). Dr. Crowther can be contacted at c.crowther@auckland.ac.nz or at the Liggins Institute, University of Auckland, Bldg. 503, Level 2, 85 Park Rd., Auckland 1142, New Zealand.

*The members of the GEMS Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2204091

CME at NEJM.org

ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΧΑΡΑΛΑΜΠΟΣ ΜΗΛΙΩΝΗΣ

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

Persistence of Risk for Type 2 Diabetes After Gestational Diabetes Mellitus

Mary V. Diaz-Santana,[1] Katie M. O'Brien,[2] Yong-Moon Mark Park,[2,3] Dale P. Sandler,[2] and Clarice R. Weinberg[1]

Diabetes Care 2022;45:864–870 | https://doi.org/10.2337/dc21-1430

OBJECTIVE

Gestational diabetes mellitus complicates ~6% of pregnancies and strongly predicts subsequent type 2 diabetes. It has not been fully elucidated how risk depends on the number of affected pregnancies or how long the excess risk persists.

RESEARCH DESIGN AND METHODS

We assessed reproductive histories in relation to risk of type 2 diabetes using a nationwide cohort of 50,884 women. Among participants who initially did not have diabetes, 3,370 were diagnosed with diabetes during 10 years of follow-up. We used Cox proportional hazards models that allowed risk to depend on age, cumulative number of pregnancies with gestational diabetes mellitus, and time since the most recent affected pregnancy, adjusting for BMI, educational level, and race/ethnicity.

RESULTS

History of one or more pregnancies with gestational diabetes mellitus predicted elevated age-specific risk of type 2 diabetes, with a hazard ratio of 3.87 (95% CI 2.60–5.75) 6–15 years after an affected pregnancy. Risk increased steeply with multiple affected pregnancies. The age-specific associations attenuated over time after an affected pregnancy, with an estimated 24% reduction of the hazard ratio per decade. Risk remained elevated, however, for >35 years.

CONCLUSIONS

Gestational diabetes mellitus predicted markedly increased rates of type 2 diabetes. Relative risk increased substantially with each additional affected pregnancy. The estimated hazard ratio declined with time after a pregnancy with gestational diabetes mellitus but remained elevated for >35 years. Women recalling a history of gestational diabetes mellitus should be screened regularly for type 2 diabetes, even late in life.

Gestational diabetes mellitus (GDM) is defined as hyperglycemia with onset during the second or third trimester of pregnancy in women without a previous diagnosis of non-GDM (1). The estimated per-pregnancy rates of GDM range from 4.6 to 9.2%, depending on the diagnosis strategy and data source (2).

GDM is believed to typically be a result of pancreatic β-cell dysfunction in women with preexisting insulin resistance (3). These deficiencies can progress, which increases a woman's risk of developing type 2 diabetes after pregnancy (4).

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This article is featured in a podcast available at diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

JAMA Network Open

Original Investigation | Cardiology

Association of Concomitant Gestational Hypertensive Disorders and Gestational Diabetes With Cardiovascular Disease

Justin B. Echouffo Tcheugui, MD, PhD; Jun Guan, MSc; Longdi Fu, MSc; Ravi Retnakaran, MD, MSc; Baiju R. Shah, MD, PhD

Abstract

IMPORTANCE Accruing evidence suggests that gestational hypertensive disorders (GHTD) and gestational diabetes (GD) are each associated with an increased risk of cardiovascular disease (CVD). However, the extent to which the co-occurrence of GHTD and GD is associated with the risk of CVD remains largely unknown.

OBJECTIVE To estimate the individual and joint associations of GHTD and GD with incident CVD.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used the Ministry of Health and Long-Term Care of Ontario (Canada) health care administrative databases. All women in Ontario with a GHTD and/or GD diagnosis, and a live-birth singleton delivery between July 1, 2007, and March 31, 2018, were considered for inclusion. Women with pregravid diabetes, hypertension, or cardiovascular disease were excluded. Statistical analysis was performed from November 2021 to September 2022.

EXPOSURES GD and/or GHTD, defined using diagnosis coding.

MAIN OUTCOMES AND MEASURES Individual and joint associations of GHTD and GD with incident CVD (including a composite of myocardial infarction, acute coronary syndrome, stroke, coronary artery bypass grafting, percutaneous coronary intervention, or carotid endarterectomy), estimated using Cox regression models, adjusting for relevant cardiometabolic risk factors. The follow-up extended from the index pregnancy until March 31, 2020.

RESULTS Among 886 295 eligible women (mean [SD] age, 30 [5.6] years; 43 861 [4.9%] with isolated GHTD, 54 061 [6.1%] with isolated GD, and 4975 [0.6%] with GHTD and GD), there were 1999 CVD events over 12 years of follow-up. In the early postpartum phase (first 5 years post partum), there was no association of co-occurrence of GTHD and GD (adjusted hazard ratio [aHR], 1.42, 95% CI, 0.78-2.58) or GD alone (aHR, 0.80; 95% CI, 0.60-1.06) with CVD; there was an association between isolated GTHD and incident CVD compared with no GTHD and no GD (aHR, 1.90; 95% CI, 1.51-2.35). In the late postpartum period (after the initial 5 years post partum), compared with no GD and no GHTD, isolated GHTD (aHR, 1.41, 95% CI, 1.12-1.76) and co-occurrence of GHTD and GD (aHR, 2.43, 95% CI, 1.60-3.67) were each associated with a higher risk of incident CVD. There was no association between isolated GD and incident CVD.

CONCLUSIONS AND RELEVANCE In this cohort study, GHTD was associated with a high risk of CVD post partum, and the co-occurrence of GD and GHTD was associated with a much greater postpartum CVD risk. These findings suggest that CVD preventive care is particularly needed in the aftermath of combined GD and GHTD.

JAMA Network Open. 2022;5(11):e2243618. doi:10.1001/jamanetworkopen.2022.43618

Key Points

Question What is the association of the concomitant occurrence of gestational diabetes (GD) and gestational hypertensive disorder (GHTD) with the incidence of cardiovascular diseases (CVD)?

Findings In a cohort study of 886 295 women, compared with no GD and no GHTD, the co-occurrence of GHTD and GD was associated with a 2.4-fold higher risk of incident CVD. A risk that is significantly higher than that of the CVD risk associated with each of these conditions in isolation.

Meaning These findings suggest that the co-occurrence of GD and GHTD is associated with a high postpartum CVD risk.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

ΔΙΑΤΡΟΦΗ - ΑΣΚΗΣΗ

ΔΗΜΗΤΡΙΟΣ ΚΟΥΡΕΤΑΣ

ΚΑΘΗΓΗΤΗΣ
ΦΥΣΙΟΛΟΓΙΑΣ ΖΩΙΚΩΝ ΟΡΓΑΝΙΣΜΩΝ – ΤΟΞΙΚΟΛΟΓΙΑΣ
ΣΤΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΕΡΓΑΣΤΗΡΙΟ Φυσιολογίας Ζωϊκών Οργανισμών
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ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

Σύγχρονες διατροφικές τάσεις

Δημήτριος Κουρέτας, PhD
Καθηγητής Φυσιολογίας Ζωικών Οργανισμών & Τοξικολογίας
Ιδρυτής spin-off FoodOxys
Ιδρυτής spin-out Olea Fortius

OLEA FORTIUS
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Εξατομικευμένη διατροφή

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Viewpoint | Published: 30 November 2022

Approaches to addressing the rise in obesity levels

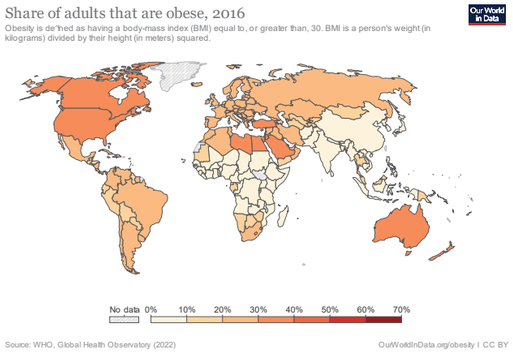
Caroline M. Apovian, Xi-Rong Guo, John A. Hawley, Shahzeer Karmali, Ruth J. F. Loos & Wilma E. Waterlander

Nature Reviews Endocrinology (2022) | Cite this article
606 Accesses | 24 Altmetric | Metrics

Abstract

Levels of obesity and overweight are increasing globally, with affected individuals often experiencing health issues and reduced quality of life. The pathogenesis of obesity is complex and multifactorial, and effective solutions have been elusive. In this Viewpoint, experts in the fields of medical therapy, adipocyte biology, exercise and muscle, bariatric surgery, genetics, and public health give their perspectives on current and future progress in addressing the rising prevalence of obesity.

- Μεγάλη συζήτηση στο χώρο της ενδοκρινολογίας για τις προσεγγίσεις στην αντιμετώπιση της παχυσαρκίας
- Ιδιαίτερη έμφαση στον τομέα της **εξατομικευμένης διατροφής** και της **παρακολούθησης**



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nature biomedical engineering
ARTICLES
https://doi.org/10.1038/s41551-022-00916-z
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A wearable electrochemical biosensor for the monitoring of metabolites and nutrients

Minqiang Wang[1,7], Yiran Yang[1,7], Jihong Min[1,7], Yu Song[1], Jiaobing Tu[1], Daniel Mukasa[2], Cui Ye[1], Changhao Xu[1], Nicole Heflin[3], Jeannine S. McCune[4], Tzung K. Hsiai[5], Zhaoping Li[6] and Wei Gao[1]✉

Wearable non-invasive biosensors for the continuous monitoring of metabolites in sweat can detect a few analytes at sufficiently high concentrations, typically during vigorous exercise so as to generate sufficient quantity of the biofluid. Here we report the design and performance of a wearable electrochemical biosensor for the continuous analysis, in sweat during physical exercise and at rest, of trace levels of multiple metabolites and nutrients, including all essential amino acids and vitamins. The biosensor consists of graphene electrodes that can be repeatedly regenerated in situ, functionalized with metabolite-specific antibody-like molecularly imprinted polymers and redox-active reporter nanoparticles, and integrated with modules for iontophoresis-based sweat induction, microfluidic sweat sampling, signal processing and calibration, and wireless communication. In volunteers, the biosensor enabled the real-time monitoring of the intake of amino acids and their levels during physical exercise, as well as the assessment of the risk of metabolic syndrome (by correlating amino acid levels in serum and sweat). The monitoring of metabolites for the early identification of abnormal health conditions could facilitate applications in precision nutrition.

Εξατομικευμένη διατροφή

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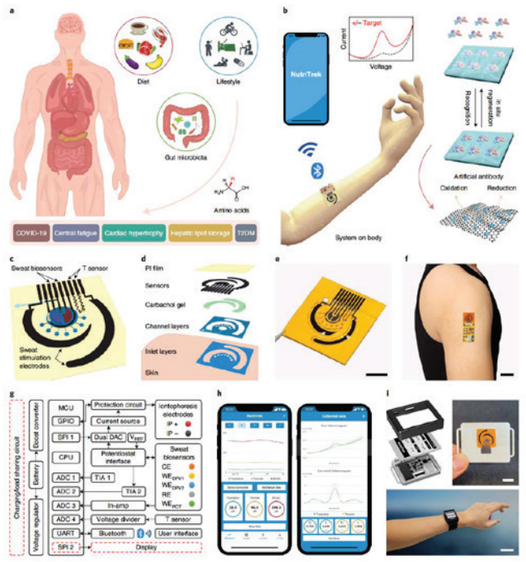

- Παρακολούθηση **μεταβολιτών** για την έγκαιρη αναγνώριση μη φυσιολογικών τιμών βιοδεικτών
- Πιθανή αποτροπή πρόκλησης σοβαρών ασθενειών
- Η φορητή τεχνολογία θα μπορούσε να παίξει καθοριστικό ρόλο στην εξατομικευμένη διατροφή μέσω της συνεχούς παρακολούθησης των βιοδεικτών
- Δυνατότητα εξατομικευμένης διατροφικής παρέμβασης με βάση τις ανάγκες του οργανισμού σε **πραγματικό χρόνο** (π.χ. άθληση, ασθένεια, διάβασμα)

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POLICY FORUM | FOOD

Research and policy for the food-delivery revolution

Implications for nutrition, environment, and work may be considerable

EVA-MARIE MEEMKEN, MARC F. BELLEMARE, THOMAS REARDON, AND CAROLINA M. VARGAS Authors Info & Affiliations

SCIENCE • 18 Aug 2022 • Vol 377, Issue 6608 • pp. 810-813 • DOI: 10.1126/science.abo2182
2,307 CHECK ACCESS

Abstract

Globally, consumers have increasingly been getting the meals they consume delivered by third parties such as Doordash, Grubhub, Wolt, or Uber Eats. This trend is attributable to broader changes in food systems and technological and institutional innovation (such as apps and digital platforms and the increased reliance on third parties for food delivery) and has sharply accelerated as a consequence of the lockdowns resulting from the COVID-19 pandemic (*1*, *2*). Global revenues for the online food delivery sector were about $90 billion in 2018, rose to $294 billion in 2021, and are expected to exceed $466 billion by 2026 (*3*). The consequences and policy implications of this "delivery revolution" remain poorly understood but de-

Τα παγκόσμια έσοδα στον τομέα της διαδικτυακής παράδοσης τροφίμων ήταν:

- 90 δισεκατομμύρια δολάρια το 2018
- 294 δισεκατομμύρια δολάρια το 2021
- 466 δισεκατομμύρια δολάρια έως το 2026 (πρόβλεψη)

Πολύ σημαντικές οι επιπτώσεις για

- ✓ Το **περιβάλλον**
- ✓ Τη **διατροφή**
- ✓ Την **αξιοπρεπή εργασία**

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Analysis | Published: 01 December 2022

Environmental impacts along the value chain from the consumption of ultra-processed foods

Emmanuelle Kesse-Guyot ✉, Benjamin Allès, Joséphine Brunin, Hélène Fouillet, Alison Dussiot, Florine Berthy, Elie Perraud, Serge Hercberg, Chantal Julia, François Mariotti, Mélanie Deschasaux-Tanguy, Bernard Srour, Denis Lairon, Philippe Pointereau, Julia Baudry & Mathilde Touvier

Nature Sustainability (2022) | Cite this article
349 Accesses | 21 Altmetric | Metrics

Abstract

Our recognition of the environmental pressures associated with dietary patterns has grown considerably over the past decade. However, few studies have analysed the impacts associated with the consumption of ultra-processed food (UPF) and which steps in the food chain contribute the most. Here, using a representative sample of French adults (2,121 enrolled in the Third French Individual and National Food Consumption survey), we

- Παραγωγή
- Επεξεργασία
- Αποθήκευση
- Συσκευασία
- Μεταφορά
- Λιανική πώληση

Κατανάλωση έτοιμου φαγητού & υγιεινά γεύματα

nutrients MDPI

Article

Convenience Food Options and Adequacy of Nutrient Intake among School Children during the COVID-19 Pandemic

Nihaal Rahman [1], Kazue Ishitsuka [1,*], Aurélie Piedvache [1], Hisako Tanaka [1], Nobuko Murayama [2] and Naho Morisaki [1]

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[2] Department of Health and Nutrition, Faculty of Human Life Studies, University of Niigata Prefecture, 471 Ebigase, Higashi-ku, Niigata 950-8680, Japan; murayama@unii.ac.jp
* Correspondence: ishitsuka-k@ncchd.go.jp; Tel.: +81-3-3416-0181

Abstract: The COVID-19 pandemic has caused changes in the family food environment, resulting in more families relying on convenience food options. This study aimed to investigate diet quality by convenience food options (namely instant, frozen, and take-out foods) among Japanese school children during the COVID-19 pandemic. We examined the relationship between the frequency of consumption of convenience food options and nutritional status of the school children. The participants (671 children, 10–14 years old) were chosen to form a nationally representative sample of the Japanese population. Using questionnaires completed by the participants' guardians, information was collected on the frequency of instant, frozen, and take-out food consumption. Habitual food and nutrient intake were collected using a validated food frequency questionnaire, completed by the children with help from their guardian(s). "Frequent" consumption was defined as consumption of instant, frozen, and/or take-out foods on more than 5 days per week. Using 19 nutrients and their respective dietary reference intake (DRI) values, an index was created to label each child's nutrient intake as "Adequate", "Inadequate", "Excess", or "Deficient." Compared to children with non-frequent consumption, school children with frequent instant food consumption had significantly higher rates of inadequate nutrient intake (risk ratio (RR) = 3.0 [95% CI: 1.6–5.6]) and excess nutrient intake (RR = 2.3 [95% CI: 1.3–4.2]), while school children with frequent take-out

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Citation: Rahman, N.; Ishitsuka, K.; Piedvache, A.; Tanaka, H.; Murayama, N.; Morisaki, N. Convenience Food Options and Adequacy of Nutrient Intake among School Children during the COVID-19 Pandemic. *Nutrients* **2022**.

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Πανδημία COVID-19

↓

✓ Αυξημένη κατανάλωση έτοιμων τροφίμων

✓ Υψηλότερα ποσοστά κατανάλωσης φαγητών απ' έξω

↓

Συσχέτιση με χαμηλότερη πρόσληψη υγιεινών τροφίμων, όπως φρούτα, λαχανικά

↓

Χαμηλότερη πρόσληψη βασικών θρεπτικών συστατικών

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Κατανάλωση έτοιμου φαγητού & υγιεινά γεύματα

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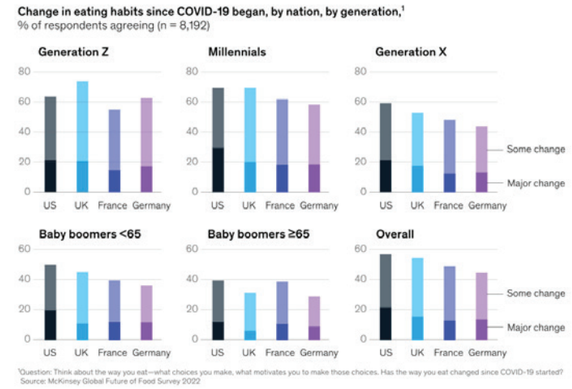
- Αλλαγές στα διατροφικά πρότυπα και τις διατροφικές συνήθειες των καταναλωτών
- Μεταβολές στις διατροφικές συνήθειες όλων των ηλικιακών ομάδων, αλλά ιδίως στους νεότερους καταναλωτές



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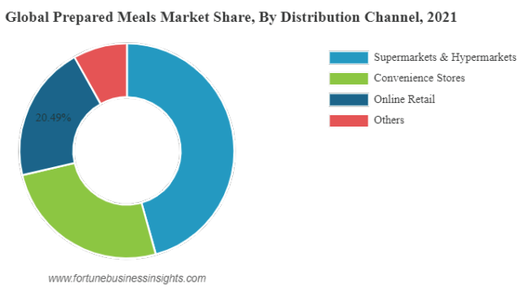
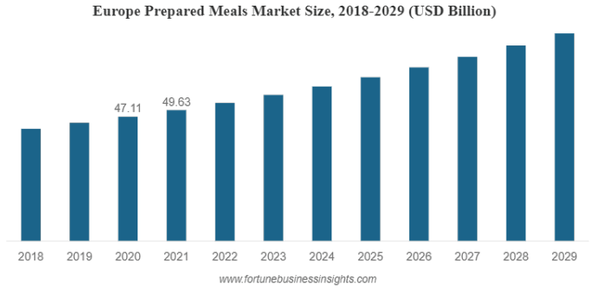
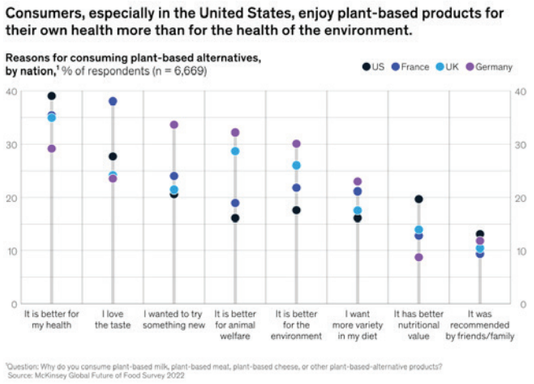
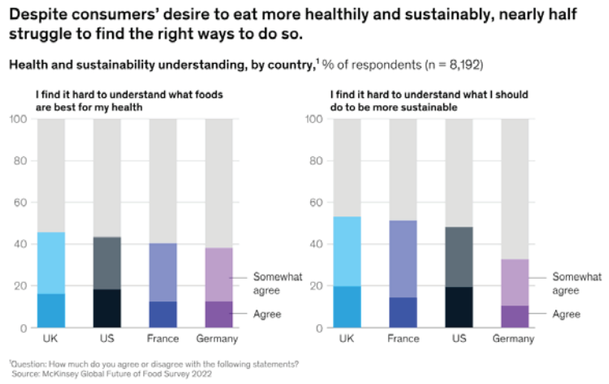




- Θετική γνώμη καταναλωτών για πρόσληψη φυτικής προέλευσης προϊόντων με σκοπό την προαγωγή της ανθρώπινης υγείας
- Έλλιπής γνώση στο καταναλωτικό κοινό για τους τρόπους υιοθέτησης ενός υγιεινού και βιώσιμου διατροφικού πλάνου





Φυτοφαγική διατροφή

- ❑ **Vegetarian**

  Περιλαμβάνει όλες τις φυτικές τροφές, καθώς και αυγά και γαλακτοκομικά

- ❑ **Vegan**

  Αποκλείει το κρέας, τα γαλακτοκομικά, τα αυγά και συχνά το μέλι

- ❑ **Whole-foods, plant-based (WFPB)**

  Vegan διατροφή με χαμηλή περιεκτικότητα σε λιπαρά

- ❑ **Pescatarian**

  Χορτοφαγική διατροφή που περιλαμβάνει θαλασσινά

Εργαλείο για γιατρούς και ασθενείς για την αντιμετώπιση χρόνιων ασθενειών σε συνδυασμό με φαρμακευτική αγωγή

Φυτοφαγική διατροφή & υγεία

Good for the planet and good for our health: the evidence for whole-food plant-based diets

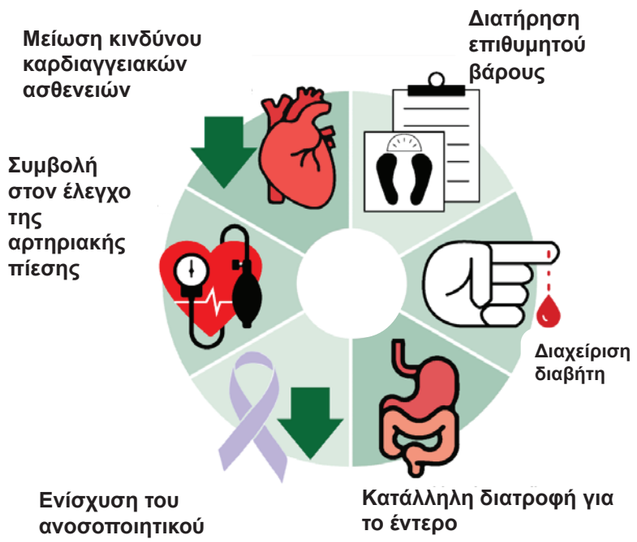
Alison Pye,[1] Kristin Bash,[2] Adam Joiner[3] and Jane Beenstock[4]

Published online by Cambridge University Press: **14 March 2022**

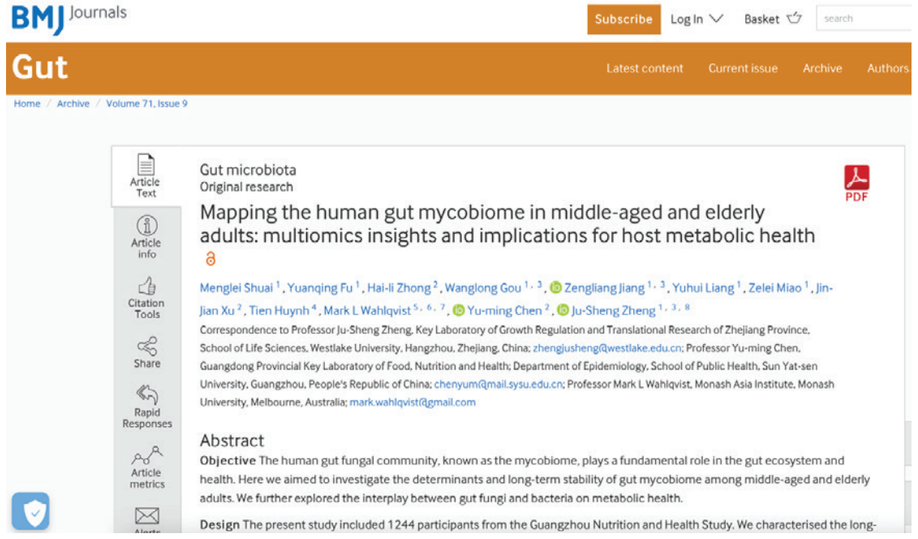
Abstract

There is growing interest in the health and environmental benefits of whole-food plant-based (WFPB) diets. The current global food system is harmful to our planet and is a key driver of climate change, pollution and biodiversity loss. A transition to WFPB diets will mitigate against these impacts and potentially reduce agriculture greenhouse gas emissions by up to 80%. Emerging evidence suggests that such diets also have significant physical and mental health benefits and can be useful in preventing and treating a range of conditions. Psychiatrists therefore have an important role to play in promoting WFPB diets among patients.

American Association of Clinical Endocrinologists και *American College of Endocrinology* συνιστούν την υιοθέτηση φυτοφαγικής δίαιτας για τα άτομα με διαβήτη τύπου 2, καθώς μπορούν να βελτιώσουν τον γλυκαιμικό έλεγχο και να μειώσουν τον κίνδυνο επιπλοκών



Προβιοτικά: η τροφή του εντέρου



Προβιοτικά: η τροφή του εντέρου

- Η μυκητιακή κοινότητα του ανθρώπινου εντέρου είναι αναπόσπαστο μέρος του μικροβιώματος με πιθανές συνέπειες για την **υγεία**
- Το μικροβίωμα του εντέρου είναι σχετικά σταθερό, ενώ ρυθμίζεται από την **ηλικία**, τη **διατροφή** και την **υγεία** του ξενιστή
- Το μικροβίωμα αλληλεπιδρά με τη βακτηριακή κοινότητα του εντέρου και σχετίζεται με διάφορες **παθήσεις**
- Τα χαρακτηριστικά του εντερικού μικροβιώματος μπορεί να είναι **θεραπευτικοί στόχοι** για **μεταβολικές ασθένειες**
- Σημαντική η **αλληλεπίδραση** μεταξύ μυκήτων και βακτηρίων του εντέρου στη **μεταβολική υγεία**

Το μικροβίωμα του εντέρου σχετίζεται στενά με τη μεταβολική υγεία του ξενιστή μέσω της ρύθμισης των βακτηριακών λειτουργιών και των μεταβολιτών του εντέρου

Σύγχρονοι ρυθμοί ζωής

- Ο **εντερικός φραγμός** προστατεύει το ξενιστή από τα μικρόβια του εντέρου, τα τροφικά αντιγόνα και τις τοξίνες του γαστρεντερικού σωλήνα

Η ακεραιότητα του εντερικού φραγμού επηρεάζεται από:

- Τη **Δυτικού τύπου διατροφή**
- Τα **αντιβιοτικά**
- Το **αλκοόλ**
- Τη διαταραχή των **κιρκάδιων ρυθμών**
- Το **ψυχολογικό στρες**

Η χρόνια διαταραχή του φραγμού του εντέρου μπορεί να οδηγήσει σε:

- Μετατόπιση μικροβιακών συστατικών στο σώμα
- Πρόκληση συστημικής φλεγμονής
- Ανάπτυξη μεταβολικών διαταραχών
- Πρόκληση αυτοάνοσων νοσημάτων

Σύγχρονοι ρυθμοί ζωής

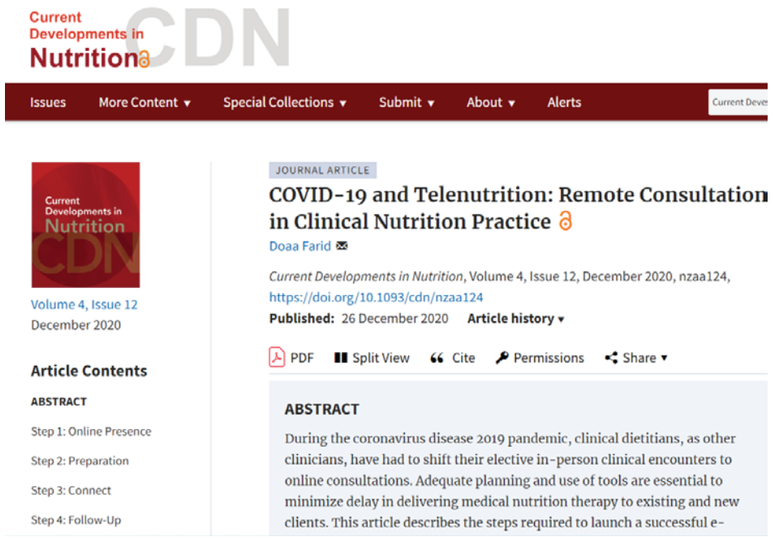
Υψηλή αναγκαιότητα αλλαγής διατροφικών προβλημάτων:

- Έλλειψη σε **μικροθρεπτικά**
- Κακή **διατροφή**
- Κακής ποιότητας **τρόφιμα**

Σημαντική η χάραξη πολυεπίπεδων πολιτικών:

- **Εκπαίδευση**
- **Πρόληψη**
- **Κοινωνική προσαρμογή**
- **Ψηφιακή ενημέρωση**

Διατροφική παρακολούθηση εξ' αποστάσεως



COVID-19

⬇

Διατροφικές διαταραχές, συναισθηματική αδυναμία, φόβος, άγχος, στρες, κατάθλιψη, αύξηση βάρους

⬇

Telenutrition

Διατροφική παρακολούθηση εξ' αποστάσεως

Παροχή διατροφικής συμβουλευτικής:

- ✓ **Διατροφική αξιολόγηση**
- ✓ **Ανάλυση**
- ✓ **Σχέδιο διαχείρισης**
- ✓ **Παρακολούθηση**

Διατροφική παρακολούθηση εξ' αποστάσεως

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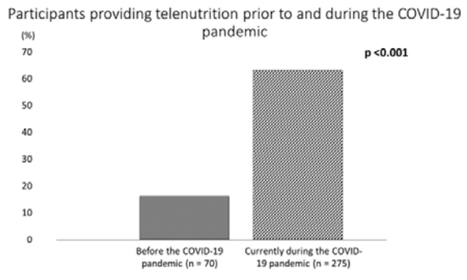
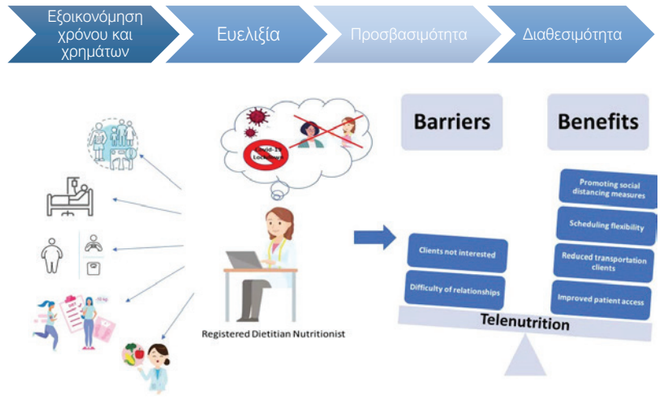
nutrients

Telenutrition: Changes in Professional Practice and in the Nutritional Assessments of Italian Dietitian Nutritionists in the COVID-19 Era

by Patrizia Gnagnarella [1,2], Yvelise Ferro [3,*], Taira Monge [1,4], Ersilia Troiano [1,5], Tiziana Montalcini [6], Arturo Pujia [3] and Elisa Mazza [1,3]





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← PREV ARTICLE MAY 1, 2015 NEXT ARTICLE →

Nutrition Myths and Healthy Dietary Advice in Clinical Practice

PDF Print Comments

LENARD I. LESSER, MD, MSHS, MARY CAROL MAZZA, PhD, AM, AND SEAN C. LUCAN, MD, MPH, MS

Am Fam Physician. 2015;91(9):634-638
Related letter: Foods Containing Saturated Fat: Dietary Limits Are Still Essential
Author disclosure: No relevant financial affiliations.

Healthy dietary intake is important for the maintenance of general health and wellness, the prevention of chronic illness, the optimization of life expectancy, and the clinical management of virtually all disease states. Dietary myths (i.e., concepts about nutrition that are poorly supported or contradicted by scientific evidence) may stand in the way of healthy dietary intake. Dietary myths exist about micronutrients, macronutrients, non-nutrients, and food energy. Representative myths of each type include that patients

- Τρόφιμα **πλούσια σε λιπαρά** είναι ανθυγιεινά
- Τρόφιμα με **υψηλή περιεκτικότητα σε χοληστερόλη** πρέπει να αποφεύγονται
- Η **μη κατανάλωση υδατανθράκων** είναι το κλειδί για απώλεια βάρους
- Το **πρωινό** είναι το πιο σημαντικό γεύμα
- Μικρά γεύματα ανά **τακτά χρονικά διαστήματα**
- Η κατανάλωση τροφής τις **βραδινές ώρες** οδηγεί σε αύξηση βάρους

Διατροφικοί μύθοι

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nutrients

Nutripedia: The Fight against the Fake News in Nutrition during Pregnancy and Early Life

by Elvira Verduci [1,2,*], Sara Vizzuso [1], Armanda Frassinetti [3], Lisa Mariotti [4], Alberico Del Torto [5], Giulia Fiore [2], Annamaria Marconi [6] and Gian Vincenzo Zuccotti [1,7]

Abstract

(1) Background. Early nutrition and lifestyle before and during pregnancy, breastfeeding, infancy, and early childhood can affect the risk of developing common non-communicable diseases during adulthood such as obesity and metabolic syndrome. To support positive long-term outcomes, it is essential to debunk fake news and provide evidence-based nutritional recommendations. "Nutripedia-Informati per Crescere" is a new tool delivering information and education on appropriate nutrition of mothers and babies during pregnancy and the first years of life. (2) Methods. Nutripedia provides the readers with evidence-based scientific contents in an easy-to-access fashion through a website, a social media page and a personalized advice app called "Nutripedia Chatbot". (3) Results. Forty articles were published on Nutripedia website with more than 220,000 total views. Social channel activation via bloggers reached over 9 million parents. 14,698 users downloaded Nutripedia chatbot, through which a total of 1930 questions were directed to experts while over 24,000 responses were provided by the app. (4) Conclusions. The use of different communication tools delivering evidence-based nutritional information such as Nutripedia is increasing and could offer supportive strategies to provide scientific information to large audiences and contribute fighting fake news. Future research could investigate the effectiveness of this important health campaign.

Keywords: pregnancy; early nutrition; fake news; Nutripedia project

Συσσώρευση πληροφοριών από αναξιόπιστα κανάλια πληροφόρησης σχετικά με την ιδανική διατροφή

↓

Εξάπλωση διατροφικών "fake news"

↓

Ανάγκη για σχεδιασμό εργαλείου με στόχο την αποτροπή της παραπληροφόρησης

Διατροφικοί μύθοι

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- Ανάπτυξη της ιστοσελίδας NutriPedia, καθώς και πιλοτικής εφαρμογής για την παροχή καθοδήγησης σε θέματα διατροφής εγκύων και βρεφών
- Αξιοποίηση των τεχνολογικών εργαλείων στη διάψευση ψευδών ειδήσεων και στην απάντηση των συχνότερων ερωτημάτων των γονέων

Χρήση σε μεγαλύτερη κλίμακα θα μπορούσε να συνεισφέρει στην υιοθέτηση σωστών διατροφικών συνηθειών και στην καταπολέμηση λανθασμένων αντιλήψεων γύρω από τη διατροφή, μέσω παροχής έγκυρης πληροφόρησης στο γενικό πληθυσμό

Ευαισθητοποίηση για την υγιεινή διατροφή

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Παράγοντες που επηρεάζουν τις γνώσεις περί διατροφής:

- ✓ Ηλικία
- ✓ Μορφωτικό επίπεδο
- ✓ Οικονομική κατάσταση
- ✓ Περιοχή κατοικίας
- ✓ Κοινωνική και πολιτισμική επιρροή

Ευαισθητοποίηση

↓

Βελτίωση διατροφικών συνηθειών, μεταβολικής υγείας και ψυχολογικής ευημερίας


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nature > european journal of clinical nutrition > articles > article

Article | Published: 13 May 2021

Nutrition and Health (including climate and ecological aspects)

Healthy eating: a privilege for the better-off?

Ricardo Alves, Carla Lopes & Julian Perelman

European Journal of Clinical Nutrition **76**, 134–142 (2022) | Cite this article

323 Accesses | 2 Citations | Metrics

Abstract

Background

Food subsidies for healthier foods and higher taxes for less healthy alternatives have been increasingly used to promote a healthy diet. Yet, some have argued that the fiscal burden on unhealthy products would fall disproportionately on the worse-off, raising equity concerns. This study estimates the association between income and the consumption of key food groups linked to the Mediterranean diet in the adult Portuguese population.

Εταιρικά προγράμματα διατροφής & ευεξίας

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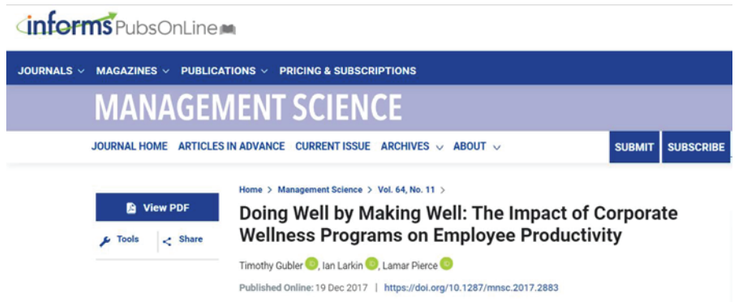
Οι εταιρείες επενδύουν ολοένα και περισσότερο στην υγεία και στην ευεξία των εργαζομένων

Τα εταιρικά προγράμματα ευεξίας μπορούν να περιλαμβάνουν:

- Απλούς βιομετρικούς ελέγχους
- Προηγμένους ελέγχους για ασθένειες
- Προγράμματα άσκησης
- Διατροφικά προγράμματα
- Έρευνες για το ιατρικό ιστορικό
- Εκπαίδευση για την προστασία και τη βελτίωση της υγείας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Home > Management Science > Vol. 64, No. 11 >

Doing Well by Making Well: The Impact of Corporate Wellness Programs on Employee Productivity

Timothy Gubler, Ian Larkin, Lamar Pierce

Published Online: 19 Dec 2017 | https://doi.org/10.1287/mnsc.2017.2883

→ Η επένδυση στην υγεία και στην ευζωία των εργαζομένων συσχετίζεται με αυξημένα εργασιακά κίνητρα και παραγωγικότητα

Ευαισθητοποίηση για την υγιεινή διατροφή

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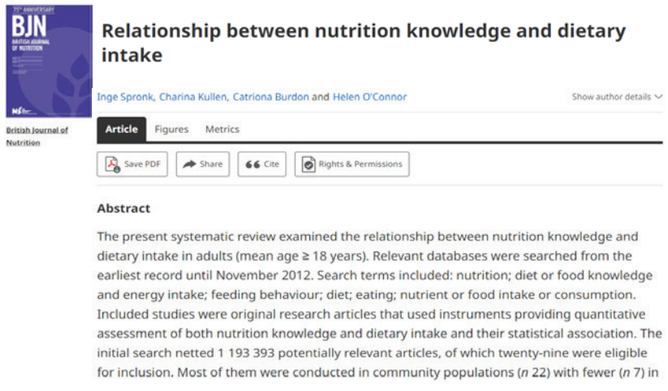
BJN — British Journal of Nutrition

Relationship between nutrition knowledge and dietary intake

Inge Spronk, Charina Kullen, Catriona Burdon and Helen O'Connor — Show author details

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Abstract

The present systematic review examined the relationship between nutrition knowledge and dietary intake in adults (mean age ≥ 18 years). Relevant databases were searched from the earliest record until November 2012. Search terms included: nutrition; diet or food knowledge and energy intake; feeding behaviour; diet; eating; nutrient or food intake or consumption. Included studies were original research articles that used instruments providing quantitative assessment of both nutrition knowledge and dietary intake and their statistical association. The initial search netted 1 193 393 potentially relevant articles, of which twenty-nine were eligible for inclusion. Most of them were conducted in community populations (*n* 22) with fewer (*n* 7) in

Γρήγορη και απλή αξιολόγηση για την ανίχνευση της παρουσίας ή του κινδύνου ελλείψεων που αφορούν θρεπτικά προσλαμβανόμενα μέσω της διατροφής

↓

BAPEN 30 Years 1992 - 2022

Putting patients at the centre of good nutritional care

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› High Blood Press Cardiovasc Prev. 2018 Sep;25(3):261-266. doi: 10.1007/s40292-018-0266-z. Epub 2018 Jun 28.

Ferrari Corporate Wellness Program: Results of a Pilot Analysis and the "Drag" Impact in the Workplace

Alessandro Biffi [1], Fredrick Fernando [2], Paolo Emilio Adami [2], Michele Messina [2], Felice Sirico [2], Fernando Di Paolo [2], Roberta Coluccia [3], Claudio Borghi [4], Flavio D'Ascenzi [5], Massimo Volpe [3 6]

Affiliations + expand

PMID: 29956111 DOI: 10.1007/s40292-018-0266-z

- Πιλοτικό πρόγραμμα ευεξίας «Ferrari Formula Benessere» στους εργαζομένους της Ferrari διάρκειας 4 ετών
- Βασικοί άξονες η εξατομικευμένη διατροφή και η τακτική άσκηση (2-3 φορές εβδομαδιαίως)

→

Σημαντικά οφέλη για την καρδιαγγειακή λειτουργία

- ✓ Μείωση σωματικού βάρους
- ✓ Μείωση χοληστερόλης
- ✓ Μείωση αρτηριακής πίεσης

Table 1 Demographic characteristics of the study population observed at the beginning and after 4 years of the wellness program

Variables	Baseline (*n* = 168)	4-year follow up (*n* = 168)	p value
Age (years)	30.8 ± 5.9	34.7 ± 6.6	< 0.0001
Female (num)	20	20	ns
Height (cm)	174.3 ± 9	174.1 ± 9	ns
Weight (kg)	78.2 ± 10	77.4 ± 8	ns
BMI (kg/m^2)	23.9 ± 2.6	23.1 ± 2.0	< 0.0001
Smokers (*n*/%): active	40/24	37/22	ns
Smokers (*n*/%): former	18/11	23/14	ns
Total Cholesterol (mg/dL)	186.3 ± 25.2	170.1 ± 20.2	< 0.0001
HDL cholesterol (mg/dL)	57.6 ± 11.8	53.2 ± 10.3	< 0.0001
LDL cholesterol (mg/dL)	110.0 ± 23.3	100.0 ± 18.7	< 0.0001
Triglycerides (mg/dL)	94.1 ± 51.0	84.5 ± 38.0	0.004
Fasting glucose (mg/dL)	83.4 ± 8.9	85.8 ± 8.4	0.003
Resting heart rate (bpm)	60 ± 13	57 ± 11	0.015
Systolic BP (mmHg)	122 ± 10	114 ± 10	< 0.0001
Diastolic BP (mmHg)	76 ± 7	73 ± 7	< 0.0001
FFM	84.5 ± 7.9	84.7 ± 8.7	0.73
FM, %	15.5 ± 7.8	14.9 ± 7.1	0.31

Data are expressed as mean ± SD

BMI body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BP* blood pressure, *FFM* fat-free mass, *FM* fat mass

Διατροφική εκπαίδευση στα σχολεία

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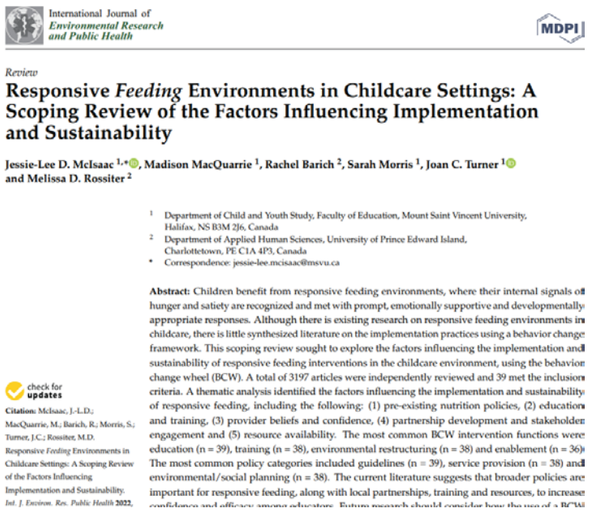

International Journal of Environmental Research and Public Health

MDPI

Review

Responsive *Feeding* Environments in Childcare Settings: A Scoping Review of the Factors Influencing Implementation and Sustainability

Jessie-Lee D. McIsaac [1,*], Madison MacQuarrie [1], Rachel Barich [2], Sarah Morris [1], Joan C. Turner [1] and Melissa D. Rossiter [2]

[1] Department of Child and Youth Study, Faculty of Education, Mount Saint Vincent University, Halifax, NS B3M 2J6, Canada
[2] Department of Applied Human Sciences, University of Prince Edward Island, Charlottetown, PE C1A 4P3, Canada
* Correspondence: jessie-lee.mcisaac@msvu.ca

Abstract: Children benefit from responsive feeding environments, where their internal signals of hunger and satiety are recognized and met with prompt, emotionally supportive and developmentally appropriate responses. Although there is existing research on responsive feeding environments in childcare, there is little synthesized literature on the implementation practices using a behavior change framework. This scoping review sought to explore the factors influencing the implementation and sustainability of responsive feeding interventions in the childcare environment, using the behavior change wheel (BCW). A total of 3197 articles were independently reviewed and 39 met the inclusion criteria. A thematic analysis identified the factors influencing the implementation and sustainability of responsive feeding, including the following: (1) pre-existing nutrition policies, (2) education and training, (3) provider beliefs and confidence, (4) partnership development and stakeholder engagement and (5) resource availability. The most common BCW intervention functions were education (n = 39), training (n = 38), environmental restructuring (n = 38) and enablement (n = 36). The most common policy categories included guidelines (n = 39), service provision (n = 38) and environmental/social planning (n = 38). The current literature suggests that broader policies are important for responsive feeding, along with local partnerships, training and resources, to increase confidence and efficacy among educators. Future research should consider how the use of a BCW

check for updates

Citation: McIsaac, J.-L.D.; MacQuarrie, M.; Barich, R.; Morris, S.; Turner, J.C.; Rossiter, M.D. Responsive *Feeding* Environments in Childcare Settings: A Scoping Review of the Factors Influencing Implementation and Sustainability. *Int. J. Environ. Res. Public Health* **2022,**

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- ✓ Έπαινος για τη δοκιμή νέων τροφών
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- ✓ Αποφυγή χρήσης τροφικών ανταμοιβών
- ✓ Πρότυπο κατανάλωσης του ίδιου φαγητού - μίμηση
- ✓ Εμπλοκή συζήτησης κατά τη διάρκεια των γευμάτων

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

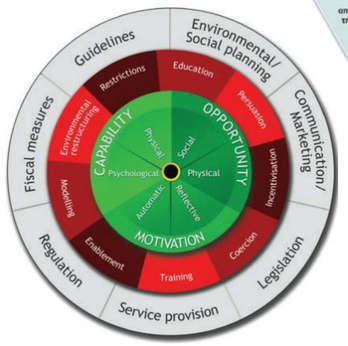
Διατροφική εκπαίδευση στα σχολεία

Τροχός αλλαγής συμπεριφοράς

Νέα μέθοδος για το χαρακτηρισμό και το σχεδιασμό παρεμβάσεων αλλαγής συμπεριφοράς

Παρεμβάσεις: δραστηριότητες που αποσκοπούν στην αλλαγή συμπεριφοράς

Πολιτικές: αποφάσεις από τις κυβερνητικές αρχές σχετικά με τις παρεμβάσεις



ΕΠΙΝΕΦΡΙΔΙΑ

ΔΕΛΗΒΑΝΗ ΔΑΝΑΗ

ΕΙΔΙΚΟΣ ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ,
MAYO CLINIC, ROCHESTER USA, CERTIFIED AMERICAN BOARD OF ENDO- CRINOLOGY,
DIABETES AND METABOLISM

Επινεφρίδια

Δεληβάνη Δανάη

Ενδοκρινολόγος, Διδάκτωρ Πανεπιστήμιου Πατρών, Assistant Professor Mayo Clinic, Rochester USA

Annals of Internal Medicine ORIGINAL RESEARCH

Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors

A Cross-Sectional Multicenter Study

Alessandro Prete, MD; Anuradhaa Subramanian, MSc; Irina Bancos, MD; Vasileios Chortis, MD, PhD; Stylianos Tsagarakis, MD, PhD; Katharina Lang, MD; Magdalena Macech, MD; Danae A. Delivanis, MD; Ivana D. Pupovac, MD; Giuseppe Reimondo, MD; Ljiljana V. Marina, MD, PhD; Timo Deutschbein, MD; Maria Balomenaki, MD; Michael W. O'Reilly, MD, PhD; Lorna C. Gilligan, MD, PhD; Carl Jenkinson, PhD; Tomasz Bednarczuk, MD, PhD; Catherine D. Zhang, MD; Tina Dusek, MD, PhD; Aristidis Diamantopoulos, MD; Miriam Asia, MSc; Agnieszka Kondracka, MD, PhD; Dingfeng Li, MD; Jimmy R. Masjkur, MD; Marcus Quinkler, MD; Grethe Å. Ueland, MD, PhD; M. Conall Dennedy, MD, PhD; Felix Beuschlein, MD; Antoine Tabarin, MD, PhD; Martin Fassnacht, MD; Miomira Ivović, MD, PhD; Massimo Terzolo, MD; Darko Kastelan, MD, PhD; William F. Young Jr., MD; Konstantinos N. Manolopoulos, MD, PhD; Urszula Ambroziak, MD, PhD; Dimitra A. Vassiliadi, MD; Angela E. Taylor, PhD; Alice J. Sitch, PhD; Krishnarajah Nirantharakumar, MD; and Wiebke Arlt, MD, DSc; for the ENSAT EURINE-ACT Investigators*

Background: Benign adrenal tumors are commonly discovered on cross-sectional imaging. Mild autonomous cortisol secretion (MACS) is regularly diagnosed, but its effect on cardiometabolic disease in affected persons is ill defined.

Objective: To determine cardiometabolic disease burden and steroid excretion in persons with benign adrenal tumors with and without MACS.

Design: Cross-sectional study.

Setting: 14 endocrine secondary and tertiary care centers (recruitment from 2011 to 2016).

Participants: 1305 prospectively recruited persons with benign adrenal tumors.

Measurements: Cortisol excess was defined by clinical assessment and the 1-mg overnight dexamethasone-suppression test (serum cortisol: <50 nmol/L, nonfunctioning adrenal tumor [NFAT]; 50 to 138 nmol/L, possible MACS [MACS-1]; >138 nmol/L and absence of typical clinical Cushing syndrome [CS] features, definitive MACS [MACS-2]). Net steroid production was assessed by multisteroid profiling of 24-hour urine by tandem mass spectrometry.

Results: Of the 1305 participants, 49.7% had NFAT (n = 649; 64.1% women), 34.6% had MACS-1 (n = 451; 67.2% women), 10.7% had MACS-2 (n = 140; 73.6% women), and 5.0% had CS (n = 65; 86.2% women). Prevalence and severity of hypertension were higher in MACS-2 and CS than NFAT (adjusted prevalence ratios [aPRs] for hypertension: MACS-2, 1.15 [95% CI, 1.04 to 1.27], and CS, 1.37 [CI, 1.16 to 1.62]; aPRs for use of ≥3 antihypertensives: MACS-2, 1.31 [CI, 1.02 to 1.68], and CS, 2.22 [CI, 1.62 to 3.05]). Type 2 diabetes was more prevalent in CS than NFAT (aPR, 1.62 [CI, 1.08 to 2.42]) and more likely to require insulin therapy for MACS-2 (aPR, 1.89 [CI, 1.01 to 3.52]) and CS (aPR, 3.06 [CI, 1.60 to 5.85]). Urinary multisteroid profiling revealed an increase in glucocorticoid excretion from NFAT over MACS-1 and MACS-2 to CS, whereas androgen excretion decreased.

Limitations: Cross-sectional design; possible selection bias.

Conclusion: A cardiometabolic risk condition, MACS predominantly affects women and warrants regular assessment for hypertension and type 2 diabetes.

Primary Funding Source: Diabetes UK, the European Commission, U.K. Medical Research Council, the U.K. Academy of Medical Sciences, the Wellcome Trust, the U.K. National Institute for Health Research, the U.S. National Institutes of Health, the Claire Khan Trust Fund at University Hospitals Birmingham Charities, and the Mayo Clinic Foundation for Medical Education and Research.

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* For a list of the ENSAT EURINE-ACT Investigators, see the **Appendix** (available at Annals.org).

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Ann Intern Med. 2022;175:325-334. doi:10.7326/M21-1737 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 4 January 2022.

* For a list of the ENSAT EURINE-ACT Investigators, see the **Appendix** (available at Annals.org).

Background: Benign adrenal tumors are common (89% of incidentalomas). Mild autonomous cortisol secretion (MACS) is regularly diagnosed, but its effect on cardiometabolic disease in affected persons is not well defined.

Aim: To determine clinical characteristics, cardiometabolic disease burden and steroid excretion in persons with benign adrenal tumors with and without MACS

Methods:

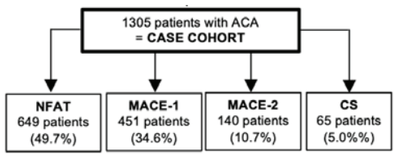
- ✓ Cross-sectional study
- ✓ 14 endocrine care centers in 11 countries (recruitment from 2011 to 2016).
- ✓ 1305 prospectively recruited persons with benign adrenal tumors (excluded PA and BIMAH)

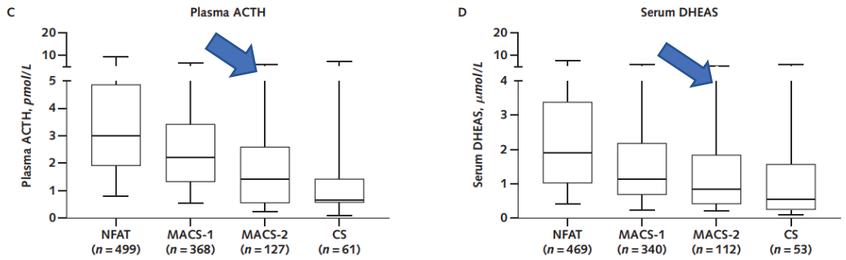
Measurements:

- ✓ Cardiometabolic risk factors (HTN, DM, pre DM, HLD)
- ✓ 24-hour urinary excretion of 16 distinct steroid
- ✓ metabolites

Results:

- ✓ **Female**: Women represented 67.3% of the participants, and the female predominance was most pronounced in MACS-2 (73.6%) and CS (86.2%)
- ✓ **AGE**: MACS were older than NFAT. CS were the youngest (median, 48 years)
- ✓ **Size**: participants with abnormal 1mg-DST results had larger adrenal tumors
- ✓ **Bilateral disease**: Persons with MACS were almost twice as likely to present with bilateral tumors than persons with NFAT

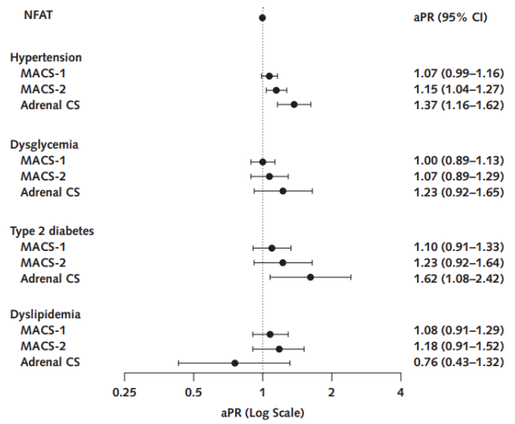




Results: Compared with persons with NFAT

- ✓ MACS-2 and CS showed a higher prevalence of hypertension and more often required 3 or more antihypertensives
- ✓ The prevalence of type 2 diabetes was increased in participants with CS
- ✓ In a subgroup analysis of persons with type 2 diabetes, both MACS-2 and CS more often required insulin treatment
- ✓ The prevalence of dyslipidemia did not differ between participants
- ✓ Persons with bilateral adrenal tumors more often required 3 or more antihypertensives and were more frequently diagnosed with dysglycemia
- ✓ MACS-1, MACS-2, and CS showed a gradual decrease in the 24-hour urinary excretion of androgen metabolites
- ✓ MACS-1, MACS-2, and CS showed a progressive increase in the excretion of cortisol and tetrahydro11-deoxycortisol, the metabolite of the immediate cortisol precursor 11-deoxycortisol. In persons with MACS-2 and CS, the excretion of cortisone was also increased

Figure 3. Effect of different degrees of cortisol excess on cardiometabolic risk.



Conclusion:

- ✓ MACS-2 carry an increased cardiometabolic burden similar to that seen in CS even if they do not display typical features of clinically overt cortisol excess
- ✓ The proportion of women increased with the degree of cortisol excess, corroborating previous observations that cortisol excess predominantly affects women
- ✓ Persons with MACS and bilateral tumors were more frequently diagnosed with dysglycemia and prescribed 3 or more antihypertensives
- ✓ Progressive changes in steroid excretion across ALL 3 groups, MACS-1, MACS-2, and CS compared with NFAT: i) Progressive decrease in androgen excretion and ii) a progressive increase in glucocorticoid excretion
- ✓ The Authors speculate that a subgroup of persons with NFAT may have underlying autonomous cortisol secretion that is not detected when the current diagnostic criterion for cortisol excess—the 1mg-DST—is applied.

Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study

Timo Deutschbein*, Giuseppe Reimondo*, Guido Di Dalmazi, Irina Bancos, Jekaterina Patrova, Dimitra Argyro Vassiliadi, Anja Barač Nekić, Miguel Debono, Pina Lardo, Filippo Ceccato, Luigi Petramala, Alessandro Prete, Iacopo Chiodini, Miomira Ivović, Kalliopi Pazaitou-Panayiotou, Krystallenia I Alexandraki, Felicia Alexandra Hanzu, Paola Loli, Serkan Yener, Katharina Langton, Ariadni Spyroglou, Tomaz Kocjan, Sabina Zacharieva, Nuria Valdés, Urszula Ambroziak, Mari Suzuki, Mario Detomas, Soraya Puglisi, Lorenzo Tucci, Danae Anastasia Delivanis, Dimitris Margaritopoulos, Tina Dusek, Roberta Maggio, Carla Scaroni, Antonio Concistrè, Cristina Lucia Ronchi, Barbara Altieri, Cristina Mosconi, Aristidis Diamantopoulos, Nicole Marie Iñiguez-Ariza, Valentina Vicennati, Anna Pia, Matthias Kroiss, Gregory Kaltsas, Alexandra Chrisoulidou, Ljiljana V Marina, Valentina Morelli, Wiebke Arlt, Claudio Letizia, Marco Boscaro, Antonio Stigliano, Darko Kastelan, Stylianos Tsagarakis, Shobana Athimulam, Uberto Pagotto, Uwe Maeder, Henrik Falhammar, John Newell-Price, Massimo Terzolo†, Martin Fassnacht†

Summary

Background The association between cortisol secretion and mortality in patients with adrenal incidentalomas is controversial. We aimed to assess all-cause mortality, prevalence of comorbidities, and occurrence of cardiovascular events in uniformly stratified patients with adrenal incidentalomas and cortisol autonomy (defined as non-suppressible serum cortisol on dexamethasone suppression testing).

Methods We conducted an international, retrospective, cohort study (NAPACA Outcome) at 30 centres in 16 countries. Eligible patients were aged 18 years or older with an adrenal incidentaloma (diameter ≥1 cm) detected between Jan 1, 1996, and Dec 31, 2015, and availability of a 1 mg dexamethasone suppression test result from the time of the initial diagnosis. Patients with clinically apparent hormone excess, active malignancy, or follow-up of less than 36 months were excluded. Patients were stratified according to the 0800–0900 h serum cortisol values after an overnight 1 mg dexamethasone suppression test: less than 50 nmol/L was classed as non-functioning adenoma, 50–138 nmol/L as possible autonomous cortisol secretion, and greater than 138 nmol/L as autonomous cortisol secretion. The primary endpoint was all-cause mortality. Secondary endpoints were the prevalence of cardiometabolic comorbidities, cardiovascular events, and cause-specific mortality. The primary and secondary endpoints were assessed in all study participants.

Findings Of 4374 potentially eligible patients, 3656 (2089 [57·1%] with non-functioning adenoma, 1320 [36·1%] with possible autonomous cortisol secretion, and 247 [6·8%] with autonomous cortisol secretion) were included in the study cohort for mortality analysis (2350 [64·3%] women and 1306 [35·7%] men; median age 61 years [IQR 53–68]; median follow-up 7·0 years [IQR 4·7–10·2]). During follow-up, 352 (9·6%) patients died. All-cause mortality (adjusted for age, sex, comorbidities, and previous cardiovascular events) was significantly increased in patients with possible autonomous cortisol secretion (HR 1·52, 95% CI 1·19–1·94) and autonomous cortisol secretion (1·77, 1·20–2·62) compared with patients with non-functioning adenoma. In women younger than 65 years, autonomous cortisol secretion was associated with higher all-cause mortality than non-functioning adenoma (HR 4·39, 95% CI 1·93–9·96), although this was not observed in men. Cardiometabolic comorbidities were significantly less frequent with non-functioning adenoma than with possible autonomous cortisol secretion and autonomous cortisol secretion (hypertension occurred in 1186 [58·6%] of 2024 patients with non-functioning adenoma, 944 [74·0%] of 1275 with possible autonomous cortisol secretion, and 179 [75·2%] of 238 with autonomous cortisol secretion; dyslipidaemia occurred in 724 [36·2%] of 1999 patients, 547 [43·8%] of 1250, and 123 [51·9%] of 237; and any diabetes occurred in 365 [18·2%] of 2002, 288 [23·0%] of 1250, and 62 [26·7%] of 232; all p values <0·001).

Interpretation Cortisol autonomy is associated with increased all-cause mortality, particularly in women younger than 65 years. However, until results from randomised interventional trials are available, a conservative therapeutic approach seems to be justified in most patients with adrenal incidentaloma.

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Background: The association between cortisol secretion and mortality in patients with adrenal incidentalomas is controversial.

Aim: To assess all-cause mortality, prevalence of comorbidities, and occurrence of cardiovascular events in patients with adrenal incidentalomas and cortisol autonomy

Methods: International, retrospective, cohort study at 30 centers in 16 countries. Eligible patients were aged > 18 years of age with an adrenal incidentaloma detected between Jan 1, 1996, and Dec 31, 2015, and availability of a 1 mg dexamethasone suppression test result from the time of the initial diagnosis

Endpoints:

- ✓ The primary endpoint was all-cause mortality
- ✓ Secondary endpoints were the prevalence of cardiometabolic comorbidities, cardiovascular events, and cause-specific mortality

Data Collected:

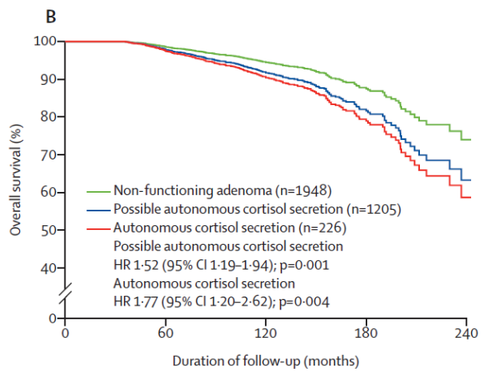
- ✓ Demographics: Age, sex, and BMI
- ✓ Medical history (CAD risk factors and events)
- ✓ Cardiometabolic comorbidities= hypertension, any diabetes, and dyslipidaemia
- ✓ Cardiovascular morbidity= myocardial infarction or coronary revascularisation (either bypass surgery or percutaneous intervention), stroke, or cardiovascular-related death
- ✓ **Results:**
- ✓ Cardiometabolic comorbidities were more prevalent in the pACS and ACS
- ✓ Higher prevalence =Hypertension
- ✓ Comorbidities showed progressively increased frequencies
- ✓ in the NFAT, pACS, ACS groups, reflecting a continuum in metabolic disturbance

	All patients (n=3656)	Non-functioning adenoma (n=2089)	Possible autonomous cortisol secretion (n=1320)	Autonomous cortisol secretion (n=247)
Sex				
Women	2350 (64·3%)	1321 (63·2%)	860 (65·2%)	169 (68·4%)
Men	1306 (35·7%)	768 (36·8%)	460 (34·8%)	78 (31·6%)
Age, years	61 (53–68)	60 (52–67)	63 (56–70)	63 (55–70)
Age <65 years	2264 (61·9%)	1404 (67·2%)	726 (55·0%)	134 (54·3%)
Follow-up, years	7·0 (4·7–10·2)	7·2 (4·8–10·5)	6·9 (4·7–10·0)	6·9 (4·5–10·0)
BMI, kg/m²*	28·1 (25·0–32·3)	28·6 (25·4–32·6)	27·8 (24·6–31·9)	27·7 (24·3–31·9)
Tumour characteristics†				
Left side	1497 (44·6%)	946 (49·8%)	468 (38·1%)	83 (36·2%)
Right side	1093 (32·6%)	646 (34·0%)	385 (31·4%)	62 (27·1%)
Bilateral	764 (22·8%)	306 (16·1%)	374 (30·5%)	84 (36·7%)
Maximum tumour diameter, mm	22 (15–30)	20 (15–25)	26 (19–33)	29 (20–37)
1 mg dexamethasone suppression test serum cortisol result, nmol/L	47 (30–72)	33 (28–50)	72 (61–94)	190 (157–253)
Comorbidities				
Hypertension‡	2309 (65·3%)	1186 (58·6%)	944 (74·0%)	179 (75·2%)
Dyslipidaemia§	1394 (40·0%)	724 (36·2%)	547 (43·8%)	123 (51·9%)
Any diabetes¶	715 (20·5%)	365 (18·2%)	288 (23·0%)	62 (26·7%)
Previous cardiovascular events				
Myocardial infarction or coronary intervention, or both‖	199 (6·0%)	87 (4·6%)	96 (8·0%)	16 (7·1%)
Stroke**	70 (2·1%)	31 (1·6%)	27 (2·3%)	12 (5·3%)
Deep vein thrombosis or pulmonary embolism, or both††	62 (1·9%)	31 (1·7%)	26 (2·2%)	5 (2·2%)
At least one cardiovascular event‡‡	319 (9·3%)	150 (7·6%)	139 (11·4%)	30 (13·2%)

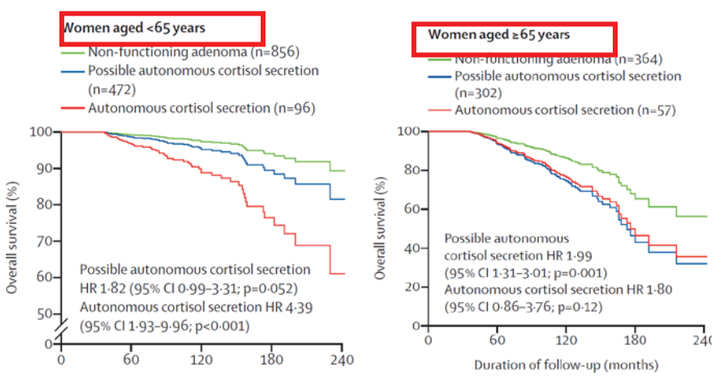
Data are n (%) or median (IQR). Centre-specific data on ethnicity are shown in the appendix (p 2). *n=3216. †n=3354. ‡n=3537. §n=3486. ¶n=3484. ‖n=3306. **n=3299. ††n=3293. ‡‡n=3415.

Table 1: **Patient characteristics at initial diagnosis of the adrenal incidentaloma**

Primary end point: All Cause Mortality: After multivariable Cox analysis adjusting for age, sex, hypertension, any diabetes, dyslipidaemia, and previous cardiovascular events all-cause mortality was increased in patients with possible autonomous cortisol secretion and autonomous cortisol secretion compared with patients with nonfunctioning adenoma.



Association between all-cause mortality and the degree of cortisol autonomy was age and sex dependent



Conclusion: Cortisol autonomy is associated with increased all-cause mortality, especially in **women <65 years.**

Secondary end point: Cardiovascular mortality

Cardiovascular events occurring either before or after the initial diagnosis of the adrenal tumor were more frequently observed in patients with pACS and ACS than in patients with NFAT. However, after adjusting for cardiometabolic comorbidities, a significant increase in MACE **was only observed in women aged 65 years or older**

	Age, years	All patients, n	All events, n	Possible autonomous cortisol secretion				Autonomous cortisol secretion			
				Patients, n	HR	95% CI	p value	Patients, n	HR	95% CI	p value
Women	<65	1377	75	466	1·20	0·74–1·95	0·46	94	1·61	0·71–3·61	0·25
	≥65	705	92	296	1·33	0·84–2·06	0·22	56	2·09	1·08–4·05	0·028
Men	<65	694	91	218	1·05	0·67–1·63	0·83	33	0·73	0·29–1·85	0·51
	≥65	466	89	193	1·10	0·70–1·72	0·69	36	1·04	0·48–2·24	0·92

The analysis was adjusted for hypertension, any diabetes, dyslipidaemia, and previous cardiovascular events. Patients with missing data for these variables were excluded from the analysis. Patients with non-functioning adenoma were the reference cohort. HR=hazard ratio. MACE=major adverse cardiovascular event.

Table 3: Multivariate Cox regression analysis of MACE by sex and age

Conclusion:

- ✓ Cardiometabolic comorbidities were significantly less frequent in NFA than in PACS and ACS
- ✓ All-cause mortality (adjusted for age, sex, comorbidities, and former CV events) was significantly increased in PACS (HR 1.52; 95%CI 1.19-1.94; p=0.001) and ACS (1.77; 1.20-2.62; p=0.04).
- ✓ In women <65 years, ACS was associated with higher mortality compared to NFA (HR 4.37; 95%CI 1.93-9.91; p<0.001), while in men this was not observed.

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ORIGINAL ARTICLE

WILEY

Adrenal venous sampling for lateralization of cortisol hypersecretion in patients with bilateral adrenal masses

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Abstract

Objective: The objective of this study was to evaluate the role of adrenal venous sampling (AVS) in guiding the management of patients with corticotropin (ACTH)-independent glucocorticoid secretory autonomy and bilateral adrenal masses.

Design and Patients: A cohort with 25 patients underwent AVS and surgical management.

Measurements: Cortisol was measured from the adrenal veins (AVs) and inferior vena cava (IVC). AV/IVC cortisol ratio and cortisol lateralization ratio (CLR) (dominant AV cortisol concentration divided by the nondominant AV cortisol concentration) were calculated. Posthoc receiver-operating characteristic curves were generated to determine the specificity of revised AV/IVC cortisol ratio and CLR in differentiating unilateral from bilateral disease.

Results: Patients underwent unilateral ($n = 21$) or bilateral ($n = 4$) adrenalectomy. The mean AV/IVC cortisol ratio for unilateral adrenalectomy was 12.1 ± 9.6 (dominant) and 4.7 ± 3.8 (contralateral) with a mean CLR of 3.6 ± 3.5. The mean AV/IVC cortisol ratio for bilateral adrenalectomy was 7.5 ± 2.1, with a mean CLR of 1.1 ± 0.6. At a mean follow-up of 22 months, one patient who underwent unilateral adrenalectomy for the predicted bilateral disease developed recurrent mild autonomous cortisol secretion. Posthoc analyses demonstrated a specificity of 95%–100% for unilateral disease with AV/IVC cortisol ratio >9 for one side, <2.0 for the opposite side and a CLR > 2.3. The specificity was 80%–90% for bilateral disease with AV/IVC cortisol ratio >5.1 bilaterally and a CLR < 1.1.

Conclusions: Among patients with bilateral adrenal masses and ACTH-independent autonomous cortisol secretion, AVS can distinguish between unilateral and bilateral disease with high specificity and may guide surgical management.

KEYWORDS
adrenal glands, adrenal venous sampling, bilateral adrenal masses, cortisol lateralization Ratio, Cushing syndrome, mild autonomous cortisol secretion, subclinical Cushing syndrome

Background: ACTH-independent glucocorticoid secretory autonomy can cause mild autonomous cortisol secretion (MACS) . Treatment of unilateral ACTH-independent cortisol-secreting adrenal adenomas is generally straightforward. For patients with bilateral adrenal masses, treatment planning is more complex since masses can occur in various combinations.

Aim: to evaluate the role of adrenal venous sampling (AVS) in guiding the management of patients with ACTH- independent glucocorticoid secretory autonomy (CS and MACS) and bilateral adrenal masses

Design and Patients: A retrospective cohort with 25 patients with B/L adrenal masses, clinical CS or subclinical MACS who underwent AVS and surgical management. Cases of PA and PHEO were excluded.

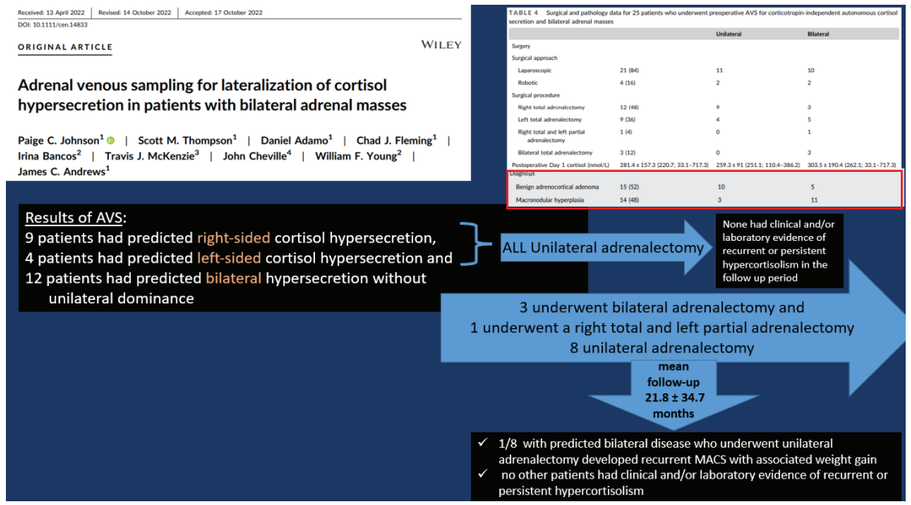

TABLE 6 Prior and revised AVS criteria

Unilateral disease	AV/IVC cortisol ratio	CLR	Specificity
Prior	>6.5 one side	>2.3	85%–90%
Current	>9 one side	>2.3[a]	95%–100%
Bilateral disease	**AV/IVC cortisol ratio**	**CLR**	**Specificity**
Prior	≥4.1 bilaterally	<2.0	65%–70%
Current	>5.1 bilaterally	<1.1	80%–90%

Abbreviations: AVS, adrenal vein sampling; CLR, cortisol lateralization ratio; IVC, inferior vena cava.

[a]CLR > 1.3 strongly argues against bilateral disease.

Conclusion :

- ✓ Among patients with bilateral adrenal masses and ACTH- independent CS or subclinical MACS, AVS can distinguish unilateral from bilateral disease and lateralize the side of greater autonomous cortisol secretion, thereby helping guide multidisciplinary treatment discussions and surgical management.
- ✓ The CLR is the most specific parameter for initially differentiating unilateral from bilateral disease with a CLR > 1.3 strongly arguing against bilateral disease. Once the unilateral disease is predicted based on CLR then the higher AV/IVC cortisol ratio and CLR dominant side can be used to guide laterality for adrenalectomy with high specificity
- ✓ The revised AVS criteria suggested here improve the specificity for distinguishing unilateral and bilateral disease, providing guidance to manage this challenging clinical situation.
- ✓ In patients with CS due to CT-confirmed PBMAH, AVS likely has no role or a limited role in guiding surgical management
- ✓ Careful patient selection and Need for an experience center in performing AVS

-

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https://doi.org/10.1007/s12020-022-03020-z

ORIGINAL ARTICLE

The role of adrenal venous sampling (AVS) in primary bilateral macronodular adrenocortical hyperplasia (PBMAH): a study of 16 patients

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Abstract

Objective Primary bilateral macronodular adrenocortical hyperplasia (PBMAH) is a rare cause of ACTH-independent Cushing's syndrome. Current guidelines recommend bilateral adrenalectomy for PBMAH, but several studies showed clinical effectiveness of unilateral adrenalectomy despite bilateral disease in selected patients. Our aim was to evaluate the gain of information which can be obtained through adrenal venous sampling (AVS) based cortisol lateralization ratios for guidance of unilateral adrenalectomy.

Design We performed a retrospective analysis of 16 patients with PBMAH and clinical overt cortisol secretion in three centers

Methods Selectivity of adrenal vein sampling during AVS was defined as a gradient of cortisol or a reference adrenal hormone ≥2.0 between adrenal and peripheral vein. Lateralization was assumed if the dominant to non-dominant ratio of cortisol to reference hormone was ≥4.0.

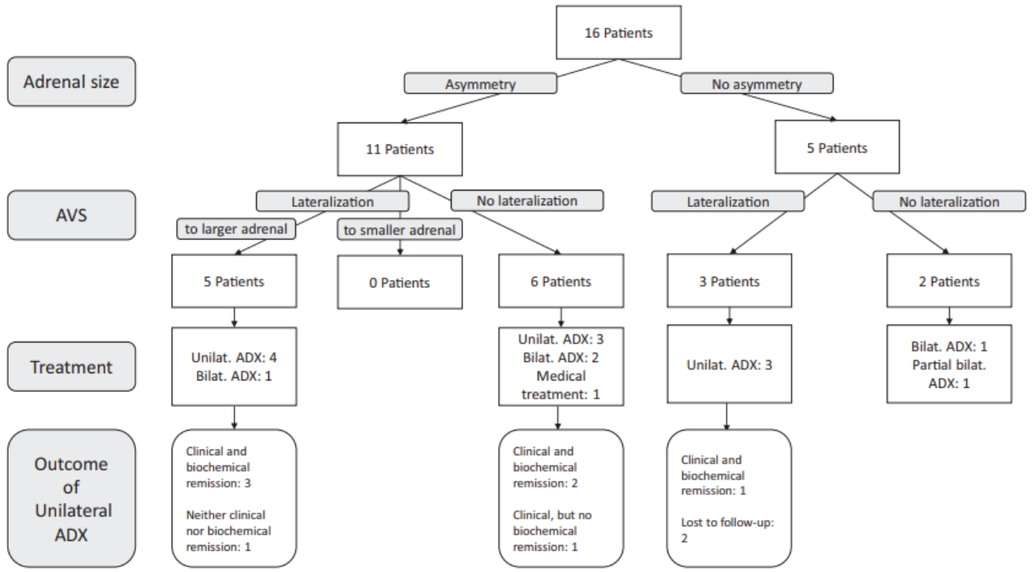
Results AVS was technically successful in all patients based on absolute cortisol levels and in 13 of 16 patients (81%) based on reference hormone levels. Lateralization was documented in 8 of 16 patients. In patients with lateralization, in 5 of 8 cases this occurred toward morphologically larger adrenals, while in 3 patients lateralization was present in bilaterally identical adrenals. The combined volume of adrenals correlated positively with urinary free cortisol, suggesting that adrenal size is the dominant determinant of cortisol secretion.

Conclusions In this study the gain of information through AVS for unilateral adrenalectomy was limited in patients with PBMAH and marked adrenal asymmetry.

Aim: The role of AVS in PBMAH

Design: a retrospective analysis of 16 patients with PBMAH and clinical overt CS

Methods: Selectivity of adrenal vein sampling during AVS was defined as a gradient of cortisol or a reference adrenalhormone ≥2.0 between adrenal and peripheral vein. Lateralization was assumed if the dominant to non-dominant ratio of cortisol to reference hormone was ≥4.0



Results:

- ✓ Lateralization was documented in 8 of 16 patients. In patients with lateralization, in 5 of 8 cases this occurred toward morphologically larger adrenals, while in 3 patients lateralization was present in bilaterally identical adrenals.
- ✓ In no case lateralization was found toward the smaller gland.
- ✓ The combined volume of adrenals correlated positively with urinary free cortisol, suggesting that adrenal size is the dominant determinant of cortisol secretion

Conclusion: In this study the gain of information through AVS for unilateral adrenalectomy was limited in patients with PBMAH and marked adrenal asymmetry.

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https://doi.org/10.1210/clinem/dgab751
Clinical Research Article

Clinical Research Article

Plasma Steroid Profiling in Patients With Adrenal Incidentaloma

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Abbreviations: ACC, adrenocortical carcinoma; ACS, autonomous cortisol secretion; CT, computed tomography; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-sulfate; DST, dexamethasone suppression test; ENS@T, European Network for the Study of Adrenal Tumors; LC-MS/MS, liquid chromatography with tandem mass spectrometry; NFAI, nonfunctional adrenal incidentaloma; NPV, negative predictive value; PA, primary aldosteronism; PHEO, pheochromocytoma, PMT, Prospective Monoamine-producing Tumor study; PPV, positive predictive value; PROSALDO, PROspective study on the diagnostic value of Steroid profiling in primary ALDOsteronism; ROC, receiver operating characteristic.

Received: 8 July 2021; Editorial Decision: 11 October 2021; First Published Online: 19 October 2021; Corrected and Typeset: 6 November 2021.

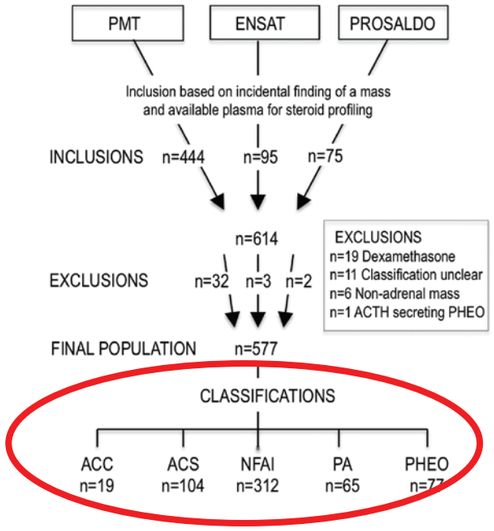
Abstract

Context: Most patients with adrenal incidentaloma have nonfunctional lesions that do not require treatment, while others have functional or malignant tumors that require intervention. The plasma steroid metabolome may be useful to assess therapeutic need.
Objective: This work aimed to establish the utility of plasma steroid profiling combined with metanephrines and adrenal tumor size for the differential diagnosis of patients with adrenal incidentaloma

Aim: to establish the utility of plasma steroid profiling combined with metanephrines and adrenal tumor size for the differential diagnosis of patients with adrenal incidentaloma.

Design: A retrospective cross-sectional study at 7 European tertiary care centers, comprised 577 patients with adrenal incidentaloma AND available plasma sample for steroid profiling

Results: A selection of these 11 steroids, combined with plasma metanephrines, proved optimal for identifying patients with ACC, PA, and PHEO at respective sensitivities and specificities. However, discrimination of ACS and NFAI remained suboptimal (70%-71% sensitivity, 89%-90% specificity).



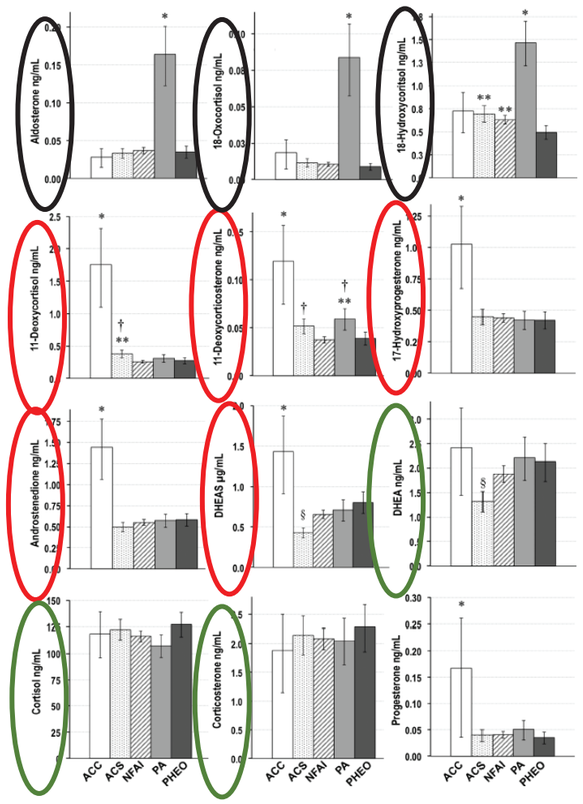


Table 2. Confusion matrices and measures of diagnostic performance derived from discriminant analyses for 3 models (A, B, C) for distinguishing patients with malignant, functional and nonfunctional adrenal incidentalomas

		Confusion matrices					Diagnostic performance			
A. Steroid panel										
		Predicted group					Percentages and 95% CI			
		ACC	ACS	NFAI	PA	PHEO	Sensitivity	Specificity	PPV	NPV
Actual group	ACC	14	0	2	2	1	74 (54-94)	98 (97-99)	56 (37-76)	99 (98-100)
	ACS	0	69	12	7	16	66 (57-75)	88 (85-91)	54 (46-63)	92 (90-95)
	NFAI	9	46	138	28	91	44 (39-50)	89 (86-93)	83 (77-89)	58 (53-62)
	PA	1	3	3	54	4	83 (74-92)	92 (89-94)	56 (46-66)	98 (96-99)
	PHEO	1	9	11	5	51	66 (56-77)	78 (75-82)	31 (24-38)	94 (92-96)
B. Steroid panel and metanephrines										
		Predicted group					Percentages and 95% CI			
		ACC	ACS	NFAI	PA	PHEO	Sensitivity	Specificity	PPV	NPV
Actual group	ACC	15	0	2	1	0	83 (66-100)	98 (97-99)	58 (39-77)	99 (99-100)
	ACS	1	74	23	4	2	71 (62-80)	89 (87-92)	59 (50-67)	94 (91-96)
	NFAI	9	49	214	35	5	69 (63-74)	89 (85-92)	88 (84-92)	71 (66-75)
	PA	1	2	3	59	0	91 (84-98)	92 (90-94)	59 (49-67)	99 (98-100)
	PHEO	0	1	2	1	73	95 (90-100)	99 (98-100)	91 (85-97)	99 (98-100)
C. Steroid panel, metanephrines and adrenal lesion size										
		Predicted group					Percentages and 95% CI			
		ACC	ACS	NFAI	PA	PHEO	Sensitivity	Specificity	PPV	NPV
Actual group	ACC	18	0	0	0	0	100 (100-100)	99 (99-100)	86 (71-100)	100 (100-100)
	ACS	0	73	24	6	1	70 (61-79)	90 (87-92)	59 (51-68)	93 (91-96)
	NFAI	3	48	217	37	3	71 (65-76)	89 (86-93)	89 (85-93)	72 (67-77)
	PA	0	2	3	60	0	92 (86-99)	91 (89-94)	58 (48-67)	99 (98-100)
	PHEO	0	0	1	1	75	97 (94-100)	99 (98-100)	95 (90-100)	100 (99-100)

Conclusion: Among patients with adrenal incidentaloma, the combination of plasma steroid metabolomics with routinely available plasma free metanephrines and data from imaging studies may facilitate the identification of almost all clinically relevant adrenal tumors.

Hypertension

ORIGINAL ARTICLE

Screening Rates for Primary Aldosteronism Among Individuals With Hypertension Plus Hypokalemia: A Population-Based Retrospective Cohort Study

Gregory L. Hundemer, Haris Imsirovic, Anand Vaidya, Nicholas Yozamp, Rémi Goupil, François Madore, Mohsen Agharazii, Greg Knoll, Manish M. Sood

ABSTRACT: Primary aldosteronism is a common, yet highly underdiagnosed, cause of hypertension that leads to disproportionately high rates of cardiovascular disease. Hypertension plus hypokalemia is a guideline-recommended indication to screen for primary aldosteronism, yet the uptake of this recommendation at the population level remains unknown. We performed a population-based retrospective cohort study of adults ≥18 years old in Ontario, Canada, with hypertension plus hypokalemia (potassium <3.5 mEq/L) from 2009 to 2015 with follow-up through 2017. We measured the proportion of individuals who underwent primary aldosteronism screening via the aldosterone-to-renin ratio based upon hypokalemia frequency and severity along with concurrent antihypertensive medication use. We assessed clinical predictors associated with screening via Cox regression. The cohort included 26 533 adults of which only 422 (1.6%) underwent primary aldosteronism screening. When assessed by number of instances of hypokalemia over a 2-year time window, the proportion of eligible patients who were screened increased only modestly from 1.0% (158/15 983) with one instance to 4.8% (71/1494) with ≥5 instances. Among individuals with severe hypokalemia (potassium <3.0 mEq/L), only 3.9% (58/1422) were screened. Among older adults prescribed ≥4 antihypertensive medications, only 1.0% were screened. Subspecialty care with endocrinology (hazard ratio [HR], 1.52 [95% CI, 1.10–2.09]), nephrology (HR, 1.43 [95% CI, 1.07–1.91]), and cardiology (HR, 1.39 [95% CI, 1.14–1.70]) were associated with an increased likelihood of screening, whereas age (HR, 0.95 [95% CI, 0.94–0.96]) and diabetes (HR, 0.66 [95% CI, 0.50–0.89]) were inversely associated with screening. In conclusion, population-level uptake of guideline recommendations for primary aldosteronism screening is exceedingly low. Increased education and awareness are critical to bridge this gap. (***Hypertension.*** **2022;79:178–186. DOI: 10.1161/HYPERTENSIONAHA.121.18118.)**
• Supplemental Material

Key Words: aldosterone ■ cardiovascular disease ■ hypertension ■ hypokalemia ■ potassium

Background: Primary aldosteronism is a common, yet highly underdiagnosed, cause of hypertension that leads to disproportionately high rates of cardiovascular disease. Hypertension plus hypokalemia is a guideline-recommended indication to screen for primary aldosteronism, yet the uptake of this recommendation at the population level remains unknown

Aim: to explore PA screening rates among individuals with hypertension plus hypokalemia.

Methods: A population-based retrospective cohort study of adults ≥18 years old in Ontario, Canada, with hypertension plus hypokalemia (potassium <3.5 mEq/L) from 2009 to 2015 with follow-up through 2017.

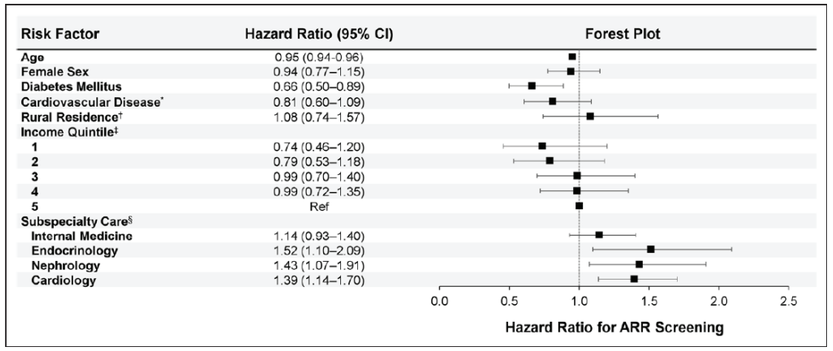
Measurements:

→Baseline characteristics

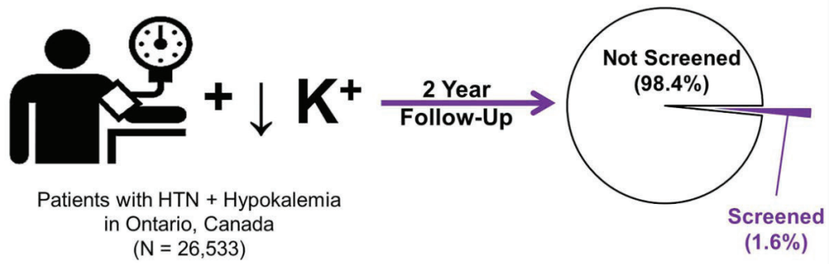
→Medication data

→PA screening via the ARR based upon hypokalemia frequency and severity along with concurrent antihypertensive medication use

Results:



How often are patients with hypertension plus hypokalemia being screened for primary aldosteronism at the population level?



Conclusion: Population-level uptake of guideline-recommended screening for primary aldosteronism is exceedingly low. This underscores a lack of awareness and testing as the primary reason for why primary aldosteronism is severely unrecognized.

Conclusion:

- ✓ the number of patients who undergo screening for PA is almost zero
- ✓ The low level of screening occurs even among individuals with recurrent hypokalemia, in those with severe hypokalemia, and in those with hypertension requiring ≥4 antihypertensive medications
- ✓ Older age and diabetes mellitus were associated with a lower likelihood of ARR screening among individuals with hypertension plus hypokalemia
- ✓ Subspecialty care from endocrinology and cardiology were associated with an increased likelihood of ARR screening

Systematic Review & Meta-Analysis | S Chen and others | Cardiovascular outcomes of hyperaldosteronism | 187:6 | S47–S58

Cardiovascular outcomes and all-cause mortality in primary aldosteronism after adrenalectomy or mineralocorticoid receptor antagonist treatment: a meta-analysis

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European Journal of Endocrinology

Abstract

Background: In patients with primary aldosteronism (PA), long-term cardiovascular and mortality outcomes after adrenalectomy vs mineralocorticoid receptor antagonist (MRA) have not been compared yet. We aim to compare the clinical outcomes of these patients after treatment.

Design and Methods: A systematic review and meta-analysis was conducted by searching PubMed, Cochrane library, and Embase from no start date restriction to 18 December 2021. Our composite primary outcomes were long-term all-cause mortality and/or major adverse cardiovascular events (MACE), including coronary artery disease (CAD), stroke, arrhythmia, and congestive heart failure. We adopted the random-effects model and performed subgroup analyses, meta-regression, and trial sequential analysis (TSA).

Results: A total of 9 studies with 8473 adult patients with PA (≥18 years) were enrolled. A lower incidence of composite primary outcomes was observed in the adrenalectomy group (odds ratio (OR): 0.46 (95% CI: 0.38–0.56), $P < 0.001$). We found a lower incidence of all-cause mortality (OR: 0.33 (95% CI: 0.15–0.73), $P = 0.006$) and MACE (OR: 0.55, (95% CI: 0.40–0.74), $P = 0.0001$) in the adrenalectomy group. The incidence of CAD (OR: 0.33 (95% CI: 0.15–0.75), $P = 0.008$), arrhythmias (OR: 0.46 (95% CI: 0.27–0.81), $P = 0.007$), and congestive heart failure (OR: 0.52 (95% CI: 0.33–0.81), $P = 0.004$) was also lower in adrenalectomy group. The metaregression showed patient's age may attenuate the benefits of adrenalectomy on composite primary outcomes (coefficient: 1.084 (95% CI: 1.005–1.169), $P = 0.036$). TSA demonstrated that the accrued sample size and effect size were sufficiently large to draw a solid conclusion, and the advantage of adrenalectomy over MRA was constant with the chronological sequence.

Conclusions: In conclusion, adrenalectomy could be preferred over MRA for patients with PA in reducing the risk of all-cause mortality and/or MACE and should be considered as the treatment of choice. That patients with PA could get less benefit from adrenalectomy as they age warrants further investigation.

European Journal of Endocrinology (2022) **187**, S47–S58

Background: In patients with primary aldosteronism (PA), long-term cardiovascular and mortality outcomes after adrenalectomy vs mineralocorticoid receptor antagonist (MRA) have not been compared yet.

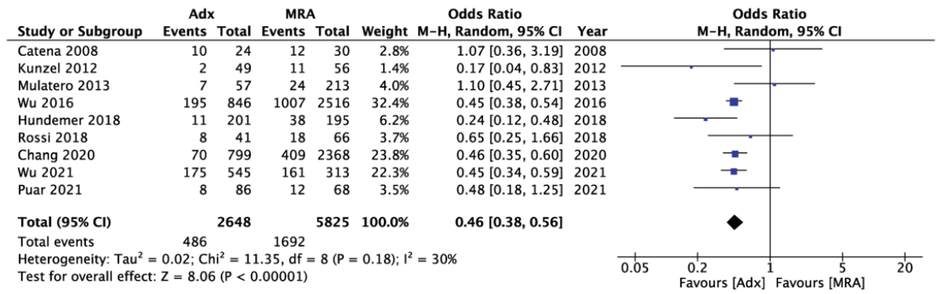
Aim: to provide an updated precise quantitative estimate of the odds ratio (OR) of all-cause mortality and cardiovascular events in patients with PA treated with adrenalectomy or MRA

Methods: A systematic review and meta-analysis was conducted and included all studies that investigated patients with PA who underwent MRA or adrenalectomy treatment, and mortality, cardiovascular or cerebrovascular events after treatment were reported from no start date restriction to 18 December 2021.

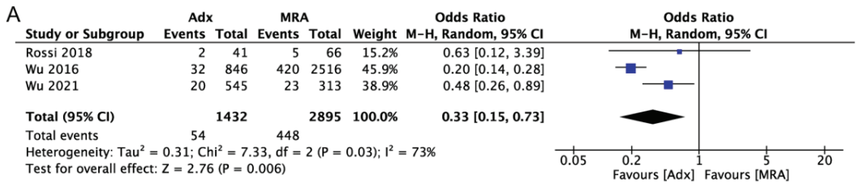
Composite primary outcome was long-term all-cause mortality and/or major adverse cardiovascular events (MACE), including coronary artery disease (CAD), stroke, arrhythmia, and congestive heart failure.

Results composite primary outcomes: Patients who underwent adrenalectomy had better

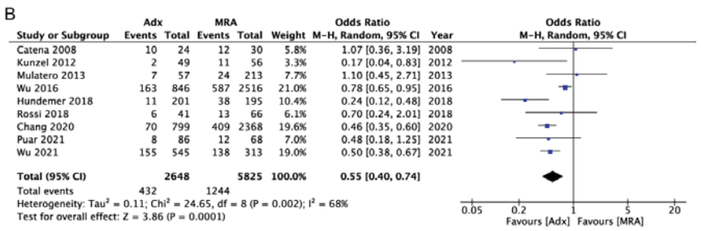
composite primary outcomes (OR: 0.46 (95% CI, 0.38– 0.56), P < 0.001, heterogeneity I2=30%) including lower all-cause mortality and/or MACE rates



Results all-cause mortality: lower all-cause mortality in the adrenalectomy group with the random-effects model (OR: 0.33 (95% CI: 0.15–0.73), P=0.006, heterogeneity I2=73%)



Results on MACE: better outcome in the surgical group with the random-effects model (OR: 0.55, (95% CI: 0.40–0.74), P=0.0001, heterogeneity I2=68%)



Subgroup analyses and meta-regression:

Serum Potassium

When the serum potassium was lower than 3.5 mmol/L (hypokalemia), indicating more advanced disease, the benefits of adrenalectomy over MRA on the composite primary outcomes could be insignificant (n =208, OR: 0.68 (95% CI: 0.33–1.40)). On the contrary, when the serum potassium was higher or equal to 3.5 mmol/L (normokalemia), implying less severe disease, the benefits of adrenalectomy over MRA on the composite primary outcomes became statistically significant (n =1,736, OR: 0.44 (95% CI: 0.35–0.57)).

Patient's age

Patient's age modified the effect of adrenalectomy on composite primary outcomes. In other words, the older the patients are, the less advantage they may receive from adrenalectomy

Patients with unilateral PA that underwent adrenalectomy had lower risk of all-cause mortality

and/or MACE

Strengths:

- ✓ most updated meta-analysis
- ✓ Most enrolled studies were within low-to-moderate risk of bias

Limitations:

- ✓ Most of the included studies did NOT match patients with PA in surgical VS medical groups for the Baseline characteristics
- ✓ Substantial heterogeneities.
- ✓ Baseline characteristics between medically or surgically treated patients were imbalanced in some studies, meaning the selection of patients for adrenalectomy might be biased (Selection Bias)
- ✓ The definitions of MACE varied among studies

Conclusion:

Patients with PA, especially the unilateral subtype, adrenalectomy should be preferred over MRA therapy in reducing all-cause mortality and/or incident MACE.

- ✓ More beneficial effects of adrenalectomy regarding CAD (MI and revascularization), arrhythmia, and congestive heart failure were also observed.
- ✓ That the benefit of surgery waned with advancing age warrants further investigation

Performance of Confirmatory Tests for Diagnosing Primary Aldosteronism: a Systematic Review and Meta-Analysis

Alexander A. Leung, **Christopher J. Symonds**, **Gregory L. Hundemer**, **Paul E. Ronksley**, **Diane L. Lorenzetti**, **Janice L. Pasieka**, **Adrian Harvey** and **Gregory A. Kline**

Originally published 2 Jun 2022 | https://doi.org/10.1161/HYPERTENSIONAHA.122.19377 | Hypertension. 2022;79:1835–1844

Other version(s) of this article

Abstract

Background:

Confirmatory tests are recommended for diagnosing primary aldosteronism, but the supporting evidence is unclear.

Methods:

We searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials. Studies evaluating any guideline-recommended confirmatory test (ie, saline infusion test, salt loading test, fludrocortisone suppression test, and captopril challenge test), compared with a reference standard were included. The Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to assess the risk of bias. Meta-analyses were conducted using hierarchical summary receiver operating characteristic models.

Results:

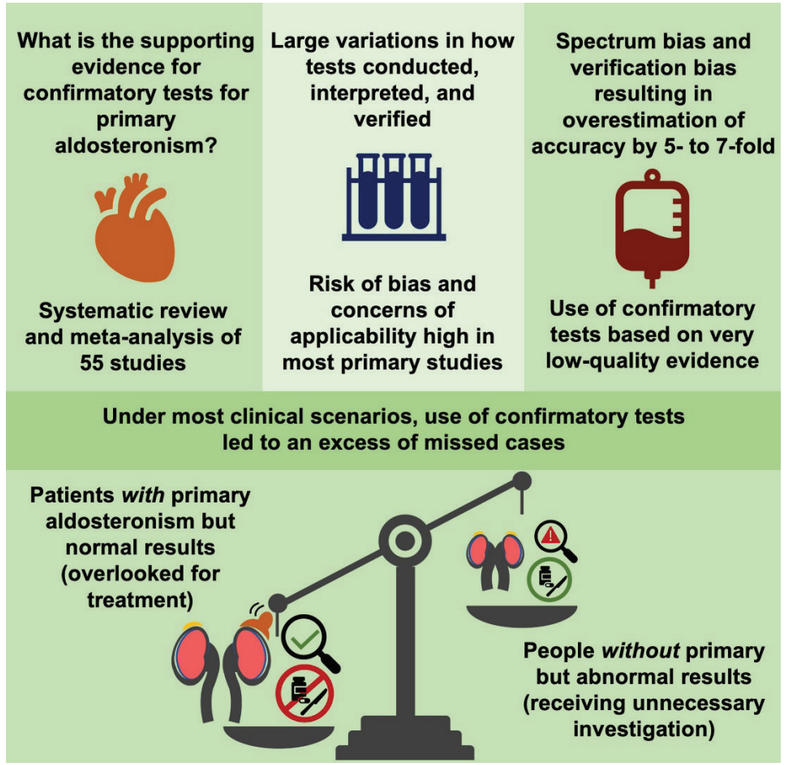
Fifty-five studies were included, comprising 26 studies (3654 participants) for the recumbent saline infusion test, 4 studies (633 participants) for the seated saline infusion test, 2 studies (99 participants) for the salt loading test, 7 studies (386 participants) for the fludrocortisone suppression test, and 25 studies (2585 participants) for the captopril challenge test. Risk of bias was high, affecting more than half of studies, and across all domains. Studies with case-control sampling overestimated accuracy by 7-fold (relative diagnostic odds ratio, 7.26 [95% CI, 2.46–21.43]) and partial verification or use of inconsistent reference standards overestimated accuracy by 5-fold (5.12 [95% CI, 1.48–17.77]). There were large variations in how confirmatory tests were conducted, interpreted, and verified. Under most scenarios, confirmatory testing resulted in an excess of missed cases. The certainty of evidence underlying each test (Grading of Recommendations, Assessment, Development, and Evaluations) was very low.

Conclusions:

Recommendations for confirmatory testing in patients with abnormal screening tests and high probability features of primary aldosteronism are based on very low-quality evidence and their routine use should be reconsidered.

Methods:

- ✓ A systematic review and Meta-Analysis of 55 studies evaluating any guideline-recommended confirmatory test, compared with a reference standard were included.
- ✓ The Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to assess the risk of bias.
- ✓ Meta-analyses were conducted using hierarchical summary receiver operating characteristic models.



Results:

- ✓ Risk of bias was high, affecting more than half of studies, and across all domains.
- ✓ Studies with case-control sampling overestimated accuracy by 7-fold (relative diagnostic odds ratio, 7.26 [95% CI, 2.46–21.43])
- ✓ and partial verification or use of inconsistent reference standards overestimated accuracy by 5-fold (5.12 [95% CI, 1.48–17.77])
- ✓ large variations in how confirmatory tests were conducted, interpreted, and verified
- ✓ Under most scenarios, confirmatory testing resulted in an excess of missed cases
- ✓ The certainty of evidence underlying each test was very low.

Conclusions:

- ✓ There are large variations in how confirmatory tests are conducted, interpreted, and verified.
- ✓ Recommendations for confirmatory testing in patients with abnormal screening tests and high probability features of primary aldosteronism are based on very low-quality evidence and their routine use should be reconsidered

Comparative Study > Eur J Endocrinol. 2022 Jan 6;186(2):265-273. doi: 10.1530/EJE-21-0625.

Enhanced performance of a modified diagnostic test of primary aldosteronism in patients with adrenal adenomas

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Abstract

Objective: Primary aldosteronism (PA) is the commonest cause of endocrine hypertension ranging from 4.6 to 16.6% according to the diagnostic tests employed. The aim of this study was to compare the traditional saline infusion test (SIT) with the modified post-dexamethasone saline infusion test (DSIT) by applying both tests on the same subjects.

Methods: We studied 68 patients (72% hypertensives) with single adrenal adenoma and 55 normotensive controls with normal adrenal imaging. Serum cortisol, aldosterone, and plasma renin concentration (PRC) were measured and the aldosterone-to-renin ratio (ARR) was calculated. Using the mean ± 2 s.d. values from the controls, we defined the upper normal limits for cortisol, aldosterone, and PRC for both the SIT and DSIT.

Results: In the controls, the post-DSIT aldosterone levels and the ARR were approximately two-fold and three-fold lower, respectively, than the corresponding post-SIT values (all P = 0.001) leading to lower cut-offs of aldosterone suppression. Applying these cut-offs to patients with adrenal adenomas, the prevalence of PA was 13.2% following the SIT and 29.4% following the DSIT, respectively. In addition, 54.5% of patients with PA had concomitant autonomous cortisol secretion (ACS). Targeted treatment of PA resulted in resolution of hypertension and restoration of normal secretory aldosterone dynamics.

Conclusions: The DSIT improves the diagnostic accuracy of PA, allowing for the detection of milder forms of PA in patients with adrenal adenomas. This is of particular importance as such patients may be at an increased risk of developing cardiovascular and renal morbidity that could be enhanced in the presence of concomitant ACS.

Aim: to compare the traditional saline infusion test (SIT) with the modified post-dexamethasone saline infusion test (DSIT) by applying both tests on the same subjects.

Methods: 68 patients (72% hypertensives) with single adrenal adenoma and 55 age- and gender matched normotensive controls with normal adrenal imaging. (Between 2011 and 2018)

Measurements: Serum cortisol, aldosterone, and PRC were measured and the ARR was calculated. Using the mean ± 2 s.d. values from the controls, we defined the upper normal limits for cortisol, aldosterone, and PRC for both the SIT and DSIT

Table 3 Comparison of post-SIT and post-DSIT PRC, aldosterone, ACTH, cortisol, and ARR between controls and patients.

	Post-SIT results			Post-DSIT results		
	Controls	Patients	*P*	Controls	Patients	*P*
PRC (mU/L)	11.20 ± 1.10	8.00 ± 0.60	0.006	12.20 ± 1.00	10.20 ± 1.40	0.003
Aldosterone (pmol/L)	77.70 ± 7.50	133.00 ± 23.5	0.65	40.20 ± 1.80	113.50 ± 24.20	0.003
ARR (pmol/mU)	12.60 ± 1.60	22.40 ± 4.20	0.20	4.40 ± 0.30	20.00 ± 5.50	0.001
ACTH (pg/mL)	17.40 ± 1.30	13.30 ± 1.00	0.01	5.30 ± 0.15	5.10 ± 0.05	0.97
Cortisol (nmol/L)	265.30 ± 20.60	247.00 ± 19.80	0.30	24.20 ± 0.91	76.60 ± 13.10	0.001

ACTH, adrenocorticotropin; ARR, aldosterone/PRC ratio; DSIT, dexamethasone saline infusion test; PRC, plasma renin concentrations; SIT, saline infusion test.

Table 4 The PA prevalence using either alone or in different combinations the UNL of basal, post-LDDST, post-SIT and post-DSIT PRC, aldosterone, and ARR.

	UNL	Patients with >UNL	Prevalence of PA (%)
Basal ARR (pmol/mU)	55.5	16/68	23.50
Post-SIT ARR (pmol/mU)	36.6	12/68	17.60
Post-SIT aldosterone (pmol/L)	181	14/68	20.60
Basal ARR (pmol/mU) + Post-SIT aldosterone (pmol/L)	55.5 + 181	9/68	13.20
Post-SIT ARR (pmol/mU) + Post-SIT aldosterone (pmol/L)	36.6 + 181	9/68	13.20
Post-LDDST aldosterone (pmol/L)	609	6/68	9.00
Post-LDDST ARR (pmol/mU)	34.4	20/68	29.40
Post-LDDST aldosterone (pmol/L) + post-LDDST ARR (pmol/mU)	609 + 34.4	6/68	9.00
Post-DSIT ARR (pmol/mU)	9.2	29/68	42.60
Post-DSIT aldosterone (pmol/L)	68	23/68	33.80
Post-DSIT ARR (pmol/mU) + post-DSIT aldosterone (pmol/L)	9.2 + 68	20/68	29.40

Table 5 Pre-operative basal, post-DSIT, and post-SIT values and post-operative basal, post-DSIT, and post-SIT values in 12 patients with PA who underwent adrenalectomy. Data are presented as mean ± S.E.

	Basal values			Post-test					
				Pre-operative			Post-operative		
	Pre-operative	Post-operative	*P*	DSIT	SIT	*P*	DSIT	SIT	*P*
SBP (mmHg)	145.40 ± 5.50	126.90 ± 1.90	0.002						
DBP (mmHg)	87.14 ± 2.90	79.57 ± 1.70	0.001						
K^+ (mmol/L)	3.80 ± 0.15	4.45 ± 0.09	0.001						
Na^+ (mmol/L)	144.50 ± 0.57	142.50 ± 0.52	0.03						
ACTH (ng/L)	15.12 ± 2.50	41.31 ± 7.10	0.0005	6.50 ± 0.70	15.10 ± 2.92	0.007	5.52 ± 0.35	30.71 ± 12.40	0.002
Cortisol (nmol/L)	517.20 ± 57.16	466.90 ± 53.80	0.3	176.60 ± 53.39	342.80 ± 77.35	0.01	25.67 ± 2.16	228.20 ± 53.65	0.003
PRC (mU/L)	8.78 ± 3.02	23.03 ± 6.73	0.005	5.97 ± 0.75	6.56 ± 1.46	0.7	8.19 ± 1.63	13.90 ± 3.35	0.05
Aldosterone (pmol/L)	520.03 ± 90.75	218.30 ± 43.21	0.003	201.50 ± 61.11	412.40 ± 150.70	0.009	34.24 ± 3.13	185.00 ± 120.20	0.007
ARR (pmol/mU)	109.70 ± 25.42	38.54 ± 25.26	0.01	37.49 ± 0.91	72.67 ± 19.6	0.02	5.78 ± 0.94	15.8 0 ± 8.91	0.1
UFC (nmol/24 h)	79.91 ± 16.72	36.56 ± 3.07	0.03						

Results:

In the controls, the post-DSIT aldosterone levels and the ARR were approximately two-fold and three-fold lower, respectively, than the corresponding post-SIT values (all P = 0.001) leading to lower cut-offs of aldosterone suppression. Applying these cut-offs to patients with adrenal adenomas, the prevalence of PA was 13.2% following the SIT and 29.4% following the DSIT, respectively. In addition, 54.5% of patients with PA had concomitant autonomous cortisol secretion (ACS). Targeted treatment of PA resulted in resolution of hypertension and restoration of normal secretory aldosterone dynamics

Conclusion:

Using the cut-offs obtained from controls, the DSIT improves the diagnostic accuracy of PA, allowing for the detection of 'milder' forms of PA in patients with adrenal adenomas

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

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ABSTRACT

BACKGROUND

Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthase is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. In preclinical and phase 1 studies, baxdrostat had 100:1 selectivity for enzyme inhibition, and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels.

METHODS

In this multicenter, placebo-controlled trial, we randomly assigned patients who had treatment-resistant hypertension, with blood pressure of 130/80 mm Hg or higher, and who were receiving stable doses of at least three antihypertensive agents, including a diuretic, to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks or placebo. The primary end point was the change in systolic blood pressure from baseline to week 12 in each baxdrostat group as compared with the placebo group.

RESULTS

A total of 248 patients completed the trial. Dose-dependent changes in systolic blood pressure of −20.3 mm Hg, −17.5 mm Hg, −12.1 mm Hg, and −9.4 mm Hg were observed in the 2-mg, 1-mg, 0.5-mg, and placebo groups, respectively. The difference in the change in systolic blood pressure between the 2-mg group and the placebo group was −11.0 mm Hg (95% confidence interval [CI], −16.4 to −5.5; P<0.001), and the difference in this change between the 1-mg group and the placebo group was −8.1 mm Hg (95% CI, −13.5 to −2.8; P=0.003). No deaths occurred during the trial, no serious adverse events were attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level to 6.0 mmol per liter or greater occurred in 2 patients, but these increases did not recur after withdrawal and reinitiation of the drug.

CONCLUSIONS

Patients with treatment-resistant hypertension who received baxdrostat had dose-related reductions in blood pressure. (Funded by CinCor Pharma; BrigHTN ClinicalTrials.gov number, NCT04519658.)

From CinCor Pharma (M.W.F., Y.-D.H., W.M., C.P.) and Brigham and Women's Hospital, Harvard Medical School (D.L.B.) — both in Boston; CinRx Pharma (M.P., J.I., B.M.) and Medpace (N.A., A.S.) — both in Cincinnati; and the Department of Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London (M.J.B.). Dr. Brown can be contacted at morris.brown@qmul.ac.uk or at Queen Mary University of London, Charterhouse Sq., London EC1M 6BQ, United Kingdom.

*The BrigHTN Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Silent pheochromocytoma and paraganglioma: Systematic review and proposed definitions for standardized terminology

Georgiana Constantinescu[1,2,3*], Cristina Preda[2], Victor Constantinescu[4], Timo Siepmann[3,5], Stefan R. Bornstein[1,6,7], Jacques W. M. Lenders[1,8], Graeme Eisenhofer[1,9] and Christina Pamporaki[1*]

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Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors with heterogeneous clinical presentations and potential lethal outcomes. The diagnosis is based on clinical suspicion, biochemical testing, imaging and histopathological confirmation. Increasingly widespread use of imaging studies and surveillance of patients at risk of PPGL due to a hereditary background or a previous tumor is leading to the diagnosis of these tumors at an early stage. This has resulted in an increasing use of the term "silent" PPGL. This term and other variants are now commonly found in the literature without any clear or unified definition. Among the various terms, "clinically silent" is often used to describe the lack of signs and symptoms associated with catecholamine excess. Confusion arises when these and other terms are used to define the tumors according to their ability to synthesize and/or release catecholamines in relation to biochemical test results. In such cases the term "silent" and other variants are often inappropriately and misleadingly used. In the present analysis we provide an overview of the literature and propose standardized terminology in an attempt at harmonization to facilitate scientific communication.

Background: Widespread use of anatomic imaging and expansion of surveillance programs for patients at risk of PPGL due to genetic predisposition has led to increased diagnosis of 'silent PPGL'. This term and other variants are now commonly found in the literature without any clear or unified definition.

Aim: to provide an overview of the literature and propose standardized terminology in an attempt at harmonization to facilitate scientific communication.

Methods:Two researchers independently searched PubMed for articles published in English from 1980 to 2021. The following search terms were used pheochromocytoma or paraganglioma AND silent or nonfunctioning.

Results: Review of literature revealed that:

-the term "silent" was used in a highly variable fashion according to widely differing circumstances

-The term "clinically silent" was appropriately used to describe the absence of symptoms of catecholamine excess

-However, definitions according to the ability of tumors to synthesize and/or release catecholamines were inconsistently used according to biochemical test results. In some cases, biochemical test results were not even mentioned.

TABLE 1 Patient characteristics.

Total Number	**157**
Female, n (%)*	58 (48%)
Age at initial diagnosis, years (SD)	45 (±14.7)
Location	
Extra-adrenal	62% (74/157)
Adrenal	38% (60/157)
Head and Neck	15% (25/157)
Diagnostic setting	
Incidentaloma	62% (97/157)
Abdominal complaints	48.3% (45/93)
Imaging performed for non-specific complaints	51.7% (48/93)
Surveillance/Follow up	36% (57/157)
Specific signs and symptoms	2% (3/157)
Tumor composition (reported in 29 cases)	
Solid	31% (9/29)
Cystic	31% (9/29)
Hemorrhagic and/or necrosis	38% (11/29)
Maximal tumor diameter (cm) (reported in 81 cases)	5.5 (0.25-25)#
Metastatic disease (reported in 68 cases)	25% (17/68)
Plasma free metanephrines (reported in 45 cases)	
Results within the normal range	89% (40/45)
Elevated results	11% (5/45)
Urinary metanephrines (reported in 57 cases)	
Results within the normal range	75.4% (43/57)
Elevated results	24.5% (14/57)

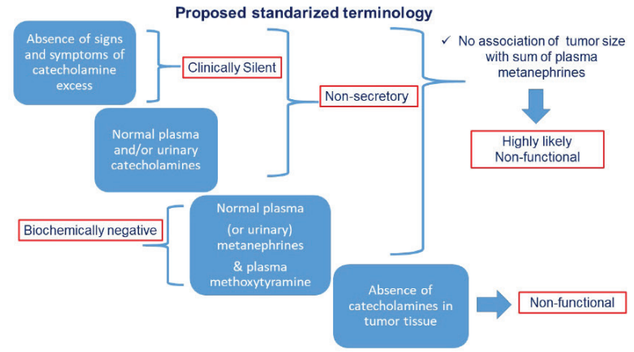

FIGURE 4
Chart flow with proposed standardized terminology for various types of "silent" PPGLs.

Summary of proposed Nomenclature

"Clinically silent" PPGLs are those characterized by the absence of signs and symptoms associated with catecholamine excess**.**

"Non-secretory" tumors are those with absence of clear catecholamine secretory activity, often adrenergic and presenting with normal plasma and/or urinary catecholamines over multiple sampling time points.

"Biochemically negative PPGLs are those characterized by plasma or urinary metanephrines below the upper cut-offs of reference intervals. If only catecholamines are measured the same term may be used with clarification

"Non-functional" tumors are those with absent catecholamine synthesis as determined from measurements of catecholamines in the tumor tissue, assessments of tumor tissue tyrosine hydroxylase or large size in association with negative results for plasma or urinary metanephrines.

Conclusion:

- ✓ "clinically silent" and "non-secretory" tumors are usually functional, and pre-surgical treatment with a-adrenoceptor blockade is essential to minimize intraoperative hemodynamic instability
- ✓ In patients presenting with negative biochemical test result, the reliability of measurements should be verified
- ✓ A negative biochemical test result cannot alone exclude functionality, especially for smaller PPGLs (<2 cm)
- ✓ Unless, functionality is correctly excluded, pre-operative blockade of adrenoreceptors remains important.

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Clinical Research Article

Recurrent Disease in Patients With Sporadic Pheochromocytoma and Paraganglioma

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Abstract

Context: Long-term follow-up has been recommended for patients with pheochromocytoma or paraganglioma (PPGL) due to potential for recurrent disease. However, the need to follow patients with sporadic PPGL has recently become controversial.

Objective: To investigate the prevalence of recurrence among patients with sporadic compared with hereditary PPGL and to identify predictors of recurrence for sporadic disease.

Methods: This multicenter study included retrospective data from 1127 patients with PPGL. In addition to sex and age at primary tumor diagnosis, clinical information included location, size, and catecholamine phenotype of primary tumors, genetic test results, and subsequent development of recurrent and/or metastatic disease. Patients with sporadic PPGL were defined as those with negative genetic test results.

Results: Prevalence of recurrence among patients with sporadic PPGL (14.7%) was lower ($P < 0.001$) than for patients with pathogenic variants that activate pseudohypoxia pathways (47.5%), but similar to those with variants that activate kinase pathways (14.9%). Among patients with sporadic recurrent PPGL, 29.1% and 17.7% were respectively diagnosed at least 10 and 15 years after first diagnosis. Multivariable regression analysis showed that a noradrenergic/dopaminergic phenotype (HR 2.73; 95% CI, 1.553-4.802; $P < 0.001$), larger size (HR 1.82; 95% CI, 1.113-2.962; $P = 0.017$) and extra-adrenal location (HR 1.79; 95% CI, 1.002-3.187; $P = 0.049$) of primary tumors were independent predictors of recurrence in sporadic PPGL.

Conclusion: Patients with sporadic PPGL require long-term follow-up, as supported by the 14.7% prevalence of recurrent disease, including recurrences at more than 10 years after first diagnosis. The nature of follow-up could be individualized according to tumor size, location, and biochemical phenotype.

Objective: To investigate the prevalence of recurrence among patients with sporadic compared with hereditary PPGL and to identify predictors of recurrence for sporadic disease.

Methods: A multicenter study including retrospective data from 1127 patients with PPGL. Patients with sporadic PPGL were defined as those with negative genetic test results.

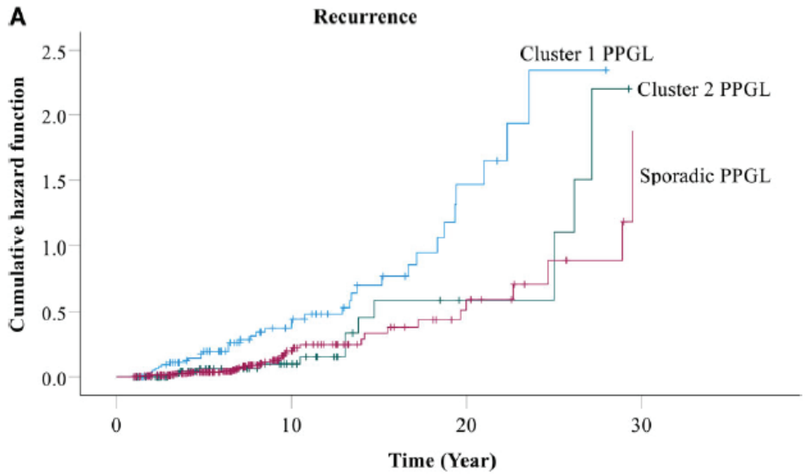
Results:

Prevalence of recurrence among patients with sporadic PPGL (14.7%) was lower (P<0.001) than for patients with pathogenic variants that activate pseudohypoxia pathways (47.5%), but similar to those with variants that activate kinase pathways (14.9%).

- ✓ Among patients with sporadic recurrent PPGL, 29.1% and 17.7% were respectively diagnosed at least 10 and 15 years after first diagnosis.
- ✓ a noradrenergic/dopaminergic phenotype. larger size and extra-adrenal location of primary tumors were independent predictors of recurrence in sporadic PPGL

Table 1. Clinical characteristics of patients enrolled at the tertiary clinical centers

	Cluster 1 PPGL	Cluster 2 PPGL	Sporadic PPGL
Number of patients	80	94	224
Age (years) at first diagnosis, median (IQR)	28.7 (20.5-43.8)	46.8 (31.9-59)[a]	52.9 (42.5-62.4)[a,b]
Males	47.5% (38/80)	41.5% (39/94)	44.6% (109/224)
Location			
Adrenal	53.8% (43/80)	98.9% (93/94)[a]	94.2% (211/224)[a]
Extra-adrenal	46.3% (37/80)	1.1% (1/94)[a]	5.8% (13/224)[a]
Biochemical phenotype			
Adrenergic	2.9% (2/68)	91.4% (74/81)[a]	62.8% (113/180)[a,b]
Noradrenergic/dopaminergic	97.1% (66/68)	8.6% (7/81)[a]	37.2% (67/180)[a,b]
Size of primary tumor (cm), medians (IQR)	3.6 (2.6-4.8)	3.5 (2.4-5.0)	4.1 (2.8-5.8)
With recurrent disease	47.5% (38/80)	14.9% (14/94)[a]	14.7% (33/224)[a]
Local recurrence/new tumor only	22.5% (18/80)	13.8% (13/94)	6.7% (15/224)[a]
With metastasis	25% (20/80)	1.1% (1/94)[a]	8% (18/224)[a,b]
Follow-up (years), median (IQR)	8.7 (5.2-16.3)	5.3 (3.1-9.8)[a]	7 (4.6-10)[a]



Conclusion:

- ✓ Patients with sporadic PPGL require long-term follow-up as they are at significant risk of recurrent disease, even 10 years after initial tumor diagnosis.
- ✓ Specific characteristics, such as tumor size and biochemical tumor phenotype could be used to guide individualized follow-up strategies for patients with sporadic PPGL.

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Clinical Research Article

Clinical Research Article

Cytoreductive Surgery of the Primary Tumor in Metastatic Adrenocortical Carcinoma: Impact on Patients' Survival

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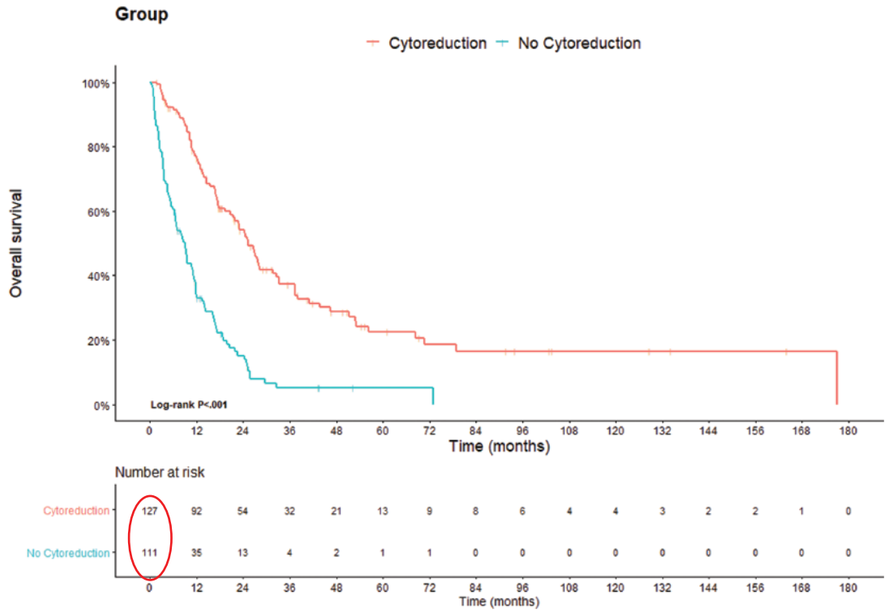
Aim: To analyze the impact of cytoreductive surgery of the primary tumor in patients with metastatic ACC.

Methods:

A multicentric, retrospective paired cohort study of 239 patients comparing the overall survival (OS) in patients with metastatic ACC who were treated either with or without cytoreductive surgery.

- ✓ The main outcome was OS, determined from the date of diagnosis until death or until last follow-up for living patients.

- ✓ Mean follow-up was 67 months



Results:

- ✓ Patients in the no-CR group had greater risk of death than did patients in the CR group (hazard ratio [HR] = 3.18;95% CI, 2.34-4.32).
- ✓ Independent predictors of survival included age (HR = 1.02; 95% CI, 1.00-1.03), hormone excess (HR = 2.56; 95% CI, 1.66-3.92), and local metastasis therapy (HR = 0.41; 95% CI, 0.47-0.65).

Conclusion:

Cytoreductive surgery of the primary tumor in patients with metastatic ACC is associated with prolonged survival.

Targeting 11–Beta Hydroxylase With [131I]IMAZA: A Novel Approach for the Treatment of Advanced Adrenocortical Carcinoma

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Abstract

Context: Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with limited treatment options. Theranostic approaches with adrenal specific radiotracers hold promise for improved diagnostics and treatment.

Objective: Here, we report a new theranostic approach to advanced ACC applying (R)-1-[1-(4-[123I]iodophenyl)ethyl]-1H-imidazole-5-carboxylic acid azetidinyl amide ([123I]IMAZA) for diagnostic imaging and [131I]IMAZA for radionuclide therapy.

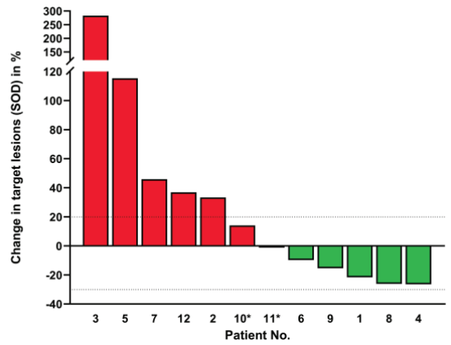
Methods: Sixty-nine patients with nonresectable, metastatic ACCs were screened using a diagnostic [123I]IMAZA scan. Patients with significant uptake in all tumoral lesions were offered treatment with [131I]IMAZA. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), and adverse effects were assessed by Common Toxicity Criteria (version 5.0).

Results: After screening, 13 patients were treated with a median of 25.7 GBq [131I]IMAZA (range 18.1-30.7 GBq). Five individuals received a second treatment course. Best response was a decrease in the RECIST target lesions of -26% in 2 patients. Five patients with disease stabilization experienced a median progression-free survival of 14.3 months (range 8.3-21.9). Median overall survival in all patients was 14.1 months (4.0-56.5) after therapy. Treatment was well tolerated, in other words no severe toxicities (CTCAE grade ≥3) were observed.

Conclusion: In patients with advanced ACC refractory to standard therapeutic regimens, [131I]IMAZA treatment was associated with disease stabilization and nonsignificant tumor size reduction in a significant patient fraction and only limited toxicities. High [131I]IMAZA-uptake in tumor lesions was observed in 38.5% of patients with advanced ACC, rendering [131I] IMAZA a potential treatment option in a limited, well-defined patient fraction. Further clinical trials will be necessary to evaluate the full potential of this novel theranostic approach.

Table 1. Characteristics of 13 patients with advanced ACC

Patient	Sex	Age	Hormone production	Sites of tumor manifestation	Time from surgery of ACC to IMAZA therapy (months)	Previous surgical treatments (n)	External radiation therapy	Previous systemic therapies (n)	Systemic therapies	Mitotane within 4 months before 1st IMAZA therapy	Subsequent systemic therapy
1	f	73	Cor, Est, And	LR, LI, LU, LN, ST	56	1	No	2	M, EDP	No	—
2	m	72	Est,	LU, SK	18	1	Yes	2	S, M	Yes[a] 0.2	—
3	f	58	Cor, Ald	LR, LU, ST	33	2	Yes	3	EDP, M, S	Yes[a] 14.8	G/C
4	f	73	Cor	LR, LU	20	1	Yes	1	M	No	S, Entrectinib
5	f	66	Cor	LU, ST	35	2	Yes	1	M	Yes [a]19.1	M
6	f	61	unknown	LR, LI, LU	19	2	No	3	EDP-M, T, G/C	No	S, EDP
7	f	31	Cor, And	LI, LU, LN, ST	25	1	Yes	4	EDP, M, G/C, S,	No	n/a
8	f	53	Cor	LU, LN, ST	174	9	Yes	5	M, S, C/E, G/C, IMTO	Yes[a] 19.2	Nivolumab, M, Endoxan/ MTX
9	f	72	no	LR, LU, ST	44	1	No	5	M, C/E, D, N, G/C,	No	S
10	f	55	unknown	LR, LU, LI, LN, SP	61	2	No	3	M, C, G/C,	Yes[b]	unknown
11	f	35	unknown	LI, LN, ST	37	3	Yes	4	M, D+C, adriamycin+etoposide, G/C,	No	unknown
12	f	70	Cor, Ald	LI, SK	13	1	Yes	3	M, G/C, IMTO,	Yes[a] 16.4	—
13	f	65	Cor, And	LR, LI, ST	41	2	No	1	M	No	unknown



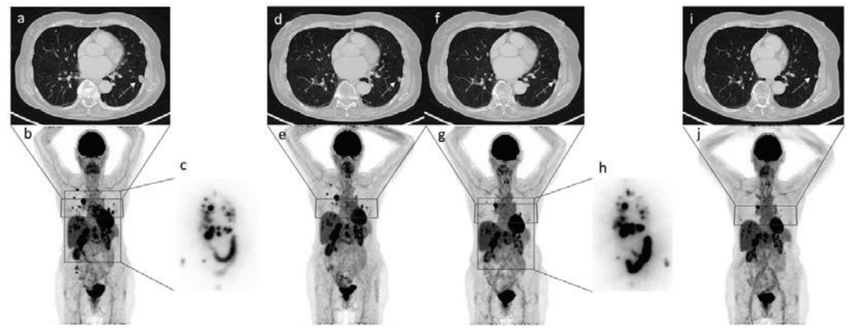


Figure 4. Response assessment of patient 1 in FDG-PET/CT scans after 2 treatments with [131I]IMAZA. Axial CT slices of a metastasis in the lungs at baseline (A), after 2.5, 5. and 14 months (D, F, I, white arrows). FDG-PET maximum intensity projection (MIP) at baseline (B), after 2.5, 5, and 14 months (E, G, J). Post-therapeutic whole-body scintigraphy 4 days after first therapy (C) and 5 days after second therapy (H) showing concordant tracer accumulation to FDG-PET/CT.

Limitations:

- ✓ Treatment and follow-up were not completely standardized
- ✓ Restaging was not always consistent at 3 months intervals
- ✓ The study group was heterogeneous as it consisted mostly of patients with late-stage disease that had received different previous treatments at different centers.
- ✓ the number of treatments and therefore the cumulative activity of [131I]IMAZA differed in this study.

Conclusion:

- ✓ In patients with advanced ACC refractory to standard therapeutic regimens, [131I]IMAZA treatment was associated with disease stabilization and nonsignificant tumor size reduction in a significant patient fraction and only limited toxicities.
- ✓ High [131I]IMAZA-uptake in tumor lesions was observed in 38.5% of patients with advanced ACC, rendering [131I] IMAZA a potential treatment option in a limited, well-defined patient fraction

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Overview of the 2022 WHO Classification of Adrenal Cortical Tumors

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Abstract

The new WHO classification of adrenal cortical proliferations reflects translational advances in the fields of endocrine pathology, oncology and molecular biology. By adopting a question–answer framework, this review highlights advances in knowledge of histological features, ancillary studies, and associated genetic findings that increase the understanding of the adrenal cortex pathologies that are now reflected in the 2022 WHO classification. The pathological correlates of adrenal cortical proliferations include diffuse adrenal cortical hyperplasia, adrenal cortical nodular disease, adrenal cortical adenomas and adrenal cortical carcinomas. Understanding germline susceptibility and the clonal-neoplastic nature of individual adrenal cortical nodules in primary bilateral macronodular adrenal cortical disease, and recognition of the clonal-neoplastic nature of incidentally discovered non-functional subcentimeter benign adrenal cortical nodules has led to redefining the spectrum of adrenal cortical nodular disease. As a consequence, the most significant nomenclature change in the field of adrenal cortical pathology involves the refined classification of adrenal cortical nodular disease which now includes (a) sporadic nodular adrenocortical disease, (b) bilateral micronodular adrenal cortical disease, and (c) bilateral macronodular adrenal cortical disease (formerly known primary bilateral macronodular adrenal cortical hyperplasia). This group of clinicopathological entities are reflected in functional adrenal cortical pathologies. Aldosterone producing cortical lesions can be unifocal or multifocal, and may be bilateral with no imaging-detected nodule(s). Furthermore, not all grossly or radiologically identified adrenal cortical lesions may be the source of aldosterone excess. For this reason, the new WHO classification endorses the nomenclature of the HISTALDO classification which uses CYP11B2 immunohistochemistry to identify functional sites of aldosterone production to help predict the risk of bilateral disease in primary aldosteronism. Adrenal cortical carcinomas are subtyped based on their morphological features to include conventional, oncocytic, myxoid, and sarcomatoid subtypes. Although the classic histopathologic criteria for diagnosing adrenal cortical carcinomas have not changed, the 2022 WHO classification underscores the diagnostic and prognostic impact of angioinvasion (vascular invasion) in these tumors. Microscopic angioinvasion is defined as tumor cells invading through a vessel wall and forming a thrombus/fibrin-tumor complex or intravascular tumor cells admixed with platelet thrombus/fibrin. In addition to well-established Weiss and modified Weiss scoring systems, the new WHO classification also expands on the use of other multiparameter diagnostic algorithms (reticulin algorithm, Lin–Weiss–Bisceglia system, and Helsinki scoring system) to assist the workup of adrenal cortical neoplasms in adults. Accordingly, conventional carcinomas can be assessed using all multiparameter diagnostic schemes, whereas oncocytic neoplasms can be assessed using the Lin–Weiss–Bisceglia system, reticulin algorithm and Helsinki scoring system. Pediatric adrenal cortical neoplasms are assessed using the Wieneke system. Most adult adrenal cortical carcinomas show > 5 mitoses per 10 mm^2 and > 5% Ki67. The 2022 WHO classification places an emphasis on an accurate assessment of tumor proliferation rate using both the mitotic count (mitoses per 10 mm^2) and Ki67 labeling index which play an essential role in the dynamic risk stratification of affected patients. Low grade carcinomas have mitotic rate of ≤ 20 mitoses per 10 mm^2, whereas high-grade carcinomas show > 20 mitoses per 10 mm^2. Ki67-based tumor grading has not been endorsed in the new WHO classification, since the proliferation indices are continuous variables rather than being static thresholds in tumor biology. This new WHO classification emphasizes the role of diagnostic and predictive biomarkers in the workup of adrenal cortical neoplasms. Confirmation of the adrenal cortical origin of a tumor remains a critical requirement when dealing with non-functional lesions in the adrenal gland which may be mistaken for a primary adrenal cortical neoplasm. While SF1 is the most reliable biomarker in the confirmation of adrenal cortical origin, paranuclear IGF2 expression is a useful biomarker

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Annals of Internal Medicine

ORIGINAL RESEARCH

Mortality and Morbidity in Mild Primary Hyperparathyroidism: Results From a 10-Year Prospective Randomized Controlled Trial of Parathyroidectomy Versus Observation

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Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder associated with increased risk for fractures, cardiovascular disease, kidney disease, and cancer and increased mortality. In mild PHPT with modest hypercalcemia and without known morbidities, parathyroidectomy (PTX) is debated because no long-term randomized trials have been performed.

Objective: To examine the effect of PTX on mild PHPT with regard to mortality (primary end point) and key morbidities (secondary end point).

Design: Prospective randomized controlled trial. (ClinicalTrials.gov: NCT00522028)

Setting: Eight Scandinavian referral centers.

Patients: From 1998 to 2005, 191 patients with mild PHPT were included.

Intervention: Ninety-five patients were randomly assigned to PTX, and 96 were assigned to observation without intervention (OBS).

Measurements: Date and causes of death were obtained from the Swedish and Norwegian Cause of Death Registries 10 years after randomization and after an extended observation period lasting until 2018. Morbidity events were prospectively registered annually.

Results: After 10 years, 15 patients had died (8 in the PTX group and 7 in the OBS group). Within the extended observation period, 44 deaths occurred, which were evenly distributed between groups (24 in the PTX group and 20 in the OBS group). A total of 101 morbidity events (cardiovascular events, cerebrovascular events, cancer, peripheral fractures, and renal stones) were also similarly distributed between groups (52 in the PTX group and 49 in the OBS group). During the study, a total of 16 vertebral fractures occurred in 14 patients (7 in each group).

Limitation: During the study period, 23 patients in the PTX group and 27 in the OBS group withdrew.

Conclusion: Parathyroidectomy does not appear to reduce morbidity or mortality in mild PHPT. Thus, no evidence of adverse effects of observation was seen for at least a decade with respect to mortality, fractures, cancer, cardiovascular and cerebrovascular events, or renal morbidities.

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* Drs. Pretorius and Lundstam share first authorship.
† Drs. Hellström and Bollerslev share last authorship.

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in nonhospitalized patients and has been associated with increased mortality (1, 2). For decades, whether asymptomatic, mild PHPT increases overall mortality and risk for cardiovascular disease (CVD) has been debated (2–4). Increased arterial stiffness, left ventricular hypertrophy, and endothelial dysfunction are related to PHPT in general and have also been found in mild PHPT (5–7). Observational studies have shown associations between PHPT and the metabolic syndrome (8, 9). Hypercalcemia is a risk factor for myocardial infarction, both independently and after adjustment for biomarkers of the metabolic syndrome (10). Calcium deposition in the vasculature and other soft tissues is strongly linked to cardiovascular events, but the atherogenic effect of PHPT is not well described (11). In addition, epidemiologic studies have shown increased risk for cancer, which can affect long-term mortality (12).

Parathyroidectomy (PTX), which normalizes calcium and parathyroid hormone (PTH) levels (13), is the curative treatment and is recommended for patients with severe hypercalcemia or overt symptoms. However, it is unclear whether PTX benefits patients in terms of life expectancy or cardiovascular morbidity (1, 14), and for mild PHPT without organ manifestations, the long-term effect of PTX is still debated (15). Several observational or case–control studies have reported increased fracture risk in PHPT (16, 17), including vertebral fractures (VFs) (17–19), and reduced risk for fractures after PTX (16, 20, 21). However, many of these studies were not restricted to mild PHPT (16–18, 20). Recommendations for the management of mild PHPT have been addressed in proceedings from several international

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Daily Low-Dose Aspirin and Risk of Serious Falls and Fractures in Healthy Older People

A Substudy of the ASPREE Randomized Clinical Trial

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IMPORTANCE Falls and fractures are frequent and deleterious to the health of older people. Aspirin has been reported to reduce bone fragility and slow bone loss.

OBJECTIVE To determine if daily low-dose aspirin (100 mg) reduces the risk of fractures or serious falls (fall-related hospital presentations) in healthy older men and women.

DESIGN, SETTING, AND PARTICIPANTS This substudy of a double-blind, randomized, placebo-controlled trial studied older adult men and women in 16 major sites across southeastern Australia. The ASPREE-FRACTURE substudy was conducted as part of the Australian component of the ASPREE trial. Between 2010 and 2014 healthy (free of cardiovascular disease, dementia or physical disability), community-dwelling volunteers aged 70 years or older were recruited to participate in the ASPREE trial. Potentially eligible participants were identified by medical practitioners and trial personnel and were then sent a letter of invitation to participate. Interested participants were screened for suitability. Eligible participants with medical practitioner authorization and adherent to a 4-week run-in medication trial were randomized. Data were analyzed from October 17, 2019, to August 31, 2022.

INTERVENTIONS Participants in the intervention group received a daily dose of oral 100 mg enteric-coated (low-dose) aspirin. The control group received a daily identical enteric-coated placebo tablet.

MAIN OUTCOMES AND MEASURES The primary outcome of ASPREE-FRACTURE was the occurrence of any fracture. The secondary outcome was serious fall resulting in hospital presentation.

RESULTS In total, 16 703 people with a median (IQR) age of 74 (72-78) years were recruited, and 9179 (55.0%) were women. There were 8322 intervention participants and 8381 control participants included in the primary and secondary outcome analysis of 2865 fractures and 1688 serious falls over the median follow-up of 4.6 years. While there was no difference in the risk of first fracture between the intervention and control participants (hazard ratio, 0.97; 95% CI, 0.87-1.06; $P = .50$), aspirin was associated with a higher risk of serious falls (total falls 884 vs 804; incidence rate ratio, 1.17; 95% CI, 1.03-1.33; $P = .01$). Results remained unchanged in analyses that adjusted for covariates known to influence fracture and fall risk.

CONCLUSIONS AND RELEVANCE In this substudy of a randomized clinical trial, the failure of low-dose aspirin to reduce the risk of fractures while increasing the risk of serious falls adds to evidence that this agent provides little favorable benefit in a healthy, White older adult population.

TRIAL REGISTRATION This substudy is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000347561).

Supplemental content

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ORIGINAL ARTICLE

Baseline bone turnover marker levels can predict change in bone mineral density during antiresorptive treatment in osteoporotic patients: the Copenhagen bone turnover marker study

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Abstract

Summary Anti-resorptive osteoporosis treatment might be more effective in patients with high bone turnover. In this registry study including clinical data, high pre-treatment bone turnover measured with biochemical markers was correlated with higher bone mineral density increases. Bone turnover markers may be useful tools to identify patients benefitting most from anti-resorptive treatment.

Introduction In randomized, controlled trials of bisphosphonates, high pre-treatment levels of bone turnover markers (BTM) were associated with a larger increase in bone mineral density (BMD). The purpose of this study was to examine this correlation in a real-world setting.

Methods In this registry-based cohort study of osteoporosis patients ($n = 158$) receiving antiresorptive therapy, the association between pre-treatment levels of plasma C-telopeptide of type I Collagen (CTX) and/or N-terminal propeptide of type I procollagen (PINP) and change in bone mineral density (BMD) at lumbar spine, total hip, and femoral neck upon treatment was examined. Patients were grouped according to their pre-treatment BTM levels, defined as values above and below the geometric mean for premenopausal women.

Results Pre-treatment CTX correlated with annual increase in total hip BMD, where patients with CTX above the geometric mean experienced a larger annual increase in BMD ($p = 0.008$) than patients with CTX below the geometric mean. The numerical pre-treatment level of CTX showed a similar correlation at all three skeletal sites (total hip ($p = 0.03$), femoral neck ($p = 0.04$), and lumbar spine ($p = 0.0003$)). A similar association was found for PINP where pre-treatment levels of PINP above the geometric mean correlated with a larger annual increase in BMD for total hip ($p = 0.02$) and lumbar spine ($p = 0.006$).

Conclusion Measurement of pre-treatment BTM levels predicts osteoporosis patients' response to antiresorptive treatment. Patients with high pre-treatment levels of CTX and/or PINP benefit more from antiresorptive treatment with larger increases in BMD than patients with lower pre-treatment levels.

Keywords Anti-resorptive treatment · Bisphosphonate · Bone turnover marker · CTX · Osteoporosis · PINP

Introduction

Osteoporosis is a disease characterized by decreased bone mass, deteriorating bone microarchitecture, and increased fracture risk and the incidence is increasing worldwide [1]. Denmark has one of the highest prevalences and it is estimated that 40% of women above 50 years have osteoporosis [2]. Bone loss after age 30–40 years is a consequence of the imbalance in bone remodeling at the basic multicellular unit (BMU) level where the resorbed bone volume is incompletely replaced during the bone formation phase of the remodeling cycle [3]. This is further aggravated after menopause where reduced estrogen production results in increased bone resorption at the individual BMU together with an increase in the activation frequency of BMUs [4, 5]

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ORIGINAL ARTICLE

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Bone Marrow Adiposity in Models of Radiation- and Aging-Related Bone Loss Is Dependent on Cellular Senescence

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ABSTRACT

Oxidative stress-induced reactive oxygen species, DNA damage, apoptosis, and cellular senescence have been associated with reduced osteoprogenitors in a reciprocal fashion to bone marrow adipocyte tissue (BMAT); however, a direct (causal) link between cellular senescence and BMAT is still elusive. Accumulation of senescent cells occur in naturally aged and in focally radiated bone tissue, but despite amelioration of age- and radiation-associated bone loss after senescent cell clearance, molecular events that precede BMAT accrual are largely unknown. Here we show by RNA-Sequencing data that BMAT-related genes were the most upregulated gene subset in radiated bones of C57BL/6 mice. Using focal radiation as a model to understand age-associated changes in bone, we performed a longitudinal assessment of cellular senescence and BMAT. Using real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR), RNA in situ hybridization of *p21* transcripts and histological assessment of telomere dysfunction as a marker of senescence, we observed an increase in senescent cell burden of bone cells from day 1 postradiation, without the presence of BMAT. BMAT was significantly elevated in radiated bones at day 7, confirming the qRT-PCR data in which most BMAT-related genes were elevated by day 7, and the trend continued until day 42 postradiation. Similarly, elevation in BMAT-related genes was observed in bones of aged mice. The senolytic cocktail of Dasatinib (D) plus Quercetin (Q) (ie, D + Q), which clears senescent cells, reduced BMAT in aged and radiated bones. MicroRNAs (miRNAs or miRs) linked with senescence marker *p21* were downregulated in radiated and aged bones, whereas miR-27a, a miR that is associated with increased BMAT, was elevated both in radiated and aged bones. D + Q downregulated miR-27a in radiated bones at 42 days postradiation. Overall, our study provides evidence that BMAT occurrence in oxidatively stressed bone environments, such as radiation and aging, is induced following a common pathway and is dependent on the presence of senescent cells. © 2022 American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: AGING; BONE MARROW ADIPOSITY; CELLULAR SENESCENCE; P21; RADIATION

Introduction

Mechanisms underlying bone deterioration during physiological and pathological conditions have been a focus of study for many years. The balance between bone-forming osteoblasts and bone-resorbing osteoclasts maintains normal bone coupling, and marked deviation from this well-orchestrated mechanism causes either osteoporosis (due to comparatively more osteoclast function) or osteopetrosis (due to relatively increased bone formation with no or minimal bone resorption).[1] In common physiological conditions, such as aging or postmenopausal status, osteoporosis is the more prevalent condition and also associated with increased marrow fat or bone marrow adipose tissue (BMAT).[2] BMAT in humans has been shown throughout the lifespan with no potential side effects on bone architecture up to a certain age; but with aging, disease, and postmenopausal status, the presence of marrow fat appears to be inversely proportional to bone mass.[3] BMAT has also been used as a predictor of bone loss, showing a direct correlation to osteoporosis.[4]

An increase in BMAT has been associated with depleted resident mesenchymal stem cells (MSCs) during aging and disease, because MSCs are a common precursor to both adipocytes and

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REVIEW

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Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop

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ABSTRACT

The last international guidelines on the evaluation and management of primary hyperparathyroidism (PHPT) were published in 2014. Research since that time has led to new insights into epidemiology, pathophysiology, diagnosis, measurements, genetics, outcomes, presentations, new imaging modalities, target and other organ systems, pregnancy, evaluation, and management. Advances in all these areas are demonstrated by the reference list in which the majority of listings were published after the last set of guidelines. It was thus, timely to convene an international group of over 50 experts to review these advances in our knowledge. Four Task Forces considered: 1. Epidemiology, Pathophysiology, and Genetics; 2. Classical and Nonclassical Features; 3. Surgical Aspects; and 4. Management. For Task Force 4 on the Management of PHPT, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology addressed surgical management of asymptomatic PHPT and non-surgical medical management of PHPT. The findings of this systematic review that applied GRADE methods to randomized trials are published as part of this series. Task Force 4 also reviewed a much larger body of new knowledge from observations studies that did not specifically fit the criteria of GRADE methodology. The full reports of these 4 Task Forces immediately follow this summary statement. Distilling the essence of all deliberations of all Task Force reports and Methodological reviews, we offer, in this summary statement, evidence-based recommendations and guidelines for the evaluation and management of PHPT. Different from the conclusions of the last workshop, these deliberations have led to revisions of renal guidelines and more evidence for the other recommendations. The accompanying papers present an in-depth discussion of topics summarized in this report. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PTH/VIT D/FGF23; ENDOCRINE PATHWAYS; PARATHYROID-RELATED DISORDERS

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Summary of Recommendations

The following recommendations are intended to guide practice and are not intended to be used for the development of reimbursement policies. With the exception of reference 4, which was based, in part, upon Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) analysis, all others either did not address issues of diagnsois, progosis, or therapy and/or the available data were evaluated without using GRADE methods (1–3, 5–9). The GRADE approach was applied only to the systematic reviews but not to the process of moving from evidence to recommendations. The approach to GRADE methodology is summarized in Methods.

1. **How should primary hyperparathyroidism (PHPT) be diagnosed?**
   - 1.1. Hypercalcemic PHPT: an elevated serum calcium adjusted for albumin in the presence of an elevated or inappropriately normal intact parathyroid hormone (PTH) (utilizing either a second or third generation assay) on two occasions at least 2 weeks apart.
   - 1.2. What is the differential diagnosis of hypercalcemia and elevated levels of PTH?
     - 1.2.1. Familial hypocalciuric hypercalcemia (FHH) may be suspected in younger individuals with a urinary calcium /creatinine clearance ratio <0.01 and/or those with a family history of hypercalcemia.
     - 1.2.2. Thiazide diuretics and lithium (see text)
     - 1.2.3. Ectopic secretion of PTH (very rare)
   - 1.3. Normocalcemic PHPT: normal adjusted total calcium and normal ionized calcium levels along with elevated intact PTH (utilizing either a second or third generation assay) on at least two occasions over 3–6 months after all alternative causes for secondary hyperparathyroidism have been ruled out.

2. **What are the clinical phenotypes of PHPT?**
   - 2.1. Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis
   - 2.2. Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation:
     - 2.2.1. with target organ involvement
     - 2.2.2. without target organ involvement
   - 2.3. Normocalcemic PHPT: Skeletal or renal complications may or may not exist in those whose presentation fits this definition.

3. **How should patients with PHPT be evaluated?**
   - 3.1. Biochemical: Measure adjusted total serum calcium (ionized if normocalcemic PHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine
   - 3.2. Skeletal: Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays); trabecular bone score (TBS) if available
   - 3.3. Renal: Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones; imaging for nephrolithiasis/nephrocalcinosis
   - 3.4. Nonclassical manifestations (neurocognitive, quality of life, cardiovascular): there are no data to support routine evaluation for these putative manifestations
   - 3.5. Genetic: genetic evaluation should be considered for patients <30 years old, those with multigland disease by history or imaging, and/or those with a family history of hypercalcemia and/or a syndromic disease

4. **What are the indications and role for surgical management of asymptomatic PHPT? (GRADEd Recommendation)**

In patients with asymptomatic PHPT, we recommend surgery to cure the disease (strong recommendation/high quality evidence).

5. **For which patients is parathyroidectomy an option?**
   - 5.1. Although parathyroidectomy is an option for all patients, with concurrence of the patient and the physician and if there are no contraindications, the panel recommends surgery in all those in whom one or more of the following is present (including those who are asymptomatic):
     - 5.1.1. Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal or
     - 5.1.2. Skeletal involvement:
       - 5.1.2.1. A fracture by VFA or vertebral X-ray or
       - 5.1.2.2. Bone mineral density (BMD) by *T*-score ≤ −2.5 at any site or
     - 5.1.3. Renal involvement:
       - 5.1.3.1. eGFR or creatinine clearance <60 mL/min
       - 5.1.3.2. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality
       - 5.1.3.3. Hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men) or.
     - 5.1.4. Age <50 years (no other indications are necessary; age <50 years is a sufficient indication)
   - 5.2. Surgery should be performed by an experienced parathyroid surgeon
   - 5.3. Surgery cannot be recommended to improve neurocognitive function, quality of life, and/or cardiovascular indices because the evidence is inconclusive.

6. **What is the role of preoperative imaging and intraoperative PTH measurements? Panel recommendations**
   - 6.1. Preoperative imaging is not recommended for diagnostic purposes.
   - 6.2. Preoperative imaging is recommended for those who are going to have parathyroid surgery in order to locate the abnormal parathyroid gland(s).
   - 6.3. Preoperative imaging modalities include high resolution neck ultrasound, technetium-99 m-sestamibi subtraction scintigraphy, and contrast-enhanced four-dimensional (4D) computed tomography (CT).
   - 6.4. With successful preoperative imaging, selective parathyroidectomy, combined or not with intraoperative PTH monitoring, achieves high cure rates in the hands of experienced surgeons.
   - 6.5. Advantages of the selective approach include: shorter operative time, less tissue scarring, less risk to surrounding structures, and reduced hospital costs. No head-to-head comparisons are available.

7. **What is the role of nonsurgical, medical management of PHPT?**

Patients with PHPT who do not meet guidelines for parathyroidectomy (see 5 above) can be followed without pharmacological intervention. For those who choose not to have surgery, but who meet specific guidelines (e.g., calcium or bone mineral density), medical options are available as recommended by the Panel.

   - 7.1. Cinacalcet to reduce the serum calcium concentration into the normal range.
   - 7.2. Calcium intake/supplementation should follow the Institute of Medicine nutritional guidelines: 800 mg/day for women <50 and men <70 years old; 1000 mg/day for women >50 and men >70 years old.
   - 7.3. Vitamin D supplementation: the panel recommends levels of 25OHD >30 ng/mL and < the upper limit of normal for the laboratory reference range (eg, <50 ng/mL).
   - 7.4. Alendronate or denosumab can be used to increase bone density if there are no contraindications.
   - 7.5. Estrogen has been shown to increase BMD. Its effect on the reduction of serum calcium is inconsistent.
   - 7.6. Raloxifene cannot be recommended because the data are insufficient to reach any conclusions.

8. **How should normocalcemic PHPT be managed? Panel recommendations**
   - 8.1. Because of limited data, we cannot recommend guidelines for surgery in normocalcemic PHPT at this time.

9. **What monitoring plan is recommended in patients who do not undergo PTX? Panel recommendations**
   - 9.1. Serum calcium and 25OHD concentrations: annually. PTH levels can also be measured, as clinically indicated.
   - 9.2. Skeletal:
     - 9.2.1. Three-site DXA every 1 or 2 years unless the BMD is normal (see text)
     - 9.2.2. Vertebral X-ray, VFA, or TBS if clinically indicated
   - 9.3. Renal:
     - 9.3.1. Creatinine clearance (preferred over eGFR), annually
     - 9.3.2. Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated
     - 9.3.3. 24-Hour urine for calcium, if clinically indicated.

10. **When should surgery be recommended in those who are being monitored? Panel recommendations**
    - 10.1. Serum calcium becomes consistently >1 mg/dL (0.25 mmol/L) above the upper limit of normal.
    - 10.2. A low trauma fracture.
    - 10.3. A kidney stone.
    - 10.4. A significant reduction in BMD to a *T*-score ≤ −2.5 at any site.
    - 10.5. A significant reduction in creatinine clearance.

11. **In patients who meet surgical guidelines but do not have surgery what non-surgical approaches are reasonable? Panel recommendations.**
    - 11.1. Calcium intake should be consistent with nutritional guidelines
    - 11.2. Vitamin D should be maintained >30 ng/mL. Cautious supplementation with parental forms of vitamin D (eg, cholecalciferol) is advised, as clinically indicated.
    - 11.3. When indicated to reduce the serum calcium, cinacalcet is effective
    - 11.4. When indicated to increase BMD, bisphosphonates or denosumab can be used
    - 11.5. When indicated to lower the serum calcium and to increase BMD bisphosphonates or denosumab in combination with cinacalcet can be considered.

12. **How should PHPT be managed during pregnancy? Panel recommendations**
    - 12.1. Mild cases should be managed by maintaining good hydration and monitoring calcium levels
    - 12.2. Bisphosphonates and denosumab should not be used
    - 12.3. Data are very limited on use of cinacalcet
    - 12.4. Consider surgery in the second trimester for patients with serum calcium >11.0 mg/dL and for whom surgery is not contraindicated
    - 12.5. Preoperative imaging should be limited to ultrasound
    - 12.6. If surgery is deferred, the neonate should be closely monitored for hypocalcemia
    - 12.7. If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy.

Introduction

The last international guidelines on the evaluation and management of primary hyperparathyroidism (PHPT) were published in 2014.[1] Since that time, advances in our understanding of the disease in its many clinical, pathophysiological, and therapeutic aspects have led to new insights into this common endocrine disorder. The new information is documented by the references a majority of which have been published since 2013. These new insights encompass epidemiology, outcomes, genetics, physiology, pathophysiology, presentations, new imaging modalities, target and other organ systems diagnosis, measurements, pregnancy, evaluation, and management. To incorporate these advances into guidelines for its evaluation and management, an international group was convened. It consisted of over 50 experts whose knowledge of this disease is broad, deep, and current. In addition, some aspects of this comprehensive review lent themselves to systematic reviews using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.[2] Altogether, the efforts of the workshop led to seven manuscripts, along with an editorial, that constitute this series. Four papers provide an evidence-based review of the Epidemiology, Pathophysiology, and Genetics of PHPT[3]; Classical and Nonclassical Manifestations[4]; Surgical Aspects[5]; and Management[6]; as well as one document following GRADE methodology for surgical and medical management of PHPT.[7] A paper describing the methodology of the evidence-based reviews is also included in this series.[8]

The summary statement maintains or revises the guidelines, based upon the expanded database of evidence currently available. In this report, we present a distillation of this information as a summary statement of conclusions and guidelines for the

TASK FORCE

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Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop

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ABSTRACT

This clinical practice guideline addresses the prevention, diagnosis, and management of hypoparathyroidism (HypoPT) and provides evidence-based recommendations. The HypoPT task forces included four teams with a total of 50 international experts including representatives from the sponsoring societies. A methodologist (GG) and his team supported the taskforces and conducted the systematic reviews. A formal process following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and the systematic reviews provided the structure for seven of the guideline recommendations. The task force used a less structured approach based on narrative reviews for 20 non-GRADEd recommendations. Clinicians may consider postsurgical HypoPT permanent if it persists for >12 months after surgery. To predict which patients will not develop permanent postsurgical HypoPT, we recommend evaluating serum PTH within 12 to 24 hours post total thyroidectomy (strong recommendation, moderate quality evidence). PTH > 10 pg/mL (1.05 pmol/L) virtually excludes long-term HypoPT. In individuals with nonsurgical HypoPT, genetic testing may be helpful in the presence of a positive family history of nonsurgical HypoPT, in the presence of syndromic features, or in individuals younger than 40 years. HypoPT can be associated with complications, including nephrocalcinosis, nephrolithiasis, renal insufficiency, cataracts, seizures, cardiac arrhythmias, ischemic heart disease, depression, and an increased risk of infection. Minimizing complications of HypoPT requires careful evaluation and close monitoring of laboratory indices. In patients with chronic HypoPT, the panel suggests conventional therapy with calcium and active vitamin D metabolites as first-line therapy (weak recommendation, low-quality evidence). When conventional therapy is deemed unsatisfactory, the panel considers the use of PTH. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PTH/VIT D/FGF23; CELL/TISSUE SIGNALING—ENDOCRINE PATHWAYS; PARATHYROID-RELATED DISORDERS; DISORDERS OF CALCIUM/PHOSPHATE METABOLISM

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SUMMARY OF RECOMMENDATIONS

The following recommendations are intended to guide practice and are not intended to be used for the development of reimbursement policies.

1. **How should chronic HypoPT be diagnosed? (un-GRADEd recommendation, i.e., not based on Grading of Recommendations, Assessment, Development and Evaluation)**
   1.1. Hypocalcemia (low ionized serum calcium or total serum calcium adjusted for albumin) in the presence of an undetectable, low or inappropriately normal intact PTH (utilizing either a second- or third-generation assay) on two occasions at least 2 weeks apart confirms the diagnosis.
   1.2. Additional abnormalities caused by low PTH that support the diagnosis: Elevation in serum phosphorus, reductions in 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and elevations in the urinary fractional excretion of calcium.
   1.3. In patients with postsurgical HypoPT, panel members regard the condition as permanent if the HypoPT persists >12 months after surgery.
2. **How can the risks of chronic postsurgical HypoPT be minimized? (un-GRADEd recommendation)**
   The panel proposes avoiding accidental parathyroidectomy as well as intraoperative parathyroid autotransplantation during neck surgery and only utilizing this in the presence of inadvertent parathyroidectomy.
3. **What is the value of determining serum calcium and PTH post-thyroidectomy to predict future permanent postsurgical HypoPT? (GRADEd recommendation)**
   We recommend using PTH measurements early (12–24 hours) after total thyroidectomy for predicting which patients will not develop permanent postsurgical HypoPT
   (strong recommendation, moderate quality evidence).
   Comments: If PTH values are >10 pg/mL (1.05 pmol/L) 12–24 hours post surgery, the development of permanent HypoPT is unlikely, and therefore there is no long-term need for treatment with active vitamin D and calcium supplements above the recommended daily allowance. Many patients with PTH values <10 pg/mL (1.05 pmol/L) 12–24 hours post surgery may still recover from temporary HypoPT.
   What is the role of genetic testing in the diagnosis and evaluation of chronic HypoPT? (un-GRADEd recommendations)
   3.1. In patients with nonsurgical HypoPT who have a positive family history of nonsurgical HypoPT, present with syndromic features, or are younger than 40 years, panel members undertake genetic testing.
   3.2. In patients with nonsurgical HypoPT who have other clinical features of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED), panel members undertake genetic testing for *autoimmune regulator (AIRE) gene* variants.
   3.3. Panel members avoid the designation of "autoimmune HypoPT" for patients who do not have APECED because there are no definitive diagnostic tests for polygenic autoimmune HypoPT.
4. **What are the most common symptoms and complications of chronic HypoPT reported in the literature? (GRADEd recommendation)**
   Observational studies comparing patients with HypoPT to controls with normal parathyroid function have identified the following complications associated with HypoPT (percentages represent the median among all studies): cataract (17%), infection (11%), nephrocalcinosis/nephrolithiasis (15%), renal insufficiency (12%), seizures (11%), depression (12%), ischemic heart disease (7%), and arrhythmias (7%).
5. **What is the optimal monitoring strategy for chronic HypoPT?**
   5.1. (Systematic Current Practice Survey)*

	New patient	Follow-up for stable patients**
Serum creatinine, estimated glomerular filtration rate (eGFR), calcium (either ionized or albumin-adjusted), magnesium, phosphorus	√	Every 3–12 months
25-hydroxyvitamin D	√	Every 6–12 months
24-hour urine for creatinine and calcium	√	Every 6–24 months

*These are graded as low-quality recommendations based on the practice of 70% of the respondents completing this at least 70% of the time.
**For unstable patients: Frequently measure serum calcium and phosphorus as clinically indicated.

   The panel also proposes the following (non-survey-based):
   5.2. Complete a baseline assessment for the presence of renal calcification or stones with renal imaging.
   5.3. Monitor serum calcium (ionized or albumin-adjusted) within several days of a significant change in medical treatment.
6. **How are patients with HypoPT managed? (GRADEd recommendations)**
   6.1. In patients with chronic HypoPT, the panel suggests conventional therapy as first-line therapy (weak recommendation, low-quality evidence).
   Comment: When conventional therapy is deemed unsatisfactory, the panel considers the use of parathyroid hormone.

un-GRADEd PANEL RECOMMENDATIONS FOR MANAGEMENT

In patients with HypoPT, the panel proposes:
6.2. Treat with calcium and an active vitamin D analogue, with the goal of raising serum calcium to the target range, i.e., the lower half of the normal reference range or just below the normal reference range. At this time, it is not clear how to best balance the doses of calcium relative to those of the active vitamin D analogue.
6.3. Alleviate symptomatic hypocalcemia while avoiding hypercalciuria.
6.4. Avoid hypercalciuria when titrating calcium and active vitamin D analogue therapy, aiming for low normal plasma calcium levels.

The panel proposes achieving a 24-hour urinary calcium level of <6.25 mmol/24 hours or 250 mg/24 hours for adult women and <7.5 mmol/24 hours or 300 mg/24 hours for adult men. Data from the general population have shown a relationship between hypercalciuria and the development of renal stones—such data do not exist in patients with HypoPT. However, panel members infer that hypercalciuria may be associated with a higher risk of renal stones in patients with HypoPT as well and thus seek to avoid hypercalciuria.

6.5. Avoid hyperphosphatemia. Panel members prescribe calcium supplements with meals to serve as phosphate binders, implement a low-phosphate diet in adults if needed, and judiciously use active vitamin D analogue therapy. No data are available on the use of other types of phosphate binders in HypoPT. Hyperphosphatemia may be associated with an increased incidence of ectopic calcification, but currently there is no evidence of this in HypoPT.

6.6. Treat to normalize plasma magnesium levels. Magnesium supplements can be used as tolerated by the patient.

6.7. Aim to achieve a 25-hydroxyvitamin D (25(OH)D) level in the normal reference range (75–125 nmol/L).

6.8. Consider treating hypercalciuria with thiazide diuretics in conjunction with a low-sodium diet with careful monitoring of blood pressure (BP), serum magnesium, potassium, and renal function.

6.9. Consider PTH replacement therapy in patients who are not adequately controlled on conventional therapy. Inadequate control is considered to be any one of the following: (i) symptomatic hypocalcemia, (ii) hyperphosphatemia, (iii) renal insufficiency, (iv) hypercalciuria, or (v) poor quality of life.

6.10. Individuals with poor compliance or malabsorption or who are intolerant of large doses of calcium and active vitamin D may also benefit from PTH therapy. Individuals requiring high doses of conventional therapy (i.e., calcium >2 g/day or active vitamin D > 2 μg/day) may also benefit from PTH therapy.

7. **un-GRADEd CONSENSUS MANAGEMENT RECOMMENDATIONS DURING PREGNANCY AND LACTATION**
In pregnant women with HypoPT, the panel proposes the following:

7.1. Aim to achieve serum calcium (ionized or albumin adjusted) in the mid to low normal reference range throughout pregnancy.

7.2. Aim to achieve serum phosphorus, magnesium, and 25OHD levels in the normal reference range.

7.3. Closely monitor serum calcium (ionized or albumin-adjusted) every 3–4 weeks during pregnancy and lactation, with increased frequency in the months preceding and following parturition as well as in the presence of symptoms of hypercalcemia or hypocalcemia.

7.4. Work closely with the obstetrician to optimize pregnancy outcomes. Coordinate with the pediatric team to ensure appropriate postnatal monitoring for transient neonatal hypo- or hypercalcemia.

7.5. Avoid using thiazide diuretics and PTH or PTH analogues during pregnancy.

Introduction

An international task force on hypoparathyroidism (HypoPT) was convened to review new findings and insights and to develop updated evidence-based guidelines on the diagnosis, evaluation, and management of HypoPT. Over the past 5 years, significant advances have been made in our understanding of the multisystem complications of HypoPT and, in particular, the skeletal and renal manifestations of this disorder. New treatment options are being developed with improvements in our understanding of calcium homeostasis and pharmacological approaches to intervention.

The international task force, consisting of 50 international experts in HypoPT and general endocrinologists from 15 countries, met over 24 months to review key issues pertaining to the diagnosis, prevention, evaluation, and management of HypoPT.

A methods team, using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, completed four systematic reviews addressing the diagnosis, management, and complications of HypoPT. In addition, narrative reviews were completed regarding the epidemiology, financial burden, and etiology of HypoPT. A survey of panel members informed the recommendations for monitoring. The diagnosis and risk factors for the development of postsurgical HypoPT were reviewed with the development of strategies to help minimize postsurgical HypoPT. The role of genetic testing in determining the underlying etiology of HypoPT was highlighted and an approach to establishing the diagnosis presented. Calcium homeostasis in pregnancy and lactation was also reviewed with the development of strategies to optimize maternal and fetal outcomes. The risks and benefits of PTH replacement therapy in comparison to conventional therapy were evaluated with application of the GRADE methodology.

These new international guidelines on HypoPT have been endorsed by over 65 professional medical and surgical societies as well as patient advocacy organizations interested in advancing the care of individuals with HypoPT. These guidelines also highlight key areas for future research in HypoPT.

Methodology

A detailed discussion of the methodology is presented in an accompanying report.[1]

To summarize, four international task forces were formed with international experts in HypoPT addressing the following areas of review, with each task force publishing its findings as a separate manuscript in this issue of the JBMR.

- Epidemiology and Financial Burden (cochairs BLC and NG)
- Etiologies and Pathophysiology (cochairs JLP and DMS)
- Genetics and Diagnosis (cochairs MM and MLB)
- Evaluation and Management (cochairs AAK and LR)

Systematic reviews and narrative reviews were completed to inform the recommendations. GRADEd recommendations followed a structured process that included framing questions in patient/intervention/comparator/outcome format; conducting a systematic evidence search and associated summary, specifying values and preferences, and classifying and presenting recommendations as strong or weak with the corresponding quality of evidence. A strong recommendation was made when the desirable effects were much greater than undesirable effects or vice versa and is worded as "we recommend."[2,3]

A weak recommendation was made if there was low certainty of evidence or a close balance between desirable and

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RESEARCH ARTICLE

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Multiple Vertebral Fractures After Denosumab Discontinuation: FREEDOM and FREEDOM Extension Trials Additional Post Hoc Analyses

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ABSTRACT

It is uncertain whether the risk of vertebral fracture (VF) and multiple vertebral fractures (MVFs; ≥2 VFs) after denosumab (DMAb) discontinuation is related to treatment duration. A prior analysis of Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) and FREEDOM Extension trials did not find a relationship with DMAb duration and may have underreported MVF incidence because it included women who did not have radiographs. In this post hoc exploratory analysis, the crude incidence and annualized rates of VF and MVF were determined in patients with ≥7 months' follow-up and ≥1 spine radiograph after discontinuing placebo or DMAb. A multivariate analysis was performed to identify predictors of MVF. Clinical characteristics of patients with ≥4 VFs were explored. This analysis included women who discontinued after placebo ($n = 327$) or DMAb either from FREEDOM or FREEDOM Extension ($n = 425$). The DMAb discontinuation group was subsequently dichotomized by treatment duration: short-term (≤3 years; $n = 262$) and long-term (>3 years; $n = 213$) treatment. For any VF, exposure-adjusted annualized rates per 100 patient-years (95% confidence interval [CI]) were 9.4 (95% CI, 6.4–13.4) for placebo, 6.7 (95% CI, 4.2–10.1) for short-term DMAb, and 10.7 (95% CI, 7.4–15) for long-term DMAb. Annualized rates for MVF were 3.6 (95% CI, 1.9–6.3), 2.9 (95% CI, 1.4–5.4), and 7.5 (95% CI, 4.8–11.1), respectively. Annualized rates for ≥4 VFs were 0.59 (95% CI, 0.1–2.1), 0.57 (95% CI, 0.1–2.1), and 3.34 (95% CI, 1.7–6.0), respectively. In a multivariate regression model, DMAb duration was significantly associated with MVF risk (odds ratio 3.0; 95% CI, 1.4–6.5). Of 15 patients with ≥4 VFs, 13 had DMAb exposure (mean ± standard deviation [SD], 4.9 ± 2.2 years). The risk of MVF after DMAb discontinuation increases with increased duration of DMAb treatment. Patients transitioning off DMAb after 3 years may warrant more frequent administration of zoledronic acid or another bisphosphonate to maintain bone turnover and bone mineral density (BMD) and prevent MVF. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEOPOROSIS; THERAPEUTICS; ANTIRESORPTIVES; CLINICAL TRIALS; FRACTURE PREVENTION

Introduction

Discontinuation of denosumab (DMAb) results in a rapid increase in the biochemical indices of bone turnover, which exceed baseline values within 9 months and remain elevated for up to 30 months after the last dose of DMAb.[1-3] In association, bone mineral density (BMD) is also lost rapidly and returns to baseline or below baseline levels within 1–2 years.[1-4] The risks of a vertebral fracture (VF) and multiple vertebral fractures (MVFs; defined as ≥2 VFs) also increase rapidly over 6–18 months after the last dose of DMAb.[3,5-8] A prior post hoc study of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) and FREEDOM Extension trials estimated the risks of new or worsening VF after DMAb discontinuation.[5] In that study, the annualized rate of MVF was higher after discontinuing DMAb (4.2%) compared with discontinuing placebo (Pbo; 3.2%). Furthermore, of the women who had any VF, the proportion who developed MVF was higher in those who discontinued DMAb versus Pbo (61% versus 39%).

Several lines of evidence suggest that a longer DMAb duration is associated with a higher rebound bone turnover and higher bone loss after discontinuation.[4,7,9-12] Longer DMAb treatment

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RESEARCH ARTICLE JBMR®

Diabetes Mellitus and the Benefit of Antiresorptive Therapy on Fracture Risk

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ABSTRACT

Type 2 diabetes (T2D) is associated with increased risk of fractures. However, it is unclear whether current osteoporosis treatments reduce fractures in individuals with diabetes. The aim of the study was to determine whether presence of T2D influences the efficacy of antiresorptive treatment for osteoporosis using the Foundation for the National Institutes of Health (FNIH)–American Society for Bone and Mineral Research (ASBMR)–Study to Advance Bone Mineral Density (BMD) as a Regulatory Endpoint (SABRE) cohort, which includes individual patient data from randomized trials of osteoporosis therapies. In this study we included 96,385 subjects, 6.8% of whom had T2D, from nine bisphosphonate trials, two selective estrogen receptor modulator (SERM) trials, two trials of menopausal hormone therapy, one denosumab trial, and one odanacatib trial. We used Cox regression to obtain the treatment hazard ratio (HR) for incident nonvertebral, hip, and all fractures and logistic regression to obtain the treatment odds ratio (OR) for incident morphometric vertebral fractures, separately for T2D and non-DM. We used linear regression to estimate the effect of treatment on 2-year change in BMD ($n = 49{,}099$) and 3-month to 12-month change in bone turnover markers ($n = 12{,}701$) by diabetes status. In all analyses, we assessed the interaction between treatment and diabetes status. In pooled analyses of all 15 trials, we found that diabetes did not impact treatment efficacy, with similar reductions in vertebral, nonvertebral, all, and hip fractures, increases in total hip and femoral neck BMD, and reductions in serum C-terminal cross-linking telopeptide (CTX), urinary *N*-telopeptide of type I collagen/creatinine (NTX/Cr) and procollagen type 1 N propeptide (P1NP) (all interactions $p > 0.05$). We found similar results for the pooled analysis of bisphosphonate trials. However, when we considered trials individually, we found a few interactions within individual studies between diabetes status and the effects of denosumab and odanacatib on fracture risk, change in BMD or bone turnover markers (BTMs). In sum, these results provide strong evidence that bisphosphonates and most licensed antiresorptive drugs are effective at reducing fracture risk and increasing BMD irrespective of diabetes status. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: BIOCHEMICAL MARKERS OF BONE REMODELING; DXA; CLINICAL TRIALS; OSTEOPOROSIS; ANTIRESORPTIVES

Introduction

Increased fracture risk is a recognized complication of type 2 diabetes mellitus (T2D) with a 33% increase in hip fracture and a 19% increase in nonvertebral fracture risk compared to those without diabetes, based on a recent meta-analysis.[1] The increased risk of fracture in T2D is associated with normal or slightly increased bone mineral density (BMD)[2] and normal or low bone turnover markers (BTMs).[3]

Low bone turnover in patients with T2D could result in reduced efficacy of anti-resorptive drugs. However, few studies have examined the efficacy of anti-osteoporosis medications in T2D. Indeed, there have been no clinical trials of anti-resorptive drugs in T2D specifically. Many large trials of anti-resorptive drugs in postmenopausal osteoporosis have included patients with T2D. However, only a few post hoc analyses have utilized the data from these trials to assess the efficacy of anti-resorptive treatments in those with T2D. In the Fracture Intervention Trial

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ORIGINAL ARTICLE JBMR®

Association Between Muscle Mass Determined by D_3-Creatine Dilution and Incident Fractures in a Prospective Cohort Study of Older Men

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ABSTRACT

The relation between a novel measure of total skeletal muscle mass (assessed by D_3-creatine dilution [D_3Cr]) and incident fracture is unknown. In 1363 men (mean age 84.2 years), we determined D_3Cr muscle mass; Fracture Risk Assessment Tool (FRAX) 10-year probability of hip and major osteoporotic (hip, humerus, vertebral, forearm) fracture; and femoral neck bone mineral density (BMD) (by dual-energy X-ray absorptiometry [DXA]). Incident fractures were centrally adjudicated by review of radiology reports over 4.6 years. Correlations adjusted for weight and height were calculated between femoral neck BMD and D_3Cr muscle mass. Across quartiles of D_3Cr muscle mass/weight, proportional hazards models calculated hazard ratios (HRs) for any ($n = 180$); nonspine ($n = 153$); major osteoporotic fracture ($n = 85$); and hip fracture ($n = 40$) after adjustment for age, femoral neck BMD, recurrent fall history, and FRAX probability. Models were then adjusted to evaluate the mediating influence of physical performance (walking speed, chair stands, and grip strength). D_3Cr muscle mass was weakly correlated with femoral BMD ($r = 0.10$, $p < 0.001$). Compared to men in the highest quartile, those in the lowest quartile of D_3Cr muscle mass/weight had an increased risk of any clinical fracture (HR 1.8; 95% confidence interval [CI], 1.1–2.8); nonspine fracture (HR 1.8; 95% CI, 1.1–3.0), major osteoporotic fracture (HR 2.3; 95% CI, 1.2–4.6), and hip fracture (HR 5.9; 95% CI, 1.6–21.1). Results were attenuated after adjustment for physical performance, but associations remained borderline significant for hip and major osteoporotic fractures ($p \geq 0.05$ to 0.10). Low D_3Cr muscle mass/weight is associated with a markedly high risk of hip and potentially other fractures in older men; this association is partially mediated by physical performance. © 2022 American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: skeletal muscle; sarcopenia; systems biology - bone interactors; bone-muscle interactions; epidemiology; practice/policy-related issues; fracture risk assessment

Introduction

Low muscle mass likely predisposes individuals to fracture for several reasons. First, bone remodels in response to muscle force. Thus, lower muscle strength (presumably due to lower muscle mass) should result in weaker bones and therefore more fractures.[1] Second, lower muscle mass also increases fall risk, whereby smaller, weaker muscles are associated with worse muscle function and physical performance, which should in turn result in more falls and fractures. There is compelling evidence that poor muscle *function* (quantified as strength and power) and impaired physical performance (gait speed, chair stands) are strongly related to risk of hip, vertebral, and other

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ORIGINAL ARTICLE

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Osteomalacia as a Complication of Intravenous Iron Infusion: A Systematic Review of Case Reports

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ABSTRACT

Randomized control trials (RCTs) have shown that certain intravenous iron preparations can induce high levels of fibroblast growth factor 23 (FGF-23) and persistent hypophosphatemia. Repeated iron infusions may lead to prolonged hypophosphatemia and osteomalacia events not captured by RCTs. Several previous case reports have described skeletal adverse effects after repeated iron infusions. To characterize these effects, we conducted a systematic review of case reports. MEDLINE, Embase, Web of Science, and Cochrane databases were searched in March 2021. We selected case reports of patients ≥16 years old. Study quality was assessed using the tool from Murad and colleagues. We report the results in a narrative summary. We identified 28 case reports, reporting 30 cases. Ages ranged from 28 to 80 years (median 50 years). Most patients ($n = 18$) received ferric carboxymaltose (FCM), whereas 8 received saccharated ferric oxide (SFO) and 3 received iron polymaltose (IPM). All but 2 cases had more than five infusions (range 2 to 198, median 17). The lowest phosphate levels ranged from 0.16 to 0.77 mmol/L (median 0.36 mmol/L). Intact FGF-23 (iFGF-23) was high when measured. Serum 25OH vitamin D was low in 10 of 21 cases measured and $1,25(OH)_2$ vitamin D in 12 of 18. Alkaline phosphatase was high in 18 of 22 cases. Bone or muscle pain was reported in 28 of the 30 cases. Twenty patients had pseudofractures, 9 had fractures, and 6 patients had both. All 15 available bone scans showed focal isotope uptake. Case reports tend to report severe cases, so potential reporting bias should be considered. Osteomalacia is a potential complication of repeated iron infusion, especially in patients with gastrointestinal disorders receiving prolonged therapy. Pain and fractures or pseudofractures are common clinical findings, associated with low phosphate, high iFGF-23, high alkaline phosphatase, and abnormal isotope bone scan. Discontinuing or switching the iron formulation was an effective intervention in most cases. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: IRON INFUSION; FGF-23; HYPOPHOSPHATEMIA; OSTEOMALACIA; FRACTURES

Introduction

Phosphate is one of the main components of the mineral bone compartment, and adequate serum levels are required for normal mineralization. Severe malnutrition and increased renal loss of phosphate are common causes of chronic phosphate depletion. Persistent hypophosphatemia leads to osteomalacia, a lack of mineralization of bone matrix.[1,2] Clinically, osteomalacia presents as muscle weakness and bone pain, biochemically as elevated alkaline phosphatase activity (ALP), and radiologically as Looser's zones (pseudofracture).[2]

Physiologically, fibroblast growth factor 23 (FGF-23) is a key positive regulator of renal phosphate excretion in response to elevated phosphate levels. Inappropriately elevated intact FGF-23 activity is associated with phosphate depletion and adverse bone and neuromuscular outcomes.[2] Hypophosphatemic diseases, such as X-linked hypophosphatemia and tumor-induced osteomalacia, are characterized by high levels of FGF-23. In X-linked hypophosphatemia, FGF-23 is not properly regulated because of a mutation on the PHEX gene, resulting in FGF-23 overactivity. Conversely, in the rare tumor-induced osteomalacia, FGF-23—and occasionally other phosphatonins—is produced by mesenchymal phosphaturic tumors. In recent randomized controlled trials of up to 5 weeks duration, intravenous iron therapy with ferric carboxymaltose (FCM) was shown to increase the concentration of circulating intact FGF23 (iFGF-

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RESEARCH

Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial

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ABSTRACT

OBJECTIVE
To investigate whether vitamin D and marine derived long chain omega 3 fatty acids reduce autoimmune disease risk.

DESIGN
Vitamin D and omega 3 trial (VITAL), a nationwide, randomized, double blind, placebo controlled trial with a two-by-two factorial design.

SETTING
Nationwide in the United States.

PARTICIPANTS
25 871 participants, consisting of 12 786 men ≥50 years and 13 085 women ≥55 years at enrollment.

INTERVENTIONS
Vitamin D (2000 IU/day) or matched placebo, and omega 3 fatty acids (1000 mg/day) or matched placebo. Participants self-reported all incident autoimmune diseases from baseline to a median of 5.3 years of follow-up; these diseases were confirmed by extensive medical record review. Cox proportional hazard models were used to test the effects of vitamin D and omega 3 fatty acids on autoimmune disease incidence.

MAIN OUTCOME MEASURES
The primary endpoint was all incident autoimmune diseases confirmed by medical record review: rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and all others.

RESULTS
25 871 participants were enrolled and followed for a median of 5.3 years. 18 046 self-identified as non-Hispanic white, 5106 as black, and 2152 as other racial and ethnic groups. The mean age was 67.1 years. For the vitamin D arm, 123 participants in the treatment group and 155 in the placebo group had a confirmed autoimmune disease (hazard ratio 0.78, 95% confidence interval 0.61 to 0.99, P=0.05). In the omega 3 fatty acids arm, 130 participants in the treatment group and 148 in the placebo group had a confirmed autoimmune disease (0.85, 0.67 to 1.08, P=0.19). Compared with the reference arm (vitamin D placebo and omega 3 fatty acid placebo; 88 with confirmed autoimmune disease), 63 participants who received vitamin D and omega 3 fatty acids (0.69, 0.49 to 0.96), 60 who received only vitamin D (0.68, 0.48 to 0.94), and 67 who received only omega 3 fatty acids (0.74, 0.54 to 1.03) had confirmed autoimmune disease.

CONCLUSIONS
Vitamin D supplementation for five years, with or without omega 3 fatty acids, reduced autoimmune disease by 22%, while omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant). Both treatment arms showed larger effects than the reference arm (vitamin D placebo and omega 3 fatty acid placebo).

STUDY REGISTRATION
ClinicalTrials.gov NCT01351805 and NCT01169259

WHAT IS ALREADY KNOWN ON THIS TOPIC
Vitamin D regulates a wide array of genes involved in inflammation and immunity, and has been inconsistently associated with reduced risk of several autoimmune diseases in previous observational studies
Dietary marine derived long chain omega 3 fatty acids decrease systemic inflammation and ameliorate symptoms in some autoimmune diseases
Evidence is needed on whether omega 3 fatty acids lower the risk of developing autoimmune disease

WHAT THIS STUDY ADDS
This trial of older adults in the United States found that vitamin D and omega 3 fatty acid supplementation for five years reduced incident autoimmune disease compared with no supplementation
The clinical importance of this trial is high because these are well tolerated, non-toxic supplements, and other effective treatments to reduce the incidence of autoimmune diseases are lacking

Introduction

Autoimmune diseases, characterized by an inflammatory autoimmune response to self-tissues, are the third leading cause of morbidity in the industrialized world and a leading cause of mortality among women.[1,2] Autoimmune diseases are chronic conditions with increasing prevalence with age and major societal and economic burdens due to a lack of effective treatments.[3,4]

Vitamin D and marine derived, long chain omega 3 fatty acids are two nutritional supplements investigated as potential autoimmune disease treatments. In vitro, the lipid soluble active form of vitamin D (1,25-hydroxyvitamin D) regulates genes involved in inflammation and acquired and innate immune responses.[5] Animal models of autoimmune disease have reported vitamin D to be beneficial because it inhibits the development or progression of disease,[5-8] but observational studies have found conflicting results[9-12]; small trials of vitamin D supplementation in people with established autoimmune disease have mainly reported disappointing results.[13,14] Whether vitamin D supplementation can prevent autoimmune disease onset is still unknown and has not been tested in clinical trials. Randomized controlled trials of people with prevalent rheumatoid arthritis, systemic

RESEARCH

Table 1 | Characteristics of VITAL trial participants at baseline according to randomized assignment to active supplementation (vitamin D or omega 3 fatty acids) or placebo. Data are numbers (%) unless indicated otherwise

Characteristic	Total (n=25 871)	Vitamin D		Omega 3 fatty acids	
		Treatment group (n=12 927)	Placebo group (n=12 944)	Treatment group (n=12 933)	Placebo group (n=12 938)
Female sex	13 085 (50.6)	6547 (50.7)	6538 (50.5)	6547 (50.7)	6538 (50.5)
Age (years), mean (SD)	67.1 (7.1)	67.1 (7.1)	67.1 (7.1)	67.2 (7.1)	67.1 (7.1)
Race or ethnic group*					
Non-Hispanic white	18 046 (71.3)	9013 (71.3)	9033 (71.4)	9044 (71.5)	9002 (71.2)
Black	5106 (20.2)	2553 (20.2)	2553 (20.2)	2549 (20.2)	2557 (20.2)
Other	2152 (8.5)	1081 (8.6)	1071 (8.5)	1060 (8.4)	1092 (8.6)
Geographical region of residence					
North east	7161 (27.7)	3603 (27.9)	3558 (27.5)	3544 (27.4)	3617 (28)
Midwest	5541 (21.4)	2774 (21.5)	2767 (21.4)	2790 (21.6)	2751 (21.3)
West	5926 (22.9)	2935 (22.7)	2991 (23.1)	2993 (23.1)	2933 (22.7)
South east	7242 (28.0)	3615 (28.0)	3627 (28.0)	3605 (27.9)	3637 (28.1)
Highest level of education					
≤High school	3304 (12.8)	1650 (12.8)	1654 (12.8)	1683 (13)	1621 (12.6)
≥High school	22 514 (87.2)	11 252 (87.2)	11 262 (87.2)	11226 (87)	11288 (87.4)
Self-reported annual income ($)†					
<50 000	8523 (36.6)	4293 (36.9)	4230 (36.4)	4238 (36.4)	4285 (36.9)
≥50 000	14 750 (63.4)	7344 (63.1)	7406 (63.6)	7405 (63.6)	7345 (63.2)
Current supplemental vitamin D use ≤800 IU/day	11 030 (42.6)	5497 (42.5)	5533 (42.7)	5498 (42.5)	5533 (42.7)
Serum 25-hydroxyvitamin D, mean (SD)	30.7 (10)	30.7 (10)	30.7 (10)	30.7 (10)	30.7 (10)
Serum 25-hydroxyvitamin D <20 ng/mL	2161 (12.9)	1049 (12.5)	1112 (13.3)	1072 (12.8)	1089 (13.0)
Serum 25-hydroxyvitamin D <30 ng/mL	7646 (45.6)	3803 (45.4)	3843 (45.9)	3823 (45.6)	3823 (45.7)
Omega index,‡ mean (SD)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)	2.6 (0.9)
Body mass index,§ mean (SD)	28.1 (5.7)	28.1 (5.7)	28.1 (5.8)	28.1 (5.7)	28.1 (5.8)
Physical activity total MET hours/week, median (IQR)	15.4 (4.6-31.6)	15.2 (4.5-31.5)	15.5 (4.7-32.0)	15.5 (4.6-31.5)	15.4 (4.5-31.7)
Current smoker	1836 (7.2)	921 (7.2)	915 (7.2)	920 (7.2)	916 (7.2)
Family history of autoimmune disease	8168 (34.3)	4092 (34.4)	4076 (34.3)	4125 (34.6)	4043 (34.1)
Randomized to active group, other arm of trial	12 933 (50.0)	6463 (50.0)	6470 (50.0)	6463 (50)	6464 (50)

IQR=interquartile range; MET=metabolic equivalent; SD=standard deviation.
Percentages might not add up to 100 because of rounding. No significant differences were found in baseline characteristics between groups. Race or ethnic group: n=25 304; serum vitamin D: n=16 757; omega index: n=16 478; body mass index: n=25 254; physical activity: n=25 619; smoking: n=25 485; family history: n=23 779. Number of participants with autoimmune disease self-reported at baseline: rheumatoid arthritis, 1279; polymyalgia rheumatica, 162; psoriasis, 846; autoimmune thyroid disease, 2075; other autoimmune disease, 851.
*Race and ethnic group were reported by participants.
†Income data missing for 10% of participants.
‡Serum eicosapentaenoic acid plus docosahexaenoic acid/total lipids.
§Body mass index is weight in kilograms divided by square of height in meters.

Table 2 | Hazard ratios and 95% confidence intervals for primary and secondary endpoints according to randomized assignment to vitamin D or placebo

Endpoint	Vitamin D group (n=12 927)	Placebo group (n=12 944)	Hazard ratio (95% CI)	P value
Primary endpoint				
Confirmed autoimmune diseases	123	155	0.78 (0.61 to 0.99)	0.05
Secondary endpoints				
Confirmed+probable autoimmune diseases	210	247	0.85 (0.70 to 1.02)	0.09
Analyses excluding all prerandomization autoimmune diseases				
Confirmed autoimmune diseases	102	128	0.79 (0.61 to 1.03)	0.08
Confirmed+probable autoimmune diseases	170	209	0.81 (0.66 to 1.00)	0.05
Analyses excluding first two years of follow-up				
Confirmed autoimmune diseases	54	87	0.61 (0.43 to 0.86)	0.005
Confirmed+probable autoimmune diseases	94	133	0.69 (0.53 to 0.90)	0.007
Individual autoimmune diseases				
Confirmed rheumatoid arthritis	15	24	0.58 (0.30 to 1.13)	0.11
Confirmed+probable rheumatoid arthritis	18	27	0.63 (0.34 to 1.15)	0.13
Confirmed polymyalgia rheumatic*	31	43	0.70 (0.44 to 1.12)	0.14
Confirmed+probable polymyalgia rheumatica	32	43	0.72 (0.46 to 1.15)	0.17
Confirmed autoimmune thyroid disease	21	11	1.63 (0.77 to 3.45)	0.20
Confirmed+probable autoimmune thyroid disease	99	94	1.05 (0.78 to 1.41)	0.74
Confirmed psoriasis†	15	23	0.72 (0.37 to 1.39)	0.32
Confirmed+probable psoriasis	17	25	0.70 (0.37 to 1.32)	0.27
Confirmed other autoimmune disease	40	56	0.74 (0.49 to 1.11)	0.15
Confirmed+probable other autoimmune disease	45	63	0.73 (0.50 to 1.08)	0.12

Analyses were from Cox regression models controlled for age, sex, race, and omega 3 fatty acid randomization group.
*Fourteen participants had confirmed polymyalgia rheumatica without giant cell arteritis, 18 had confirmed giant cell arteritis without polymyalgia rheumatica, and two were confirmed with both.
†No participants had psoriatic arthritis.

ΜΕΤΑΒΟΛΙΣΜΟΣ ΟΣΤΩΝ | ΣΠΥΡΟΣ ΚΑΡΡΑΣ

RESEARCH

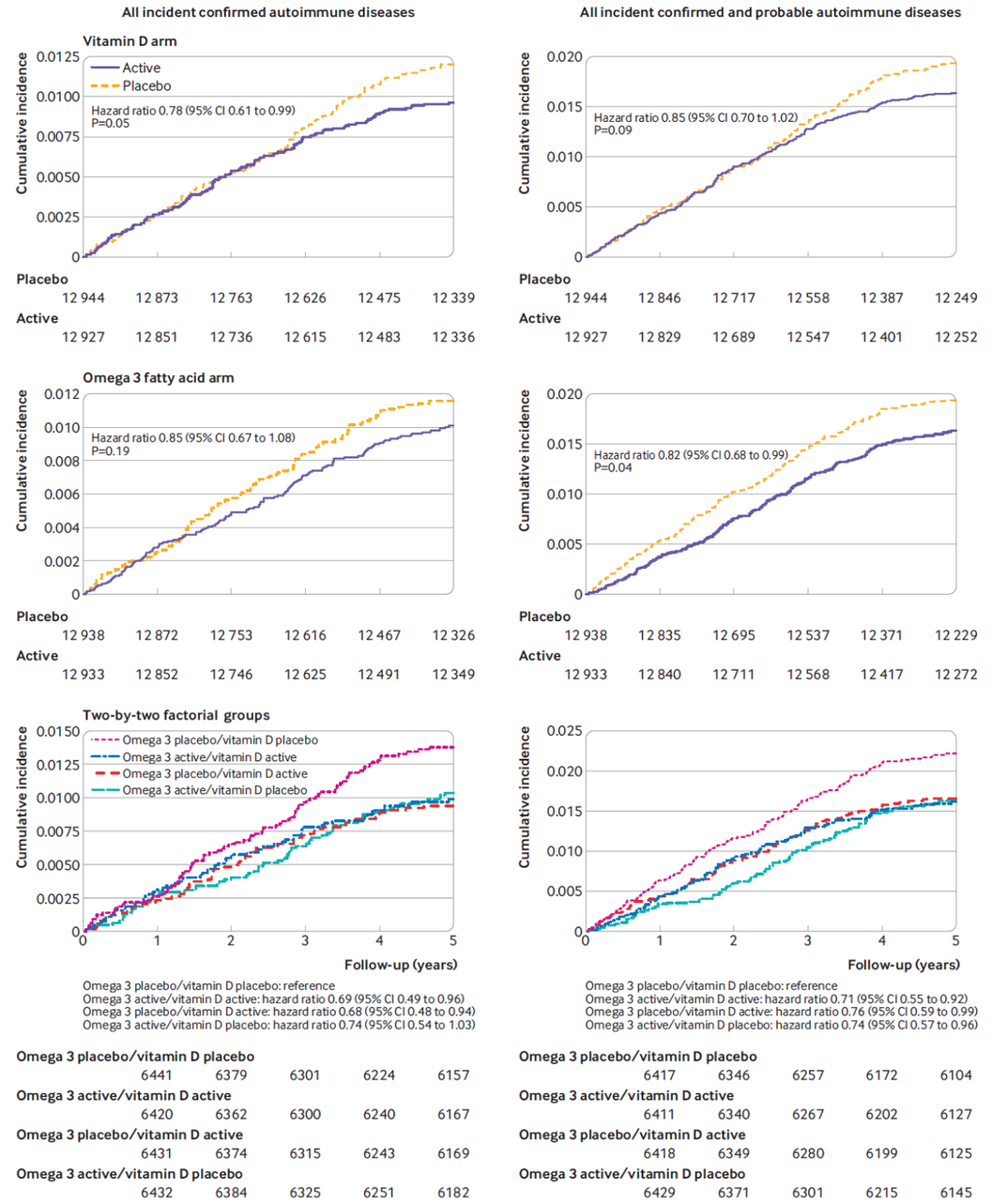

Fig 1 | Cumulative incidence rates of total autoimmune diseases in the VITAL (vitamin D and omega 3) trial. Hazard ratios are from Cox models controlled for age, sex, race, and randomization group in the opposite arm of the trial

RESEARCH ARTICLE

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A 2-Year Randomized Controlled Trial With Low-Dose B-Vitamin Supplementation Shows Benefits on Bone Mineral Density in Adults With Lower B12 Status

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ABSTRACT

Folate, vitamins B12, B6, and riboflavin are required for one-carbon metabolism and may affect bone health, but no previous randomized trial has investigated all four nutrients in this context. We investigated the effect of low-dose B-vitamins for 2 years on bone mineral density (BMD) in a dual-centered, 2-year randomized controlled trial (RCT) in adults aged ≥50 years. Eligible participants not consuming B-vitamin supplements or fortified foods >4 times weekly were randomized to receive daily either combined folic acid (200 μg), vitamin B12 (10 μg), vitamin B6 (10 mg), and riboflavin (5 mg), or "active" placebo, whereby both the intervention and placebo groups received vitamin D (10 μg). BMD was assessed before and after intervention using dual-energy X-ray absorptiometry (DXA) scanning of the total hip, femoral neck, and lumbar spine (L1 to L4). Of 205 eligible participants randomized, 167 completed the trial in full. B-vitamin intervention resulted in increases in serum folate ($p < 0.001$), serum B12 ($p < 0.001$), and plasma pyridoxal-5-phosphate ($p < 0.001$) and decreases in functional biomarkers of B-vitamin status, erythrocyte glutathione reductase activation coefficient ($p < 0.001$), serum methylmalonic acid (MMA; $p < 0.001$), and serum total homocysteine ($p < 0.001$). B-vitamin intervention had no overall effect on BMD, which declined in both treatment groups by approximately 1% (ranging from −0.7% to −1.4%). However, in participants with lower baseline B12 status (serum B12 <246 pmol/L or MMA ≥0.22 μmol/L), B-vitamin intervention reduced the 2-year BMD decline versus placebo: adjusted mean (95% confidence interval [CI]) change of −0.003 (−0.008, 0.002) versus −0.015 (−0.021, −0.010) g/cm^2 at the total hip and −0.004 (−0.010, 0.001) versus −0.013 (−0.018, −0.007) g/cm^2 at the femoral neck. In conclusion, the findings indicate that although low-dose B-vitamin intervention for 2 years had no overall effect on BMD, improving B-vitamin status appears to have specific benefits for bone health in adults with lower B12 status. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: B-VITAMINS; ONE-CARBON METABOLISM; BONE MINERAL DENSITY; OSTEOPOROSIS; AGING

Introduction

Osteoporosis, characterized by a reduction in bone mineral density (BMD) and deterioration of bone microarchitecture,[1] represents a substantial public health challenge that affects more than 200 million people globally.[2] Osteoporotic fractures are a particular source of disability in older adults[3] and carry a huge economic burden, with costs estimated at more than €56 billion annually in Europe alone.[4] Nutrition is a key modifiable factor in the development of osteoporosis and an obvious cost-effective

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Additional Supporting Information may be found in the online version of this article.
#MC, MH, LCD, and RHM contributed equally to running this randomized trial across two study centers.
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RESEARCH ARTICLE

JBMR®

The Efficacy and Safety of Abaloparatide-SC in Men With Osteoporosis: A Randomized Clinical Trial

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ABSTRACT

Abaloparatide significantly increased bone mineral density (BMD) in women with postmenopausal osteoporosis and decreased risk of vertebral, nonvertebral, and clinical fractures compared with placebo. The Abaloparatide for the Treatment of Men with Osteoporosis (ATOM; NCT03512262) study evaluated the efficacy and safety of abaloparatide compared with placebo in men. Eligible men aged 40 to 85 years with osteoporosis were randomized 2:1 to daily subcutaneous injections of abaloparatide 80 μg or placebo for 12 months. The primary endpoint was change from baseline in lumbar spine BMD. Key secondary endpoints included BMD change from baseline at the total hip and femoral neck. A total of 228 men were randomized (abaloparatide, $n = 149$; placebo, $n = 79$). Baseline characteristics were similar across treatment groups (mean age, 68.3 years; mean lumbar spine BMD *T*-score, −2.1). At 12 months, BMD gains were greater with abaloparatide compared with placebo at the lumbar spine (least squares mean percentage change [standard error]: 8.48 [0.54] versus 1.17 [0.72]), total hip (2.14 [0.27] versus 0.01 [0.35]), and femoral neck (2.98 [0.34] versus 0.15 [0.45]) (all $p < 0.0001$). The most common (≥5%) treatment-emergent adverse events were injection site reaction, dizziness, nasopharyngitis, arthralgia, bronchitis, hypertension, and headache. During 12 months of abaloparatide treatment, men with osteoporosis exhibited rapid and significant improvements in BMD with a safety profile consistent with previous studies. These results suggest abaloparatide can be considered as an effective anabolic treatment option for men with osteoporosis. © 2022 Radius Health Inc and The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ABALOPARATIDE; MEN; OSTEOPOROSIS; FRACTURE; BONE MINERAL DENSITY

Introduction

Osteoporosis in men is an important but underappreciated public health problem.[1] Approximately one in four men over 50 years of age will incur a fragility fracture in their lifetime, with men accounting for up to 30% of the societal burden of osteoporosis and fractures.[1-4] Although osteoporosis prevalence is lower in men than in women, men have greater fracture-related morbidity and mortality.[5] Further, lower proportions of men initiate an appropriate osteoporosis treatment

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RESEARCH ARTICLE

JBMR®

Impaired Bone Architecture in Peripubertal Children With HIV, Despite Treatment With Antiretroviral Therapy: A Cross-Sectional Study From Zimbabwe

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ABSTRACT

HIV infection has multi-system adverse effects in children, including on the growing skeleton. We aimed to determine the association between chronic HIV infection and bone architecture (density, size, strength) in peripubertal children. We conducted a cross-sectional study of children aged 8 to 16 years with HIV (CWH) on antiretroviral therapy (ART) and children without HIV (CWOH) recruited from schools and frequency-matched for age strata and sex. Outcomes, measured by tibial peripheral quantitative computed tomography (pQCT), included 4% trabecular and 38% cortical volumetric bone mineral density (vBMD), 4% and 38% cross-sectional area (CSA), and 38% stress–strain index (SSI). Multivariable linear regression tested associations between HIV status and outcomes, stratified by sex and puberty (Tanner 1–2 versus 3–5), adjusting for age, height, fat mass, physical activity, and socioeconomic and orphanhood statuses. We recruited 303 CWH and 306 CWOH; 50% were female. Although CWH were similar in age to CWOH (overall mean ± SD 12.4 ± 2.5 years), more were prepubertal (ie, Tanner 1; 41% versus 23%). Median age at ART initiation was 4 (IQR 2–7) years, whereas median ART duration was 8 (IQR 6–10) years. CWH were more often stunted (height-for-age *Z*-score <−2) than those without HIV (33% versus 7%). Both male and female CWH in later puberty had lower trabecular vBMD, CSA (4% and 38%), and SSI than those without HIV, whereas cortical density was similar. Adjustment explained some of these differences; however, deficits in bone size persisted in CWH in later puberty (HIV*puberty interaction $p = 0.035$ [males; 4% CSA] and $p = 0.029$ [females; 38% CSA]). Similarly, puberty further worsened the inverse association between HIV and bone strength (SSI) in both males (interaction $p = 0.008$) and females (interaction $p = 0.004$). Despite long-term ART, we identified deficits in predicted bone strength in those living with HIV, which were more overt in the later stages of puberty. This is concerning, as this may translate to higher fracture risk later in life. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ANALYSIS/QUANTIFICATION OF BONE; DISEASES AND DISORDERS OF/RELATED TO BONE; EPIDEMIOLOGY

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Additional Supporting Information may be found in the online version of this article.

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RESEARCH ARTICLE

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The Association of Cold Ambient Temperature With Fracture Risk and Mortality: National Data From Norway—A Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Study

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ABSTRACT

Norway is an elongated country with large variations in climate and duration of winter season. It is also a high-risk country for osteoporotic fractures, in particular hip fractures, which cause high mortality. Although most hip fractures occur indoors, there is a higher incidence of both forearm and hip fractures during wintertime, compared with summertime. In a nationwide longitudinal cohort study, we investigated whether cold ambient (outdoor) temperatures could be an underlying cause of this high incidence and mortality. Hospitalized/outpatient forearm fractures (International Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] code S52) and hospitalized hip fractures (ICD-10 codes S72.0–S72.2) from 2008 to 2018 were retrieved from the Norwegian Patient Registry. Average monthly ambient temperatures (degrees Celsius, °C) from the years 2008 to 2018 were provided by the Norwegian Meteorological Institute and linked to the residential area of each inhabitant. Poisson models were fitted to estimate the association (incidence rate ratios [IRRs], 95% confidence intervals [CIs]) between temperature and monthly incidence of total number of forearm and hip fractures. Flexible parametric survival models (hazard ratios [HR], 95% CI) were used to estimate the association between temperature and post–hip fracture mortality, taking the population mortality into account. Monthly temperature ranged from −20.2°C to 22.0°C, with a median of −2.0°C in winter and 14.4°C in summer. At low temperatures (<0°C) compared to ≥0°C, there was a 53% higher risk of forearm fracture (95% CI, 51%–55%) and 21% higher risk of hip fracture (95% CI, 19%–22%), adjusting for age, gender, calendar year, urbanization, residential region, elevation, and coastal proximity. When taking the population mortality into account, the post–hip fracture mortality in both men (HR 1.08; 95% CI, 1.02–1.13) and women (HR 1.09; 95% CI, 1.04–1.14) was still higher at cold temperatures. There was a higher risk of forearm and hip fractures, and an excess post–hip fracture mortality at cold ambient temperatures. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: GENERAL POPULATION STUDIES; FOREARM FRACTURE; HIP FRACTURE; POST–HIP FRACTURE MORTALITY; AMBIENT TEMPERATURE

Introduction

Extreme temperatures, in particular cold, have been termed the "underrated risk factor" for many health conditions, and there is a higher winter mortality in several countries.[1] Norway is an elongated country in Northern Europe (mainland extending from 58 to 71 degrees north), and with large variations in the duration and degree of winter season.[2] It is also a high-incidence country for osteoporotic fractures, in particular hip fractures, with among the highest rates in the world.[3,4] Surges of forearm fractures, the most common osteoporotic fracture, often occur during the winter months, and the high incidence has been attributed to increased precipitation around 0°C outdoor temperature, which results in slippery and icy

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Additional Supporting Information may be found in the online version of this article.

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CLINICAL TRIAL

JBMR®

Effect of Denosumab Compared With Risedronate on Bone Strength in Patients Initiating or Continuing Glucocorticoid Treatment

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ABSTRACT

In a randomized clinical trial in patients initiating glucocorticoid therapy (GC-I) or on long-term therapy (GC-C), denosumab every 6 months increased spine and hip bone mineral density at 12 and 24 months significantly more than daily risedronate. The aim of this study was to evaluate the effects of denosumab compared with risedronate on bone strength and microarchitecture measured by high-resolution peripheral quantitative computed tomography (HR-pQCT) in GC-I and GC-C. A subset of 110 patients had high-resolution peripheral quantitative computed tomography (HR-pQCT) scans of the distal radius and tibia at baseline and at 12 and 24 months. Cortical and trabecular microarchitecture were assessed with standard analyses and failure load (FL) with micro-finite element analysis. At the radius at 24 months, FL remained unchanged with denosumab and significantly decreased with risedronate in GC-I (−4.1%, 95% confidence interval [CI] −6.4, −1.8) and, in GC-C, it significantly increased with denosumab (4.3%, 95% CI 2.1, 6.4) and remained unchanged with risedronate. Consequently, FL was significantly higher with denosumab than with risedronate in GC-I (5.6%, 95% CI 2.4, 8.7, $p < 0.001$) and in GC-C (4.1%, 95% CI 1.1, 7.2, $p = 0.011$). We also found significant differences between denosumab and risedronate in percentage changes in cortical and trabecular microarchitectural parameters in GC-I and GC-C. Similar results were found at the tibia. To conclude, this HR-pQCT study shows that denosumab is superior to risedronate in terms of preventing FL loss at the distal radius and tibia in GC-I and in increasing FL at the radius in GC-C, based on significant differences in changes in the cortical and trabecular bone compartments between treatment groups in GC-I and GC-C. These results suggest that denosumab could be a useful therapeutic option in patients initiating GC therapy or on long-term GC therapy and may contribute to treatment decisions in this patient population. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: GLUCOCORTICOID-INDUCED OSTEOPOROSIS; DENOSUMAB; RISEDRONATE; BONE STRENGTH; HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY (HR-pQCT)

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CLINICAL TRIAL

JBMR®

Calcium Citrate Versus Calcium Carbonate in the Management of Chronic Hypoparathyroidism: A Randomized, Double-Blind, Crossover Clinical Trial

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ABSTRACT

In hypoparathyroidism (HypoPT), calcium supplementation is virtually always required, although the disease is likely to be associated with an increased risk of nephrolithiasis. The use of calcium citrate (Ca-Cit) theoretically could have a positive impact on the nephrolithiasis risk because citrate salts are used to reduce this risk. Our objective was to evaluate the potential therapeutic advantage of Ca-Cit in comparison with calcium carbonate ($CaCO_3$) in HypoPT, on nephrolithiasis risk factors, as well as to their ability to maintain desirable serum calcium levels. We also evaluated these preparations on quality of life (QOL). This randomized, double-blind, crossover trial recruited 24 adults with postsurgical chronic hypoparathyroidism at Campus Bio-Medico University of Rome. Participants were randomized 1:1 to Ca-Cit or $CaCO_3$ for 1 month and then crossed over to the other treatment for another month. The primary outcomes were changes in albumin-adjusted serum calcium and in ion activity product of calcium oxalate levels (AP[CaOx] index). Secondary efficacy outcomes included changes in SF-36 survey score, fatigue score, constipation, and adverse events. No difference in terms of AP(CaOx) index was observed between the two groups. However, Ca-Cit was associated with a significant reduction in the oxalate/creatinine ratio compared with $CaCO_3$ (−2.46 mmol/mol [SD 11.93] versus 7.42 mmol/mol [SD 17.63], $p = 0.029$). Serum calcium and phosphorus concentration was not different between the two calcium preparations. Ca-Cit was associated with less constipation ($p = 0.047$). No difference was found in QOL scores. Although Ca-Cit did not modify the AP(CaOx) index when compared with $CaCO_3$, it was associated with a reduction in urinary oxalate excretion that could have a potential beneficial effect on nephrolithiasis risk. These results are likely to have clinical implications in HypoPT, particularly those who do not tolerate $CaCO_3$ and those affected by nephrolithiasis. A longer-term experience is needed to confirm these findings. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: HYPOPARATHYROIDISM; CALCIUM CITRATE; CALCIUM CARBONATE; PTH; NEPHROLITHIASIS

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Table 1. Comparison of Study Population at Baseline When Assigned to Calcium Citrate or Carbonate Supplementation

Variable	Calcium citrate mean (SD)	Calcium carbonate mean (SD)	*p* Value
Body mass index (kg/m^2)	28.95 (5.09)	28.92 (5.06)	0.984
Urinary calcium oxalate supersaturation	4.60 (2.76)	4.09 (2.51)	0.507
Urinary pH	5.85 (0.68)	5.77 (0.81)	0.701
Urinary volume (mL)	2174.62 (1007.53)	2380.00 (524.69)	0.281
Urinary phosphate excretion (mmol/24 h)	16.34 (10.95)	13.53 (8.19)	0.318
Urinary potassium excretion (mEq/24 h)	60.92 (24.97)	52.68 (16.21)	0.183
Urinary sodium excretion (mEq/24 h)	127.18 (78.57)	111.63 (57.31)	0.437
Urinary calcium excretion (mg/24 h)	206.55 (136.72)	196.24 (107.18)	0.772
Urinary calcium/creatinine (24 h) (mg/mg)	0.19 (0.09)	0.18 (0.08)	0.885
Urinary oxalate excretion (mmol/24 h)	0.40 (0.16)	0.36 (0.14)	0.358
Urinary oxalate/creatinine (24 h) (mmol/mol)	42.29 (14.62)	39.21 (13.90)	0.458
Urinary citrate excretion (mmol/24 h)	5.61 (2.88)	5.52 (2.46)	0.912
Urinary citrate/creatinine (24 h) (mol/mol)	0.59 (0.23)	0.59 (0.23)	0.985
Serum calcium (mg/dL)	8.80 (0.56)	8.86 (0.41)	0.704
Serum ionized calcium (mmol/L)	1.10 (0.05)	1.11 (0.06)	0.260
Serum phosphorus (mg/dL)	4.05 (0.63)	4.07 (0.57)	0.905
Serum creatinine (mg/dL)	0.78 (0.17)	0.82 (0.19)	0.430
Serum 25-OH Vitamin D (ng/mL)	27.00 (7.49)	29.00 (9.09)	0.280
Renal clearance of creatinine (24 h) (mL/min)	63.30 (21.39)	61.12 (20.96)	0.402
Net alkali absorption (mEq/d)	32.80 (33.25)	35.20 (28.96)	0.791
Daily dose of calcium supplements (mg)	1171.46 (311.89)	1090.91 (301.51)	0.260
Daily dose of calcitriol (mcg)	0.54 (0.37)	0.48 (0.21)	0.310

We reported the results as means and standard deviation (SD), means and 95% confidence intervals (CI), or mean and standard error (SE), as appropriate.

We used the software IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA) to perform all statistical analyses. For all tests, we set a two-sided alpha level of $p < 0.05$ for statistical significance.

The study was registered with ClinicalTrials.gov ID NCT03425747 on February 8, 2018.

Results

During the study period, we screened 35 consecutive patients with postsurgical chronic HypoPT for eligibility. Nine subjects did not meet the inclusion criteria and were excluded. Fig. 1 shows a summary of patient recruitment and exclusion. Twenty-six patients meeting the eligibility criteria were randomized for the first phase of the crossover trial. After crossover, two participants withdrew from the study due to the COVID-19 outbreak (Fig. 1). Consequently, 24 patients (mean age 54.7 [SD 12.5] years, 21 [87.5%] women) constituted the final study population with a mean PTH value of 15.04 pg/mL (SD 8.68). The dose of active vitamin D at baseline was not different between Ca-Cit and $CaCO_3$ groups (0.54 ± 0.37 versus 0.48 ± 0.21, $p = 0.310$). The prevalence of hypercalciuria in our study population was 33%. No difference in baseline anthropometric characteristics and laboratory biomarkers was found between calcium supplement groups (Table 1).

Biochemical analysis

No difference in terms of AP(CaOx) index was recorded between the two groups. Both absolute variations of serum creatinine, urinary 24-hour oxalate/creatinine ratio, and urinary 24-hour potassium excretion showed a statistically significant group × time interaction in the mixed-model ANOVA. In particular, a reduction of both urinary potassium excretion (−5.66 mEq/24 hours [SD 14.36] versus 5.00 mEq/24 hours [SD 14.90], $p = 0.013$) and oxalate/creatinine ratio (−2.46 mmol/mol [SD 11.93] versus 7.42 mmol/mol (SD 17.63), $p = 029$) was found in association with Ca-Cit supplementation, while the same variable increased in patients treated with $CaCO_3$. No further significant interactions were found for the other measured laboratory biomarkers (Table 2). When we evaluated the change rate of study variables between baseline and 4-week follow-up, the finding was confirmed only for urinary 24-hour oxalate/creatinine ratio (Table 3). No statistically significant difference in the rate of patients with out-of-range serum calcium concentration was detected, neither at baseline (29.2% in Ca-Cit versus 8.3% in $CaCO_3$, $p = 0.137$) nor at the follow-up control.

QOL evaluation

At follow-up, 7 patients (30.4%) treated with $CaCO_3$ supplementation suffered from constipation compared with one (4.3%) receiving Ca-Cit ($p = 0.047$). No difference between groups was found for relative changes in SF-36–PCS score (Ca-Cit: 3.59% [SD 26.44]; $CaCO_3$: 4.90% [SD 35.46]; $p = 0.878$), SF-36–MCS score (Ca-Cit: 6.17% [SD 31.43]; $CaCO_3$: 7.75% [SD 50.67]; $p = 0.904$) and fatigue score (Ca-Cit: −2.60% [SD 33.67]; $CaCO_3$: 36.52% [SD 128.03]; $p = 0.175$).

Discussion

In this prospective double-blind crossover trial, we showed that Ca-Cit is as effective as $CaCO_3$ in maintaining target calcium levels in chronic postsurgical HypoPT. It is believed that Ca-Cit salts, due to their more rapid metabolism and lack of CO_2 production, may increase calcium bioavailability more efficiently and to a greater degree than $CaCO_3$ salts[5] as clearly shown in the setting of bariatric surgery.[15] This reasoning could also lead

Table 2. Comparison of Modifications in Laboratory Tests According to the Type of Calcium Supplementation in the Study Population

Variable	Study arm	Mean baseline (SD)	Mean follow-up (SD)	Mean difference (SD)	Mean difference between groups (95% CI)	*p* Value
Blood tests						
Serum calcium (mg/dL)	Ca citrate	8.80 (0.56)	8.70 (0.41)	−0.11 (0.39)	0.006 (−0.119 to 0.131)	0.336
	Ca carbonate	8.86 (0.41)	8.63 (0.58)	−0.23 (0.40)		
Serum phosphorus (mg/dL)	Ca citrate	4.05 (0.63)	4.04 (0.59)	−0.01 (0.40)	−0.027 (−0.158 to 0.103)	0.924
	Ca carbonate	4.07 (0.57)	4.07 (0.55)	0.00 (0.49)		
Serum creatinine (mg/dL)	Ca citrate	0.78 (0.17)	0.83 (0.19)	0.05 (0.10)	−0.014 (−0.039 to 0.011)	**0.031**
	Ca carbonate	0.82 (0.19)	0.81 (0.18)	−0.01 (0.07)		
Urine tests						
Calcium excretion (mg/24 h)	Ca citrate	206.55 (136.72)	208.63 (127.32)	2.07 (83.42)	9.077 (−13.558 to 31.712)	0.913
	Ca carbonate	196.24 (107.18)	200.79 (131.57)	4.55 (73.01)		
Calcium/creatinine (24 h) (mg/mg)	Ca citrate	0.19 (0.09)	0.19 (0.08)	0.00 (0.08)	−0.008 (−0.042 to 0.027)	0.506
	Ca carbonate	0.18 (0.08)	0.21 (0.16)	0.02 (0.14)		
CaOx supersaturation	Ca citrate	4.60 (2.76)	3.92 (2.16)	−0.68 (3.25)	0.070 (−0.753 to 0.892)	0.287
	Ca carbonate	4.09 (2.51)	4.29 (2.12)	0.20 (2.31)		
Creatinine excretion (g/24 h)	Ca citrate	1.08 (0.42)	1.13 (0.34)	0.05 (0.23)	−0.003 (−0.078 to 0.071)	0.849
	Ca carbonate	1.09 (0.34)	1.12 (0.40)	0.03 (0.27)		
Citrate excretion (mmol/24 h)	Ca citrate	5.61 (2.88)	5.84 (2.82)	0.23 (1.85)	0.068 (−0.534 to 0.670)	0.952
	Ca carbonate	5.52 (2.46)	5.79 (2.96)	0.27 (2.25)		
Citrate/creatinine (24 h) (mol/mol)	Ca citrate	0.59 (0.23)	0.58 (0.21)	−0.01 (0.17)	−0.059 (−0.158 to 0.040)	0.226
	Ca carbonate	0.59 (0.23)	0.70 (0.54)	0.11 (0.45)		
Oxalate excretion (mmol/24 h)	Ca citrate	0.40 (0.16)	0.38 (0.19)	−0.02 (0.16)	0.002 (−0.039 to 0.043)	0.073
	Ca carbonate	0.36 (0.14)	0.42 (0.14)	0.06 (0.11)		
Oxalate/creatinine (24 h) (mmol/mol)	Ca citrate	42.29 (14.62)	39.83 (16.95)	−2.46 (11.93)	−1.854 (−6.254 to 2.546)	**0.029**
	Ca carbonate	39.21 (13.90)	46.62 (16.03)	7.42 (17.63)		
Sodium excretion (mEq/24 h)	Ca citrate	127.18 (78.57)	140.24 (77.80)	13.06 (46.32)	6.416 (−12.711 to 25.543)	0.341
	Ca carbonate	111.63 (57.31)	142.96 (77.63)	31.33 (74.70)		
Potassium excretion (mEq/24 h)	Ca citrate	60.92 (24.97)	55.26 (21.95)	−5.66 (14.36)	2.902 (−1.263 to 7.067)	**0.013**
	Ca carbonate	52.68 (16.21)	57.69 (21.22)	5.00 (14.90)		
Magnesium excretion (mg/24 h)	Ca citrate	85.43 (40.89)	84.66 (34.96)	−0.77 (26.86)	0.778 (−8.877 to 7.322)	0.447
	Ca carbonate	81.56 (30.86)	86.96 (35.16)	5.40 (28.70)		
Phosphate excretion (mmol/24 h)	Ca citrate	16.34 (10.95)	13.66 (8.98)	−2.68 (7.81)	0.781 (−1.560 to 3.123)	0.087
	Ca carbonate	13.53 (8.19)	14.91 (8.54)	1.38 (8.33)		
pH (spot sample)	Ca citrate	5.85 (0.68)	5.96 (0.79)	0.10 (0.75)	0.083 (−0.102 to 0.268)	1.000
	Ca carbonate	5.77 (0.81)	5.88 (0.76)	0.10 (0.49)		
Urine volume (24 hours) (mL)	Ca citrate	2417.50 (972.25)	2450.83 (1089.87)	33.33 (561.22)	−124.792 (−296.925 to 47.342)	0.875
	Ca carbonate	2306.59 (764.21)	2312.50 (818.44)	6.25 (647.11)		
Net alkali absorption (mEq/d)	Ca citrate	32.80 (33.25)	38.10 (30.27)	5.30 (44.19)	−9.628 (−26.643 to 7.387)	0.261
	Ca carbonate	35.20 (28.96)	54.95 (51.73)	19.75 (47.54)		

CI = confidence interval; SD = standard deviation; Ca = calcium; CaOx = calcium oxalate.

to an expectation that Ca-Cit may maintain calcium levels at lower doses than $CaCO_3$. However, the lack of PTH and the mean high dosage of calcium supplementation might have prevented this conclusion to be drawn.

The other endpoint of the study was the evaluation of risk factors for nephrolithiasis assessed by the AP(CaOx) index changes. Although there was a trend toward reduction of AP(CaOx) index in Ca-Cit treated patients, it was not significant. This index is

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Original Investigation | Diabetes and Endocrinology

Association of Preconception Thyrotropin Levels With Fecundability and Risk of Spontaneous Abortion in China

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Abstract

IMPORTANCE Abundant evidence suggests thyroid dysfunction is associated with adverse pregnancy outcomes. However, associations of preconception thyrotropin levels outside of reference range with reproductive health outcomes are not well characterized.

OBJECTIVE To evaluate the associations of preconception thyrotropin levels with time to pregnancy (TTP) and risk of spontaneous abortion (SA).

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used data from the Chinese National Free Prepregnancy Checkups Project. Female participants aged 20 to 49 years who were trying to conceive were enrolled between January 1, 2013, and December 31, 2016, for the analysis of TTP or SA. Data were analyzed between August 1, 2020, and July 5, 2021.

EXPOSURES Levels of thyrotropin within 1 year prior to pregnancy.

MAIN OUTCOMES AND MEASURES The main outcomes were TTP, assessed using hazard ratios (HRs), and SA, assessed using odds ratios (ORs), according to preconception thyrotropin levels. Thyrotropin dose-response associations were assessed using restricted cubic spline regression.

RESULTS Among 11 194 002 female participants (mean [SD] age, 27.56 [5.10] years) in the TTP cohort, 4 739 421 (42.34%) participants became pregnant within 1 year. Both low and high preconception thyrotropin levels were associated with delayed TTP compared with thyrotropin levels of 0.37 to 2.49 mIU/L (thyrotropin <0.10 mIU/L: HR, 0.90; 95% CI, 0.89-0.92; thyrotropin 4.88-9.99 mIU/L: HR, 0.86; 95% CI, 0.86-0.87; thyrotropin ≥10.00 mIU/L: HR, 0.78; 95% CI, 0.77-0.79). In the SA analysis cohort including 4 678 679 pregnancies, 108 064 SA events (2.31%) were documented. High thyrotropin groups showed an increased risk of SA compared with the group with thyrotropin levels of 0.37 to 2.49 mIU/L (thyrotropin 4.88-9.99 mIU/L: OR, 1.33; 95% CI, 1.28-1.38; thyrotropin ≥10.00 mIU/L: OR, 1.25; 95% CI, 1.14-1.36). Preconception thyrotropin levels showed an inverted J-shaped dose-response association with TTP (χ^2 = 311.29; nonlinear P < .001) and a J-shaped dose-response association with SA (χ^2 = 58.29; nonlinear P < .001).

CONCLUSIONS AND RELEVANCE In this cohort study, preconception thyrotropin levels outside of reference range were associated with increased risk of reduced fecundity and SA. These findings may provide insights for the implementation of preconception thyroid function screening and the design of future levothyroxine supplementation trials.

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Key Points

Question Are preconception thyrotropin levels associated with fecundability and risk of spontaneous abortion?

Findings In this cohort study of 11 194 002 participants in China, participants with preconception thyrotropin levels outside reference range were significantly more likely to experience delayed time to pregnancy and increased risk of spontaneous abortion. A preconception thyrotropin level of 0.37 to 2.49 mIU/L was associated with the lowest risk of these unfavorable outcomes.

Meaning The findings of this study suggest that interventional studies investigating the benefits of preconception thyroid function screening and levothyroxine supplementation are warranted.

+ Invited Commentary

+ Supplemental content

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Meta-Analysis

TSH and FT4 Reference Intervals in Pregnancy: A Systematic Review and Individual Participant Data Meta-Analysis

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Abstract

Context: Interpretation of thyroid function tests during pregnancy is limited by the generalizability of reference intervals between cohorts due to inconsistent methodology.

Objective: (1) To provide an overview of published reference intervals for thyrotropin (TSH) and free thyroxine (FT4) in pregnancy, (2) to assess the consequences of common methodological between-study differences by combining raw data from different cohorts.

Methods: (1) Ovid MEDLINE, EMBASE, and Web of Science were searched until December 12, 2021. Studies were assessed in duplicate. (2) The individual participant data (IPD) meta-analysis was performed in participating cohorts in the Consortium on Thyroid and Pregnancy.

Results: (1) Large between-study methodological differences were identified, 11 of 102 included studies were in accordance with current guidelines; (2) 22 cohorts involving 63 198 participants were included in the meta-analysis. Not excluding thyroid peroxidase antibody–positive participants led to a rise in the upper limits of TSH in all cohorts, especially in the first (mean +17.4%; range +1.6 to +30.3%) and second trimester (mean +9.8%; range +0.6 to +32.3%). The use of the 95th percentile led to considerable changes in upper limits, varying from –10.8% to –21.8% for TSH and –1.2% to –13.2% for FT4. All other additional exclusion criteria changed reference interval cut-offs by a maximum of 3.5%. Applying these findings to the 102 studies included in the systematic review, 48 studies could be used in a clinical setting.

Conclusion: We provide an overview of clinically relevant reference intervals for TSH and FT4 in pregnancy. The results of the meta-analysis indicate that future studies can adopt a simplified study setup without additional exclusion criteria.

Key Words: thyroid, pregnancy, reference values, thyrotropin (TSH), free thyroxine (FT4)

Abbreviations: ATA, American Thyroid Association; BMI, body mass index; FT4, free thyroxine; IPD, individual patient data; IVF, in vitro fertilization; SGA, small for gestational age; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyrotropin.

Adequate thyroid hormone availability during pregnancy is important for an uncomplicated pregnancy as well as optimal fetal growth and development. Thyroid function test abnormalities during pregnancy are associated with a higher risk of adverse pregnancy and child outcomes (1-4). However, identifying thyroid function abnormalities during pregnancy is complicated by changes in maternal physiology. Furthermore, there is no universal reference interval for thyrotropin (TSH) or free thyroxine (FT4) during pregnancy due to considerable differences between assays as well as population characteristics (5-7). Current guidelines from international thyroid or endocrine societies, including the most recent 2017 guidelines by the American Thyroid Association (ATA), recommend the use of population- and trimester-specific TSH and FT4 reference intervals as the gold standard, calculated in a population with no known thyroid disease, optimal iodine status, and negative thyroid peroxidase antibody (TPOAb) status (4, 8, 9). However, for many laboratories these are unavailable because calculating reference intervals from a local reference population is often not feasible. Another option recently provided in the ATA guidelines either is to use a fixed cut-off for the upper limit of TSH of 4.0 mU/L or to subtract 0.5 mU/L from the nonpregnancy upper reference limit of TSH in the first trimester (4). While the method of using a fixed upper limit for TSH may lead to considerable under- and overdiagnosis compared with the gold standard because of interpopulation and interassay differences (10), the method of subtracting an absolute number from the nonpregnancy reference interval has not been thoroughly researched.

The most recent addition to the ATA guidelines is the option to adopt reference intervals that were calculated in a center with a similar population and using the same assay, which is a step in between the gold standard and fixed upper TSH limit approach (4). However, identification of adoptable TSH and FT4 reference intervals is cumbersome due to a lack of overview of all published data regarding thyroid hormone reference intervals. Moreover, large methodological differences exist between studies as a result of new insights and changing guidelines (4, 8, 11). One example of this is the use of additional exclusion criteria on top of those recommended by the current ATA guidelines, most of which remain of unknown significance, such as thyroglobulin antibody (TgAb) positivity, conception by in vitro fertilization (IVF), pregnancy complications, and characteristics including preexisting diabetes mellitus, hypertension, aberrant body mass index (BMI), and active smoking. Although some of these factors are determinants of TSH and FT4 concentrations, only some, but not all, studies show that exclusion of women

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PREGNANCY AND FETAL DEVELOPMENT

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Association of Thyroid Peroxidase Antibodies and Thyroglobulin Antibodies with Thyroid Function in Pregnancy: An Individual Participant Data Meta-Analysis

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This study was presented as an oral presentation at the 43rd Annual Meeting of the European Thyroid Association, Virtual Conference, September 4–7, 2021.

Objectives: Thyroid autoimmunity is common in pregnant women and associated with thyroid dysfunction and adverse obstetric outcomes. Most studies focus on thyroid peroxidase antibodies (TPOAbs) assessed by a negative–positive dichotomy and rarely take into account thyroglobulin antibodies (TgAbs). This study aimed at determining the association of TPOAbs and TgAbs, respectively, and interdependently, with maternal thyroid function.
Methods: This was a meta-analysis of individual participant cross-sectional data from 20 cohorts in the Consortium on Thyroid and Pregnancy. Women with multiple pregnancy, pregnancy by assisted reproductive technology, history of thyroid disease, or use of thyroid interfering medication were excluded. Associations of (log2) TPOAbs and TgAbs (with/without mutual adjustment) with cohort-specific z-scores of (log2) thyrotropin (TSH), free triiodothyronine (fT3), total triiodothyronine (TT3), free thyroxine (fT4), total thyroxine (TT4), or triiodothyronine:thyroxine (T3:T4) ratio were evaluated in a linear mixed model.
Results: In total, 51,138 women participated (51,094 had TPOAb-data and 27,874 had TgAb-data). Isolated TPOAb positivity was present in 4.1% [95% confidence interval, CI: 3.0 to 5.2], isolated TgAb positivity in 4.8% [CI: 2.9 to 6.6], and positivity for both antibodies in 4.7% [CI: 3.1 to 6.3]. Compared with antibody-negative women, TSH was higher in women with isolated TPOAb positivity (z-score increment 0.40, CI: 0.16 to 0.64) and TgAb positivity (0.21, CI: 0.10 to 0.32), but highest in those positive for both antibodies (0.54, CI: 0.36 to 0.71). There was a dose–response effect of higher TPOAb and TgAb concentrations with higher TSH (TSH z-score increment for TPOAbs 0.12, CI: 0.09 to 0.15, TgAbs 0.08, CI: 0.02 to 0.15). When adjusting analyses for the other antibody, only the association of TPOAbs remained statistically significant. A higher TPOAb concentration was associated with lower fT4 ($p < 0.001$) and higher T3:T4 ratio (0.09, CI: 0.03 to 0.14), however, the association with fT4 was not significant when adjusting for TgAbs ($p = 0.16$).
Conclusions: This individual participant data meta-analysis demonstrated an increase in TSH with isolated TPOAb positivity and TgAb positivity, respectively, which was amplified for individuals positive for both antibodies. There was a dose-dependent association of TPOAbs, but not TgAbs, with TSH when adjusting for the other antibody. This supports current practice of using TPOAbs in initial laboratory testing of pregnant women suspected of autoimmune thyroid disease. However, studies on the differences between TPOAb- and TgAb-positive women are needed to fully understand the spectrum of phenotypes.

Keywords: meta-analysis, pregnancy, thyroglobulin antibodies, thyroid, thyroid autoimmunity, thyroid peroxidase antibodies

Introduction

Thyroid autoimmunity in pregnant women is associated with altered thyroid function and adverse obstetric outcomes (1–5). Whether the latter arises from a general immune dysregulation or insufficient thyroid hormone production, or both, is uncertain. Because thyroid hormones regulate fetal development (1,6), maternal thyroid hormone physiology and metabolism change during pregnancy (7). This includes the pregnancy hormone human chorionic gonadotropin stimulating the thyrotropin (TSH) receptor to increase thyroid hormone production. Also, estrogen-induced increase in thyroxine (T4) binding globulin increases circulating total thyroxine (TT4) to 150% of prepregnancy levels by midgestation (7). Women with thyroid autoimmunity are less likely to meet the increased demands for thyroid hormone production during pregnancy (8).

Thyroid autoimmunity is the most common autoimmune aberration in women of reproductive age, with a prevalence up to 17% depending on population and cutoff for positivity (2,9). A distinction between thyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs) is rarely applied and most studies focus on TPOAbs. Up to 95% of patients with Hashimoto's thyroiditis have circulating TPOAbs, making this the preferred laboratory marker for autoimmune hypothyroidism (10–12). Thus, the American Thyroid Association' guidelines on thyroid and pregnancy recommend measurement of TPOAbs to assess thyroid autoimmunity (9). However, in some populations, TgAbs may be highly prevalent and could be an equally sensitive marker of thyroid dysfunction. Unuane *et al.* (13) found TgAbs associated with lower thyroid function in infertile women, with isolated TgAbs in 5% of the women. In a cohort of Danish pregnant women, the presence of either antibody was associated with higher TSH concentrations, however, only TgAb positivity was significantly associated with lower free thyroxine (fT4) concentrations (14,15). Positivity for both antibodies had the highest association with thyroid dysfunction (15). This was also the case in the First and Second Trimester Assessment of Aneuploidy Risk (FaSTER) trial of 9562 healthy pregnant women, finding higher TSH concentrations in TgAb-positive women than antibody-negative women, even higher in TPOAb-positive women, and highest in women positive for both (16).

Studies investigating the role of thyroid autoimmunity often focus on TPOAbs assessed by a dichotomous negative–positive distinction, which may be too simplistic. Korevaar *et al.* demonstrated a dose–response relationship of higher TPOAb concentrations with higher TSH in healthy pregnant

Articles

Association between maternal thyroid function and risk of gestational hypertension and pre-eclampsia: a systematic review and individual-participant data meta-analysis

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Summary

Background Adequate maternal thyroid function is important for an uncomplicated pregnancy. Although multiple observational studies have evaluated the association between thyroid dysfunction and hypertensive disorders of pregnancy, the methods and definitions of abnormalities in thyroid function tests were heterogeneous, and the results were conflicting. We aimed to examine the association between abnormalities in thyroid function tests and risk of gestational hypertension and pre-eclampsia.

Methods In this systematic review and meta-analysis of individual-participant data, we searched MEDLINE (Ovid), Embase, Scopus, and the Cochrane Database of Systematic Reviews from date of inception to Dec 27, 2019, for prospective cohort studies with data on maternal concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT_4), thyroid peroxidase (TPO) antibodies, individually or in combination, as well as on gestational hypertension, pre-eclampsia, or both. We issued open invitations to study authors to participate in the Consortium on Thyroid and Pregnancy and to share the individual-participant data. We excluded participants who had pre-existing thyroid disease or multifetal pregnancy, or were taking medications that affect thyroid function. The primary outcomes were documented gestational hypertension and pre-eclampsia. Individual-participant data were analysed using logistic mixed-effects regression models adjusting for maternal age, BMI, smoking, parity, ethnicity, and gestational age at blood sampling. The study protocol was registered with PROSPERO, CRD42019128585.

Findings We identified 1539 published studies, of which 33 cohorts met the inclusion criteria and 19 cohorts were included after the authors agreed to participate. Our study population comprised 46 528 pregnant women, of whom 39 826 (85·6%) women had sufficient data (TSH and FT_4 concentrations and TPO antibody status) to be classified according to their thyroid function status. Of these women, 1275 (3·2%) had subclinical hypothyroidism, 933 (2·3%) had isolated hypothyroxinaemia, 619 (1·6%) had subclinical hyperthyroidism, and 337 (0·8%) had overt hyperthyroidism. Compared with euthyroidism, subclinical hypothyroidism was associated with a higher risk of pre-eclampsia (2·1% *vs* 3·6%; OR 1·53 [95% CI 1·09–2·15]). Subclinical hyperthyroidism, isolated hypothyroxinaemia, or TPO antibody positivity were not associated with gestational hypertension or pre-eclampsia. In continuous analyses, both a higher and a lower TSH concentration were associated with a higher risk of pre-eclampsia (p=0·0001). FT_4 concentrations were not associated with the outcomes measured.

Interpretation Compared with euthyroidism, subclinical hypothyroidism during pregnancy was associated with a higher risk of pre-eclampsia. There was a U-shaped association of TSH with pre-eclampsia. These results quantify the risks of gestational hypertension or pre-eclampsia in women with thyroid function test abnormalities, adding to the total body of evidence on the risk of adverse maternal and fetal outcomes of thyroid dysfunction during pregnancy. These findings have potential implications for defining the optimal treatment target in women treated with levothyroxine during pregnancy, which needs to be assessed in future interventional studies.

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Introduction

Hypertensive disorders of pregnancy are some of the leading causes of maternal, fetal, and perinatal mortality worldwide, especially in low-income and middle-income countries.[1–3] The group of pregnancy-induced hypertensive disorders includes gestational hypertension, pre-eclampsia (de novo or superimposed on chronic hypertension), and eclampsia, which are all characterised

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REVIEW AND SCHOLARLY DIALOG

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Impact of Thyroid Autoimmunity on Assisted Reproductive Technology Outcomes and Ovarian Reserve Markers: An Updated Systematic Review and Meta-Analysis

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Background: Thyroid autoimmunity (TAI) has a high prevalence among women of reproductive age. Investigating its possible impact on ovarian function and fertility is, thus, of utmost relevance. The aim of this systematic review and meta-analysis was to elucidate the effect of TAI on both assisted reproductive technology (ART) outcomes and ovarian reserve.
Methods: This systematic review and meta-analysis was restricted to two groups of research articles investigating the association between TAI and: (1) autologous ART outcomes (i.e., fertilization rate [FR], implantation rate, clinical pregnancy rate [CPR], miscarriage rate, and live birth rate), (2) markers of ovarian reserve (i.e., anti-Müllerian hormone, basal follicle stimulating hormone, antral follicle count, and number of oocytes retrieved). Studies including women affected by overt hypo/hyperthyroidism were excluded. Relevant studies were identified by a systematic search in PubMed, MEDLINE, ClinicalTrials.gov, Embase, and Scopus, from database inception to May 1, 2022.
Results: From a total of 432 identified publications, 22 studies were included in Group 1 and 26 studies in Group 2. The presence of TAI was associated with a higher risk of miscarriage (7606 participants, odds ratio [OR] 1.52, confidence interval [CI 1.14–2.01], $p=0.004$, $I^2=53\%$), lower chance of embryo implantation (7118 participants, OR 0.72, [CI 0.59–0.88], $p=0.001$, $I^2=36\%$), and live birth (11417 participants, OR 0.73, [CI 0.56–0.94], $p=0.02$, $I^2=71\%$). These associations were no longer observed in a subgroup analysis of patients who exclusively underwent intracytoplasmic sperm injection (ICSI). The FR and CPR as well as the mean values of surrogate markers of oocyte quantity appeared not to be affected by TAI.
Conclusions: This data synthesis suggest a higher risk of adverse ART outcomes in women with positive TAI. However, the reliability of these findings is hampered by the relatively low quality of the evidence and significant heterogeneity in many of the meta-analyses. The possible protective effect of ICSI is promising but should be confirmed in controlled prospective clinical trials.
PROSPERO Registration ID: CRD42021236529.

Keywords: ART, female fertility, oocyte quality, ovarian reserve, thyroid autoimmunity

Introduction

OVARIAN RESERVE IS the number of oocytes that a woman possesses at a particular time in her life and inversely correlates with age.[1] Both follicular atresia and ovulation over time cooperate in determining the slow depletion of the initial pool of non-growing follicles.[1] Ovarian reserve may be evaluated by measuring biochemical (i.e., Anti-Müllerian hormone [AMH], basal follicle stimulating hormone [FSH], estradiol [E2], or inhibin B serum concentration) and

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Articles

Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Women positive for thyroid peroxidase antibodies (TPO-Ab) have a higher risk of recurrent pregnancy loss. Evidence on whether levothyroxine treatment improves pregnancy outcomes in women who are TPO-Ab positive women with recurrent pregnancy loss is scarce. The aim of this study was to determine if levothyroxine increases live birth rates in women who were TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

Methods The T4LIFE trial was an international, double-blind, placebo-controlled, phase 3 study done in 13 secondary and tertiary hospitals in the Netherlands, one tertiary hospital in Belgium, and one tertiary hospital in Denmark. Women (18–42 years) who were TPO-Ab positive, had two or more pregnancy losses, and had a thyroid stimulating hormone (TSH) concentration within the institutional reference range were eligible for inclusion. Women were excluded if they had antiphospholipid syndrome (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or β2-glycoprotein-I IgG or IgM antibodies), other autoimmune diseases, thyroid disease, previous enrolment in this trial, or contraindications for levothyroxine use. Before conception, women were randomly assigned (1:1) to receive either levothyroxine or placebo orally once daily. The daily dose of levothyroxine was based on preconception TSH concentration and ranged from 0·5–1·0 µg/kg bodyweight. Levothyroxine or placebo was continued until the end of pregnancy. The primary outcome was live birth, defined as the birth of a living child beyond 24 weeks of gestation measured in the intention-to-treat population. The trial was registered within the Netherlands Trial Register, NTR3364 and with EudraCT, 2011-001820-39.

Results Between Jan 1, 2013, and Sept 19, 2019, 187 women were included in the study: 94 (50%) were assigned to the levothyroxine group and 93 (50%) were assigned to the placebo group. The trial was prematurely stopped when 187 (78%) of the 240 predefined patients had been included because of slow recruitment. 47 (50%) women in the levothyroxine group and 45 (48%) women in the placebo group had live births (risk ratio 1·03 [95% CI 0·77 to 1·38]; absolute risk difference 1·6% [95% CI −12·7 to 15·9]). Seven (7%) women in the levothyroxine group and seven (8%) in the placebo group reported adverse events, none of them were directly related to the study procedure.

Interpretation Compared with placebo, levothyroxine treatment did not result in higher live birth rates in euthyroid women with recurrent pregnancy loss who were positive for TPO-Ab. On the basis of our findings, we do not advise routine use of levothyroxine in women who are TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

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Introduction

Recurrent pregnancy loss—defined as the loss of two or more pregnancies—is a significant health problem, affecting the physical and psychological wellbeing of prospective parents. It is a devastating experience for most couples and often leads to a long process of consulting multiple physicians and clinics in search for a cause and treatment.[1] Approximately 2% of women trying to conceive have recurrent pregnancy loss.[2]

Women positive for thyroid peroxidase antibodies (TPO-Ab) have a higher risk of single pregnancy loss and recurrent pregnancy loss.[3,4] TPO-Ab positivity is also associated with other pregnancy complications, including unexplained subfertility, preterm birth, and postpartum

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Subclinical Hypothyroidism with Negative for Thyroid Peroxidase Antibodies in Pregnancy: Intellectual Development of Offspring

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Background: The adverse impact of maternal negative TPOAb of gestational subclinical hypothyroidism (SCH-TPOAb$^-$) on the development of the offspring has not yet been clearly identified. A lingering controversy exists over the treatment of SCH-TPOAb$^-$ diagnosed during pregnancy. Therefore, this study was designed to evaluate the intellectual development of children of mothers who had SCH-TPOAb$^-$.
Methods: A number of 139 children were recruited; 112 children were born to SCH TPOAb$^-$ and 27 children were born to euthyroid TPOAb$^-$ mothers. Based on the mothers' thyrotropin (TSH) levels during pregnancy and whether or not they received levothyroxine (LT4) treatment, the children were assigned to four groups: Group A (2.5 mIU/L < TSH ≤4.0 mIU/L, $n=31$) and Group B (4.0 mIU/L < TSH ≤10.0 mIU/L, $n=26$), whose mothers were treated with LT4 before eight gestational weeks, and Group C (2.5 mIU/L < TSH ≤4.0 mIU/L, $n=27$) and Group D (4.0 mIU/L < TSH ≤10.0 mIU/L, $n=28$), whose mothers received no treatment. A total number of 27 children whose mother's serum TSH was <2.5 mIU/L and were TPOAb$^-$ during their pregnancy served as the control group (Group E). The intellectual development of two-year-old children was assessed and compared using the Gesell Development Diagnosis Scale.
Results: The developmental quotient (DQ) in Group D was 8.67 lower than this in Group E ($p<0.001$). More specifically, gross motor quotient, fine motor quotient, adaptability quotient (ABQ), language quotient (LQ), and individual social behavior quotient (ISBQ) of DQ in Group D were significantly lower than those in Group E. No significant differences were observed in DQ among Group A, Group B, Group C, and Group E ($p>0.05$). Spearman's rank correlation analysis showed that DQ, FMQ, ABQ, LQ, and ISBQ were significantly negatively correlated with the TSH level ($r=-0.417$, -0.253, -0.273, -0.436, and -0.272; $p<0.05$). In addition, multivariate logistic regression analysis revealed that mothers' education (short education), mothers' education (medium education), and TSH level (4.0 mIU/L < TSH ≤10.0 mIU/L) were both risk factors affecting the intellectual development of the offspring ($p<0.05$).
Conclusion: The effects of the intellectual development of the offspring with SCH-TPOAb$^-$ are related to the level of TSH. Standardized treatment for SCH-TPOAb$^-$ pregnant women before eight gestational weeks, whose TSH level was from 4.0 to 10.0 mIU/L, may significantly improve the intellectual development levels of the approximately two-year-old offspring. Although our study was a historical cohort study, the data analyzed provide the foundation for further investigation. Further prospective intervention trials with large numbers of participants are needed to confirm our conclusions. The Clinical Trial Registration number is 2021-K-84-02.

Keywords: intellectual development, pregnancy, subclinical hypothyroidism, thyroid peroxidase antibody

Introduction

SUBCLINICAL HYPOTHYROIDISM (SCH) is characterized by an elevated thyrotropin (TSH), accompanied by normal free thyroxine (fT4) levels. Results regarding whether a mildly elevated TSH concentration could increase adverse pregnancy outcomes have been vigorously debated (1,2). Therefore, the definitions of SCH in pregnancy have been changed in recent years. The 2011 ''Guidelines of the American Thyroid Association (ATA) for the Diagnosis and

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Research

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Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults

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IMPORTANCE Switching among generic levothyroxine sodium products made by different manufacturers typically occurs at the pharmacy and may affect serum thyrotropin (TSH) levels.

OBJECTIVE To compare TSH levels between patients who continued taking the same sourced generic levothyroxine product and those who switched.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness research study with 1:1 propensity matching used data from OptumLabs Data Warehouse, a national administrative claims database linked to laboratory test results. Adults aged 18 years or older were included if they filled a generic levothyroxine prescription between January 1, 2008, and June 30, 2019, and had a stable drug dose, the same drug manufacturer, and a normal TSH level (0.3-4.4 mIU/L) for at least 3 months before either continuing to take the same product or switching among generic levothyroxine products (index date). Patients were excluded if they were pregnant, had diagnosed hypopituitarism or hyperthyroidism, or had a medical condition or used medications that could affect thyrotropin levels. They were also excluded if they filled a prescription for other forms of thyroid replacement therapy between 6 months before the index date and when the first TSH level was obtained 6 weeks to 12 months after the index date. Data were analyzed from December 1, 2019, to November 24, 2021.

MAIN OUTCOMES AND MEASURES Proportion of individuals with a normal (0.3-4.4 mIU/L) or markedly abnormal (<0.1 or >10.0 mIU/L) TSH level using the first available laboratory result 6 weeks to 12 months after the index date. A propensity score model was developed to minimize confounding using logistic regression with the binary outcome of continuing the same sourced levothyroxine product vs switching generic levothyroxine. Covariates were demographics, comorbidities, and baseline TSH level. The balance among the treatment groups was evaluated by comparing standardized mean differences of baseline covariates between the groups.

RESULTS A total of 15 829 patients filled generic levothyroxine (mean [SD] age, 58.9 [14.6] years; 73.4% [11 624] were women; 4.5% [705] were Asian, 10.2% [1617] were Black, 11.4% [1801] were Hispanic, and 71.4% [11 295] were White individuals); of these patients, 56.3% [8905] received a daily levothyroxine dose of 50 µg or less. A total of 13 049 patients (82.4%) continued taking the same sourced preparation, and 2780 (17.6%) switched among generic levothyroxine preparations. Among 2780 propensity-matched patient pairs, the proportion of patients with a normal TSH level after the index date was 82.7% (2298) among nonswitchers and 84.5% (2348) among switchers (risk difference, −0.018; 95% CI, −0.038 to 0.002; *P* = .07). The proportion of patients with a markedly abnormal TSH level after the index date was 3.1% (87) among nonswitchers and 2.5% (69) among switchers (risk difference, 0.007; 95% CI, −0.002 to 0.015; *P* = .14). The mean (SD) TSH levels after the index date were 2.7 (2.3) mIU/L among nonswitchers and 2.7 (3.3) mIU/L among switchers (*P* = .94).

CONCLUSIONS AND RELEVANCE Results of this comparative effectiveness research study suggest that switching among different generic levothyroxine products was not associated with clinically significant changes in TSH level. These findings conflict with the current guideline recommendation that warns clinicians about potential changes in TSH level associated with switching among levothyroxine products sourced from different manufacturers.

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Supplemental content

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Extended Absorption of Liothyronine from Poly-Zinc-Liothyronine: Results from a Phase 1, Double-Blind, Randomized, and Controlled Study in Humans

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Background: L-triiodothyronine (LT3) has been increasingly used in combination with levothyroxine in the treatment of hypothyroidism. A metal coordinated form of LT3, known as poly-zinc-liothyronine (PZL), avoided in rats the typical triiodothyronine (T3) peak seen after oral administration of LT3.
Objectives: To evaluate in healthy volunteers (i) the pharmacokinetics (PK) of PZL-derived T3 after a single dose, (ii) the pharmacodynamics of PZL-derived T3, (iii) incidence of adverse events, and (iv) exploratory analysis of the sleep patterns after LT3, PZL, or placebo (PB) administration.
Methods: Twelve healthy volunteers 18–50 years of age were recruited for a Phase 1, double-blind, randomized, single-dose PB-controlled, crossover study to compare PZL against LT3 or PB. Subjects were admitted three separate times to receive a randomly assigned capsule containing PB, 50 μg LT3, or 50 μg PZL, and were observed for 48 hours. A 2-week washout period separated each admission.
Results: LT3-derived serum T3 levels exhibited the expected profile, with a T_{max} at 2 hours and return to basal levels by 24–36 hours. PZL-derived serum T3 levels exhibited ∼30% lower C_{max} that was 1 hour delayed and extended into a plateau that lasted up to 6 hours. This was followed by a lower but much longer plateau; by 24 hours serum T3 levels still exceeded ½ of C_{max}. Thyrotropin levels were similarly reduced in both groups.
Conclusion: PZL possesses the necessary properties to achieve a much improved T3 PK. PZL is on track to provide hypothyroid patients with stable levels of serum T3.

Keywords: liothyronine, slow release, metal coordination, hypothyroidism, thyroid, thyroxine

Introduction

For decades, hypothyroidism was treated with desiccated extracts of porcine thyroid glands, which contain thyroxine (T4) and triiodothyronine (T3) (1,2). With the development of thyrotropin (TSH) radioimmunoassay and the discovery that humans activate T4 to T3 (3), treatment with levothyroxine (LT4) became the standard of care (4,5). Nonetheless, deiodination of T4 to T3 may not be sufficient to account for the normal thyroidal secretion of T3. First noticed around 1974 (6), subsequent studies revealed that LT4-treated patients maintain ∼10% lower serum T3 levels compared with euthyroid individuals with similar TSH levels (7,8).

Some LT4-treated patients with normal TSH levels complain of residual symptoms of hypothyroidism (9–11). Compared with the general population, LT4-treated patients weigh ∼10 pounds more (7), have a slower rate of energy expenditure (12), show slightly higher serum cholesterol levels (13), and are more likely to be on therapy to lower cholesterol levels (14). The extent to which lower T3 levels contribute to the residual symptoms is unknown. In LT4-treated thyroidectomized rats, tissue euthyroidism only occurs after normalization of serum T3 (15). Such clear-cut evidence is not available for LT4-treated patients.

L-triiodothyronine (LT3) has been commercially available since 1956, but the pharmacokinetics (PK) of current LT3

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Effects of Acute Triiodothyronine Treatment in Patients with Anterior Myocardial Infarction Undergoing Primary Angioplasty: Evidence from a Pilot Randomized Clinical Trial (ThyRepair Study)

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Background: Thyroid hormone has a differential action on healthy and ischemic heart. Triiodothyronine (T3) administration improved postischemic cardiac function while it limited apoptosis in experimentally induced ischemia. Thus, the present study investigated the potential effects of acute liothyronine (LT3) treatment in patients with anterior myocardial infarction.
Methods: This study is a pilot, randomized, double-blind, placebo-controlled trial (ThyRepair study). We randomized 52 patients and analyzed data from 37 patients ($n=16$ placebo and $n=21$ LT3), per prespecified per protocol analysis. We excluded three patients who had died of cardiovascular causes (one in placebo and two in LT3 arm), four with small infarct size below a pre-specified threshold (in the placebo arm), and the rest, who lacked follow-up data. LT3 treatment started after stenting as an intravenous (i.v.) bolus injection of 0.8 μg/kg of LT3 followed by a constant infusion of 0.113 μg/kg/h i.v. for 48 hours. All patients had cardiac magnetic resonance (CMR) at hospital discharge and 6 months follow-up. The primary end point was CMR left ventricular (LV) ejection fraction (LVEF) and secondary endpoints were LV volumes, infarct volume (IV), and safety.
Results: The CMR LVEF% at 6 months was 53.6 ± 9.5 for the LT3-treated group and 48.6 ± 11 for placebo, $p=0.15$. Acute LT3 treatment resulted in a significantly lower LV end-diastolic volume index (92.2 ± 16.8 mL/m^2 vs. 107.5 ± 22.2, $p=0.022$) and LV systolic volume index (47.5 ± 13.9 mL/m^2 vs. 61.3 ± 21.7, $p=0.024$) at hospital discharge, but not at 6 months. There was no statistically significant difference in CMR IV at hospital discharge between the groups ($p=0.24$). CMR IV tended to be lower in the LT3-treated group at 6 months (18.7 ± 9.5 vs. 25.9 ± 11.7, in placebo, $p=0.05$). Serious, life-threatening events related to LT3 treatment were not observed. A tendency for an increased incidence of atrial fibrillation (AF) was found in the LT3 group during the first 48 hours (19% for T3 group vs. 5% for placebo, $p=0.13$).
Conclusion: This pilot randomized, placebo-controlled trial study suggests potential favorable effects (acute cardiac dilatation and 6-month IV) as well as potential concerns regarding a higher risk of AF after LT3 administration early after myocardial infarction, which should be tested in a larger scale study.

Keywords: cardiac remodeling, heart failure, myocardial infarction, reperfusion, thyroid hormone

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Association of Thyroid Hormone Treatment Intensity With Cardiovascular Mortality Among US Veterans

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Abstract

IMPORTANCE Cardiovascular disease is the leading cause of death in the United States. Synthetic thyroid hormones are among the 3 most commonly prescribed medications, yet studies evaluating the association between the intensity of thyroid hormone treatment and cardiovascular mortality are scarce.

OBJECTIVE To evaluate the association between thyroid hormone treatment intensity and cardiovascular mortality.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data on 705 307 adults who received thyroid hormone treatment from the Veterans Health Administration Corporate Data Warehouse between January 1, 2004, and December 31, 2017, with a median follow-up of 4 years (IQR, 2-9 years). Two cohorts were studied: 701 929 adults aged 18 years or older who initiated thyroid hormone treatment with at least 2 thyrotropin measurements between treatment initiation and either death or the end of the study period, and, separately, 373 981 patients with at least 2 free thyroxine (FT_4) measurements. Data were merged with the National Death Index for mortality ascertainment and cause of death, and analysis was conducted from March 25 to September 2, 2020.

EXPOSURES Time-varying serum thyrotropin and FT_4 levels (euthyroidism: thyrotropin level, 0.5-5.5 mIU/L; FT_4 level, 0.7-1.9 ng/dL; exogenous hyperthyroidism: thyrotropin level, <0.5 mIU/L; FT_4 level, >1.9 ng/dL; exogenous hypothyroidism: thyrotropin level, >5.5 mIU/L; FT_4 level, <0.7 ng/dL).

MAIN OUTCOMES AND MEASURES Cardiovascular mortality (ie, death from cardiovascular causes, including myocardial infarction, heart failure, or stroke). Survival analyses were performed using Cox proportional hazards regression models using serum thyrotropin and FT_4 levels as time-varying covariates.

RESULTS Of the 705 307 patients in the study, 625 444 (88.7%) were men, and the median age was 67 years (IQR, 57-78 years; range, 18-110 years). Overall, 75 963 patients (10.8%) died of cardiovascular causes. After adjusting for age, sex, traditional cardiovascular risk factors (eg, hypertension, smoking, and previous cardiovascular disease or arrhythmia), patients with exogenous hyperthyroidism (eg, thyrotropin levels, <0.1 mIU/L: adjusted hazard ratio [AHR], 1.39; 95% CI, 1.32-1.47; FT_4 levels, >1.9 ng/dL: AHR, 1.29; 95% CI, 1.20-1.40) and patients with exogenous hypothyroidism (eg, thyrotropin levels, >20 mIU/L: AHR, 2.67; 95% CI, 2.55-2.80; FT_4 levels, <0.7 ng/dL: AHR, 1.56; 95% CI, 1.50-1.63) had increased risk of cardiovascular mortality compared with individuals with euthyroidism.

(continued)

Key Points

Question Is there an association between the intensity of thyroid hormone treatment and cardiovascular mortality?

Findings In this population-based cohort study of 705 307 adults who received thyroid hormone treatment, 10.8% died of cardiovascular causes. Both exogenous hyperthyroidism and exogenous hypothyroidism were associated with increased risk of cardiovascular mortality after adjusting for a comprehensive set of demographic and traditional cardiovascular risk factors.

Meaning These findings suggest that the intensity of thyroid hormone treatment may be a modifiable risk factor for cardiovascular mortality.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE This study suggests that both exogenous hyperthyroidism and exogenous hypothyroidism were associated with increased risk of cardiovascular mortality. These findings emphasize the importance of maintaining euthyroidism to decrease cardiovascular risk and death among patients receiving thyroid hormone treatment.

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Introduction

Despite widespread efforts at prevention and advances in diagnosis and treatment, cardiovascular disease remains the leading cause of death in the United States and affects nearly 50% of individuals in the US aged 20 years or older.[1,2] In addition, it is estimated that the annual financial burden of heart disease in the United States is more than $200 billion.[1] Although many cardiovascular risk factors are known (eg, hypertension, diabetes, and smoking), the persistent public health impact of cardiovascular disease mandates a more complete understanding of novel risk factors.[1,3] A recent study has shown that the intensity of thyroid hormone treatment is a modifiable risk factor for incident atrial fibrillation and stroke[4]; however, its association with cardiovascular mortality remains unclear.

Thyroid hormone treatment is widespread, with levothyroxine prescriptions consistently among the top 3 of all prescription medications in the United States in the past decade.[5-7] However, up to 50% of patients who receive thyroid hormone treatment may exhibit exogenous hyperthyroidism or hypothyroidism (ie, have thyrotropin levels below or above the reference range, respectively).[8,9] The associations of long-term exogenous hyperthyroidism and hypothyroidism with clinical outcomes, including cardiovascular risk and all-cause mortality, have recently been investigated.[4,10-13] Previous studies have shown that serum thyrotropin concentrations outside the euthyroid range correlated with increased cardiovascular risk and all-cause mortality among patients who received thyroid hormone treatment for hypothyroidism[11,13,14]; however, studies focusing specifically on the association between the intensity of thyroid hormone treatment and cardiovascular mortality are lacking.

The objective of this study was to evaluate the association between the intensity of thyroid hormone treatment and cardiovascular mortality using a nationwide, population-based cohort of adults receiving thyroid hormone treatment. We hypothesized that both exogenous hyperthyroidism and hypothyroidism would be associated with increased cardiovascular mortality, even when adjusting for age, sex, and traditional cardiovascular risk factors, such as hypertension and smoking.

Methods

Data Source and Study Population

We conducted a population-based, retrospective cohort study between January 1, 2004, and December 31, 2017, using data from the Veterans Health Administration.[15] This large, integrated health care system provides care to more than 9 million US veterans annually.[16] Deidentified patient-level data were obtained using the Veterans Health Administration Corporate Data Warehouse database, which is a national centralized data repository for the Veterans Health Administration. This database provides clinical and administrative information, including diagnoses, laboratory data, pharmacy prescription fills, health factors, and demographic information.[17-19] These data were then linked to the National Death Index for mortality ascertainment and to identify cause of death.[20] The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[21] This study was exempt from the University of Michigan institutional review board and approved by the Ann Arbor Veteran Affairs institutional review board, which included a waiver of informed consent as data were deidentified.

The study population included 705 307 patients aged 18 years or older who initiated thyroid hormone treatment during the study period. Of these patients, 701 929 had at least 2 outpatient measurements of serum thyrotropin between initiation of thyroid hormone treatment and either death or the end of the study. We also studied patients aged 18 years or older receiving thyroid hormone treatment who had at least 2 outpatient free thyroxine (FT_4) measurements between initiation of thyroid hormone treatment and death or study conclusion (n = 373 981). Patients with a history of thyroid cancer (n = 15 090) were excluded because lower thyrotropin levels are often targeted to reduce the risk of disease recurrence. In addition, patients prescribed lithium (n = 23 715) or amiodarone (n = 70 358) were excluded because these medications have a known association with abnormal thyroid function test results. Patients who did not have a documented date of birth (n = 17) were also excluded prior to attaining the final analytic sample.

Measures

Study Outcome

The study outcome was cardiovascular mortality as determined by cause of death from cardiovascular diseases based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes (including codes I00-I99). The incident event (ie, death from cardiovascular causes) occurred after initiation of thyroid hormone treatment and through December 31, 2017, with a median follow-up of 4 years (IQR, 2-9 years).

Exposure Variables

The exposure variables were time-varying serum thyrotropin and FT_4 levels. Serum thyrotropin and FT_4 levels were compiled using the patients' laboratory records and assembled into 2 separate longitudinal data sets. Prior to analyses, thyrotropin levels were log transformed owing to nonnormal distribution, as has been done in prior studies cited in the literature.[4,10,22] Although there is some variation by laboratory, the reference ranges for thyrotropin and FT_4 levels at the Ann Arbor VA laboratory were used for analyses (thyrotropin level, 0.5-5.5 mIU/L; FT_4 level, 0.7-1.9 ng/mL [to convert to picomoles per liter, multiply by 12.87]). Of note, 99.1% of patients (370 603 of 373 981) who had at least 2 FT_4 measurements also had at least 2 thyrotropin measurements.

Covariates

Fixed covariates included patient sex, age, race, ethnicity, and smoking status. Data on sex were obtained from the Veterans Health Administration Corporate Data Warehouse database at study entry and recorded as male or female. Age was analyzed both as a continuous variable and as a categorical variable using clinically meaningful categories (18-49, 50-64, 65-74, 75-84, and ≥85 years). Race was self-reported as Alaska Native or American Indian, Asian, Black, Native Hawaiian or Pacific Islander, White, multiracial, or unknown. Because the number of patients who identified as Alaska Native or American Indian, Asian, Native Hawaiian or Pacific Islander, or multiracial was small, these groups were collapsed and classified as "other" for analyses. Ethnicity was self-described as Hispanic, non-Hispanic, or unknown. Smoking status was determined at the time of initiation of thyroid hormone treatment and was recorded as never smoker, current or former smoker, or unknown. Time-varying covariates included hypertension, hyperlipidemia, diabetes, prior history of cardiovascular disease (coronary artery disease, ischemic heart disease, heart failure, or stroke), and prior history of cardiac arrhythmia and were determined by using *International Classification of Diseases, Ninth Revision*; *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; and *Current Procedure Terminology, Fourth Edition* codes.

Statistical Analysis

Data were analyzed from March 25 to September 2, 2020. Descriptive information was tabulated for both the thyrotropin and FT_4 cohorts. Univariate associations between individual factors and the outcome were examined. We then performed separate survival analyses using Cox proportional hazards regression models to determine correlates for the study outcome (ie, cardiovascular mortality). In these models, the exposure variables (thyrotropin and FT_4 levels) were treated as time-varying covariates, which allowed us to better account for variability in these measures during the study period. Serum thyrotropin and FT_4 levels were treated as categorical variables. Exogenous hyperthyroidism was defined by thyrotropin levels lower than 0.5 mIU/L (categorized as <0.1 mIU/L and 0.1-0.5 mIU/L) or by FT_4 levels higher than 1.9 ng/dL; euthyroidism was defined by thyrotropin levels from 0.5 to 5.5 mIU/L and FT_4 levels from 0.7 to 1.9 ng/dL; and exogenous hypothyroidism was defined by thyrotropin levels higher than 5.5 mIU/L (categorized as >5.5 to <7.5 mIU/L, 7.5 to <10 mIU/L, 10-20 mIU/L, and >20 mIU/L) or by FT_4 levels lower than 0.7 ng/dL. When multiple measurements were present in an annual time period (defined as a calendar year), which occurred for 5.9% of the thyrotropin cohort (41 414 of 701 929) and 2.7% of the FT_4 cohort (10 097 of 373 981), the geometric mean was calculated for the thyrotropin cohort, and the arithmetic mean was calculated for the FT_4 cohort; these values were used for analyses. For both models, additional fixed covariates included patient sex, age, race, ethnicity, and smoking status, and additional time-varying covariates included hypertension, hyperlipidemia, diabetes, prior history of cardiovascular disease, and prior history of cardiac arrhythmia. No observations were excluded from the statistical analyses owing to missing information.

All statistical analyses were conducted using SAS, version 7.15 HF8 (SAS Institute Inc). A 95% CI was used to determine statistical significance, and $P < .05$ from 2-sided tests was considered statistically significant for all analyses. Model adequacy was assessed using generalized residuals-based diagnostics in SAS PROC PHREG.

Results

Table 1 provides key demographic, comorbidity, and mortality data for the 705 307 patients receiving thyroid hormone treatment. Most patients were male (625 444 [88.7%]), White (559 173 [79.3%]), non-Hispanic (609 537 [86.4%]), had a history of hypertension (582 061 [82.5%]) or hyperlipidemia (582 389 [82.6%]), and were current or former smokers (467 606 [66.3%]). The median age was 67 years (IQR, 57-78 years; range, 18-110 years). During the study period, 224 943 patients (31.9%) died of any cause, and 75 963 patients (10.8%) died of cardiovascular disease.

The frequency distributions of the number of thyrotropin measurements and the number of FT_4 measurements overall and in association with the number of years, as well as the mean number of thyrotropin measurements and FT_4 measurements per patient per year, are shown in eTable 1 and eFigures 1 and 2 in the Supplement. In univariate analyses, patient sex, age, race, ethnicity, smoking status, hypertension, hyperlipidemia, diabetes, prior history of cardiovascular disease, prior history of cardiac arrhythmia, and serum thyrotropin and FT_4 levels were significantly associated with cardiovascular mortality.

Table 2 shows results from survival analyses using Cox proportional hazards regression models demonstrating patient characteristics associated with cardiovascular mortality for the thyrotropin and FT_4 cohorts. When adjusting for age, sex, and other relevant demographic and traditional cardiovascular risk factors (such as hypertension and smoking), patients with exogenous hyperthyroidism (eg, thyrotropin levels <0.1 mIU/L: adjusted hazard ratio [AHR], 1.39; 95% CI, 1.32-1.47; FT_4 levels >1.9 ng/dL: AHR, 1.29; 95% CI, 1.20-1.40) and patients with exogenous hypothyroidism (eg, thyrotropin levels >20 mIU/L: AHR, 2.67; 95% CI, 2.55-2.80; FT_4 levels <0.7 ng/dL: AHR, 1.56; 95% CI, 1.50-1.63) had an increased risk of cardiovascular mortality compared with individuals with euthyroidism. Furthermore, the risk of cardiovascular mortality increased

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progressively with lower and higher thyrotropin levels compared with euthyroidism. Similar findings were obtained when age was treated as a continuous variable (eTable 2 in the Supplement).

The forest plot in the **Figure** illustrates the association between serum thyrotropin and FT_4 levels with cardiovascular mortality after adjustment for relevant demographic and cardiovascular risk factors. Cardiovascular mortality was higher among patients with exogenous hyperthyroidism (thyrotropin levels <0.1 mIU/L: AHR, 1.39; 95% CI, 1.32-1.47; thyrotropin levels of 0.1 to <0.5 mIU/L: AHR, 1.13; 95% CI, 1.09-1.17; FT_4 levels >1.9 ng/dL: AHR, 1.29; 95% CI, 1.20-1.40) and those with exogenous hypothyroidism (thyrotropin levels from >5.5 to <7.5 mIU/L: AHR, 1.42; 95% CI, 1.38-1.46; thyrotropin levels from 7.5 to <10 mIU/L: AHR, 1.76; 95% CI, 1.70-1.82; thyrotropin levels of 10-20 mIU/L: AHR, 2.13; 95% CI, 2.05-2.21; thyrotropin levels >20 mIU/L: AHR, 2.67; 95% CI, 2.55-2.80; FT_4 levels <0.7 ng/dL: AHR, 1.56; 95% CI, 1.50-1.63), with risk increasing with higher serum thyrotropin levels compared with individuals with euthyroidism.

Discussion

In this population-based study of a large cohort of adults receiving thyroid hormone treatment, we found that the intensity of thyroid hormone treatment was associated with cardiovascular mortality.

Table 1. Characteristics of Patients Receiving Thyroid Hormone Therapy

Characteristic	Patients, No. (%)		
	All patients (N = 705 307)	Patients with at least 2 thyrotropin measurements (n = 701 929)	Patients with at least 2 free thyroxine measurements (n = 373 981)[a]
Sex			
Male	625 444 (88.7)	622 396 (88.7)	325 217 (87.0)
Female	79 863 (11.3)	79 533 (11.3)	48 764 (13.0)
Age, y			
18-49	89 765 (12.7)	89 462 (12.7)	57 046 (15.2)
50-64	224 876 (31.9)	223 986 (31.9)	133 202 (35.6)
65-74	169 177 (24.0)	168 408 (24.0)	85 917 (23.0)
75-84	165 944 (23.5)	164 939 (23.5)	74 762 (20.0)
≥85	55 545 (7.9)	55 134 (7.9)	23 054 (6.2)
Race			
Black	49 535 (7.0)	49 113 (7.0)	31 219 (8.3)
White	559 173 (79.3)	556 879 (79.3)	299 043 (80.0)
Other[b]	15 903 (2.3)	15 833 (2.3)	8594 (2.3)
Unknown	80 696 (11.4)	80 104 (11.4)	35 125 (9.4)
Ethnicity			
Hispanic	37 740 (5.4)	37 636 (5.4)	20 685 (5.5)
Non-Hispanic	609 537 (86.4)	606 759 (86.4)	328 766 (87.9)
Unknown	58 030 (8.2)	57 534 (8.2)	24 530 (6.6)
Smoking			
Never	92 057 (13.1)	91 757 (13.1)	56 815 (15.2)
Current or former	467 606 (66.3)	465 392 (66.3)	248 501 (66.4)
Unknown	145 644 (20.7)	144 780 (20.6)	68 665 (18.4)
Hypertension	582 061 (82.5)	579 453 (82.6)	308 899 (82.6)
Hyperlipidemia	582 389 (82.6)	580 049 (82.6)	313 044 (83.7)
Diabetes	302 641 (42.9)	301 407 (42.9)	163 373 (43.7)
Prior history of cardiovascular disease	114 534 (16.2)	113 993 (16.2)	65 453 (17.5)
Prior history of cardiac arrhythmia	184 822 (26.2)	184 167 (26.2)	102 573 (27.4)
Study outcome			
Death from cardiovascular causes	75 963 (10.8)	75 319 (10.7)	33 142 (8.9)

[a] There were 99.1% of patients who had at least 2 free thyroxine measurements and also at least 2 thyrotropin measurements.

[b] Composed of the following races: Alaska Native or American Indian, Asian, Native Hawaiian or Pacific Islander, and multiracial.

Table 2. Characteristics of Patients Receiving Thyroid Hormone Therapy Associated With Cardiovascular Mortality

Patient characteristic	Adjusted hazard ratio (95% CI)
Thyrotropin cohort	
Thyrotropin level (annual geometric mean), mIU/L	
<0.1	1.39 (1.32-1.47)
0.1 to <0.5	1.13 (1.09-1.17)
0.5 to 5.5	1 [Reference]
>5.5 to <7.5	1.42 (1.38-1.46)
7.5 to <10	1.76 (1.70-1.82)
10 to 20	2.13 (2.05-2.21)
>20	2.67 (2.55-2.80)
Sex	
Male	1 [Reference]
Female	0.68 (0.66-0.71)
Age, y	
18-49	1 [Reference]
50-64	2.87 (2.68-3.07)
65-74	5.97 (5.59-6.38)
75-84	14.55 (13.63-15.53)
≥85	27.40 (25.62-29.29)
Race	
Black	0.96 (0.93-1.00)
White	1 [Reference]
Other[a]	0.90 (0.85-0.95)
Unknown	1.34 (1.30-1.37)
Ethnicity	
Hispanic	0.65 (0.62-0.67)
Non-Hispanic	1 [Reference]
Unknown	1.74 (1.69-1.78)
Smoking	
Never	1 [Reference]
Current or former	1.22 (1.19-1.25)
Unknown	1.52 (1.48-1.56)
Hypertension	1.60 (1.56-1.65)
Hyperlipidemia	0.92 (0.90-0.93)
Diabetes	1.41 (1.38-1.43)
Prior history of cardiovascular disease	1.40 (1.38-1.42)
Prior history of cardiac arrhythmia	1.97 (1.94-2.00)
Free thyroxine cohort	
Free thyroxine level (annual arithmetic mean), ng/dL[b]	
<0.7	1.56 (1.50-1.63)
0.7-1.9	1 [Reference]
>1.9	1.29 (1.20-1.40)
Sex	
Male	1 [Reference]
Female	0.64 (0.60-0.67)
Age, y	
18-49	1 [Reference]
50-64	2.50 (2.29-2.72)
65-74	4.98 (4.58-5.43)
75-84	11.81 (10.86-12.84)
≥85	20.44 (18.74-22.28)

(continued)

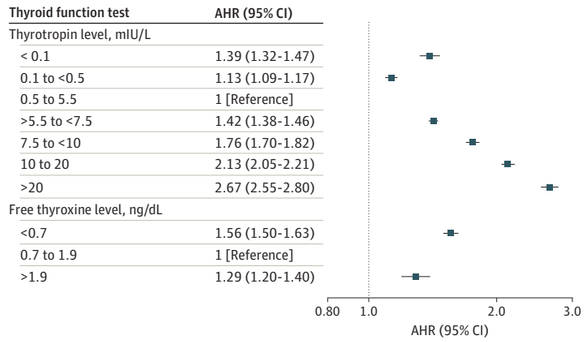
Table 2. Characteristics of Patients Receiving Thyroid Hormone Therapy Associated With Cardiovascular Mortality (continued)

Patient characteristic	Adjusted hazard ratio (95% CI)
Race	
Black	0.93 (0.89-0.98)
White	1 [Reference]
Other[a]	0.98 (0.90-1.06)
Unknown	1.36 (1.31-1.41)
Ethnicity	
Hispanic	0.65 (0.61-0.69)
Non-Hispanic	1 [Reference]
Unknown	1.64 (1.57-1.71)
Smoking	
Never	1 [Reference]
Current or former	1.22 (1.18-1.26)
Unknown	1.44 (1.38-1.49)
Hypertension	1.75 (1.68-1.82)
Hyperlipidemia	0.95 (0.92-0.98)
Diabetes	1.41 (1.37-1.44)
Prior history of cardiovascular disease	1.47 (1.43-1.50)
Prior history of cardiac arrhythmia	2.07 (2.02-2.12)

[a] Composed of the following races: Alaska Native or American Indian, Asian, Native Hawaiian or Pacific Islander, and multiracial.

[b] To convert free thyroxine to picomoles per liter, multiply by 12.87.

Figure. Association of Thyrotropin and Free Thyroxine Levels With Cardiovascular Mortality



This forest plot illustrates the association of serum thyrotropin and free thyroxine levels with cardiovascular mortality after adjustment for relevant demographic and cardiovascular risk factors. To convert free thyroxine to picomoles per liter, multiply by 12.87. AHR indicates adjusted hazard ratio.

Both exogenous hyperthyroidism and hypothyroidism were associated with increased risk of cardiovascular mortality, even when adjusting for relevant demographic and traditional cardiovascular risk factors as well as previous history of cardiovascular disease and/or arrhythmia. In addition, our findings suggest that the risk of cardiovascular mortality is directly associated with the degree of thyrotropin abnormality outside the euthyroid range, such that thyrotropin levels lower than 0.1 mIU/L and higher than 20 mIU/L were associated with the highest increased risk. We observed that the AHRs increased more rapidly for older age categories in the thyrotropin cohort compared with the FT_4 cohort. This finding may suggest that the thyrotropin level is more strongly associated with cardiovascular risk than is the FT_4 level in older adults. From a clinical perspective, older adults, and particularly the oldest old (aged ≥85 years), appear to be the most vulnerable, with increased risk of cardiovascular mortality with both exogenous hyperthyroidism and hypothyroidism.

A few prior studies have evaluated the association between serum thyrotropin levels and cardiovascular outcomes among patients receiving thyroid hormone treatment.[4,10,11,13] Flynn et al[10] used a time-weighted mean thyrotropin level to group patients and demonstrated increased risk of a

composite outcome of cardiovascular admission or death with suppressed or elevated serum thyrotropin levels in a cohort of 17 684 patients treated with levothyroxine. In addition, Lillevang-Johansen et al[11] performed a case-control study of 20 487 patients with incident cardiovascular disease nested within a larger cohort of individuals with hypothyroidism and showed that, compared with matched controls, patients with treated hypothyroidism (n = 636) had increased odds of incident cardiovascular disease and all-cause mortality for each 6-month period of overtreatment or undertreatment. Finally, Thayakaran et al[13] evaluated the association between thyrotropin concentration and incident cardiovascular outcomes, but not mortality, among patients with hypothyroidism (N = 160 439), adjusting for levothyroxine treatment. This study found that compared with a thyrotropin level of 2 to 2.5 mIU/L, a thyrotropin level higher than 10 mIU/L was associated with an increased risk of ischemic heart disease and heart failure. None of these studies evaluated the association of the intensity of thyroid hormone treatment with cardiovascular mortality, possibly because of inadequate power. Our study is novel because, unlike these prior studies, it specifically evaluated the association between cardiovascular mortality and serum thyrotropin or FT_4 level, while adjusting for a comprehensive list of possible confounders, exclusively in a large cohort of patients receiving thyroid hormone treatment.

Our study findings have the potential to affect how we think about the risks and benefits associated with thyroid hormone treatment, particularly for vulnerable populations, such as older adults or those with underlying cardiovascular disease. Because synthetic thyroid hormones have consistently been one of the top 3 most frequently prescribed medications in the United States in the past decade,[5-7] and because cardiovascular disease remains the leading cause of death, an association between the intensity of thyroid hormone treatment and cardiovascular death has far-reaching implications for both patients and physicians. Although the variability in thyrotropin and FT_4 levels and thyroid hormone dose adjustments are an inevitable reality for most patients, our study emphasizes the importance of regular monitoring of thyroid function test results and correction of both overtreatment and undertreatment with exogenous thyroid hormones to reduce patient harm, particularly for older adults who are at higher risk for adverse effects.[4,8,9,23]

Strengths and Limitations

Our study has several strengths. First, it is a large, population-based study using data from the largest integrated health care system in the United States. Second, we used serum thyrotropin and FT_4 levels as time-varying covariates, which allowed us to incorporate all qualifying thyrotropin and FT_4 levels measured during the study period. Because prior studies have shown wide variability in thyroid function test results over time among patients receiving thyroid hormone treatment,[8,9,24,25] this method facilitates a more comprehensive evaluation of the association between thyroid function test results and cardiovascular mortality than would be possible using a single value at study entry in a cross-sectional design. Third, while the use of an internal comparator cannot completely eliminate risk of confounding, it avoids the inherent limitations of comparing an exposed group with the background population. Fourth, because the Veterans Health Administration Corporate Data Warehouse includes comprehensive information on patient demographic characteristics, comorbid conditions, and smoking status, we were able to account for most traditional cardiovascular risk factors.

Population-based studies using databases have some inherent limitations that merit consideration. Although we were able to account for most known cardiovascular risk factors, we were not able to control for other potential confounders, such as alcohol status and body mass index or rates of obesity, because these could not be accurately captured in the Veterans Health Administration data. Adjusting for a comprehensive list of cardiovascular risk factors, including hypertension, hyperlipidemia, diabetes, and prior history of cardiovascular disease, which represent some of the downstream effects of obesity, partially mitigates this limitation. In addition, we were unable to determine the degree to which risk factors for cardiovascular mortality, such as diabetes and hypertension, were appropriately treated. We also acknowledge that we were not able to

account for all medications and supplements that could interfere with thyroid hormone metabolism and action and/or thyroid function test results. Furthermore, because cause of death in the National Death Index relies on death certificates, risk of misclassification is possible.[26] Because the Veterans Health Administration population is predominantly male, women are generally underrepresented in studies using this database. However, because the risk of cardiovascular disease is higher for men than for women[27] and because more than 70 000 women were included in this cohort, the results of this study are highly clinically relevant. Additionally, this was an observational study, and a causal relationship between the intensity of thyroid hormone treatment and cardiovascular mortality could not be definitively established.

Conclusions

In this population-based cohort of patients receiving thyroid hormone treatment, we found that both exogenous hyperthyroidism and hypothyroidism were associated with an increased risk of cardiovascular mortality after adjusting for a comprehensive set of demographic and traditional cardiovascular risk factors. Cardiovascular disease remains the leading cause of death in the United States, and its economic impact is enormous. Identifying and addressing modifiable risk factors continues to be critically important to reducing the rates of cardiovascular disease and mortality. The emergence of the intensity of thyroid hormone treatment as a potential associated risk factor provides a highly relevant and easily modifiable clinical parameter for patients who receive thyroid hormone treatment.

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Author Contributions: Mr Reyes-Gastelum and Dr Papaleontiou 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.

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ΘΥΡΟΕΙΔΗΣ | ΣΠΥΡΙΔΟΥΛΑ ΜΑΡΑΚΑ

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SUPPLEMENT.

eTable 1. Frequency Distributions of the Number of Thyrotropin and Free Thyroxine Measurements
eFigure 1. Mean Number of Thyrotropin Measurements per Patient, by Year
eFigure 2. Mean Number of Free Thyroxine Measurements per Patient, by Year
eTable 2. Characteristics of Patients on Thyroid Hormone Therapy Associated With Cardiovascular Mortality (Age as a Continuous Variable)

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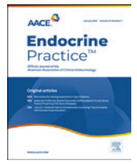

Original Article

Brain Fog in Hypothyroidism: Understanding the Patient's Perspective

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ABSTRACT

Objective: Patient-centered studies have shown that several patients on thyroid hormone replacement therapy for hypothyroidism exhibit persistent symptoms, including "brain fog." Here, we aimed to determine which of these specific symptoms are associated with brain fog, identify patient-reported factors that modify these symptoms, and identify patient concerns related to brain fog not included in thyroid-specific questionnaires.

Methods: A survey on brain fog symptoms adapted from thyroid-specific patient-reported outcome was distributed online. Textual data analysis was performed to identify common areas of concern from open-ended survey responses.

Results: A total of 5170 participants reporting brain fog while being treated for hypothyroidism were included in the analysis. Of these, 2409 (46.6%) participants reported symptom onset prior to the diagnosis of hypothyroidism, and 4096 (79.2%) participants experienced brain fog symptoms frequently. Of the symptoms listed, participants associated fatigue and forgetfulness most frequently with brain fog. More rest was the most common factor provided for improving symptoms. The textual data analysis identified areas of concern that are not often included in thyroid-specific quality of life questionnaires, including a focus on the diagnosis of hypothyroidism, the types and doses of medications, and the patient-doctor relationship.

Conclusion: Brain fog in patients treated for hypothyroidism was associated most frequently with fatigue and cognitive symptoms. Several additional areas of patient concern were found to be associated with brain fog, which are not typically addressed in thyroid-specific questionnaires.

Introduction

It has become common in medical practice that many patients taking thyroid hormone complain of "brain fog," which often refers to perceived cognitive impairment, physical fatigue, or mood disturbances. Brain fog has also been associated with several other disorders and patient conditions, including menopause syndrome, chemotherapy treatment, celiac disease, lupus, chronic fatigue syndrome, COVID-19 (most recently), and others.[1-7] Due to the nonspecific nature of the term and the fact that the condition is not well characterized in the endocrine literature, brain fog represents a significant diagnostic and therapeutic challenge in patients with hypothyroidism.

The complaint of brain fog in patients with hypothyroidism may signify a state of persistent hypothyroidism despite treatment. In several cases, this may be due to undertreatment with thyroid hormone replacement, given that it has been observed that up to 35% of patients with hypothyroidism have elevated serum thyroid-stimulating hormone (TSH) levels.[8,9] The presence of other

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Abbreviations: ECUs, elementary context units; LT3, liothyronine; LT4, levothyroxine; OR, odds ratio; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.

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Clinical Research Article

SARS-CoV-2 mRNA Vaccination and Graves' Disease: A Report of 12 Cases and Review of the Literature

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Abstract

Context and objective: Thyroid autoimmunity has been reported to be associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the SARS-CoV-2 vaccination recently. We report a series of patients who presented with new onset or relapse of Graves' disease-related hyperthyroidism shortly after receiving the SARS-CoV-2 messenger RNA (mRNA) vaccine at a single tertiary institution in Singapore.

Methods and results: We describe 12 patients who developed hyperthyroidism within a relatively short interval (median onset, 17 [range, 5-63] days) after receiving the SARS-CoV-2 mRNA vaccine. The majority were females (11/12) with median age of 35.5 (range, 22-74) years. Six patients had new-onset hyperthyroidism, whereas the other 6 had relapse of previously well-controlled Graves' disease. TSH receptor antibody concentrations ranged from 2.4 to 32 IU/L. The majority of the patients were able to go for the second dose of the vaccine without any further exacerbations. Literature review revealed 21 other similar cases reported from across the world.

Conclusion: Our case series provides insight into the characteristics of individuals in whom Graves' disease was triggered by the SARS-CoV-2 vaccination. Clinicians need to be vigilant of precipitation or exacerbation of autoimmune thyroid disorders in predisposed individuals after exposure to the SARS-CoV-2 vaccination. Further epidemiological and mechanistic studies are required to elucidate the possible associations between the SARS-CoV-2 vaccines and the development of thyroid autoimmunity.

Key Words: SARS-CoV-2 vaccine, Graves' disease, hyperthyroidism

Abbreviations: ASIA, autoimmune/inflammatory syndrome; IFN, interferon; IQR, interquartile range; mRNA, messenger RNA; RI, reference interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th, T-helper

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus pandemic has affected more than 275 million people worldwide (1). Globally, vaccination efforts are being ramped up to reduce mortality and transmission of the virus. To date, there are 9 vaccines approved by the World Health Organization (2), which can be classified broadly based on the types of viral components (whole virus vs individual viral component) used in the production (3). The RNA-based vaccines (Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273) are 2 widely administered vaccines.

The global prevalence of hyperthyroidism ranges from 0.1% to 2.5% in iodine-sufficient countries, of which approximately 70% to 80% are Graves' disease. In iodine-deficient regions, the prevalence of hyperthyroidism ranges from 0.4% to 2.9%. Graves' disease accounts for 50% of these cases (4). New onset or relapse of Graves' disease is reported to occur within days (up to 38 days) after receiving the first or second dose of SARS-CoV-2 vaccines, predominantly the RNA-based ones (5-17).

Singapore is an iodine-sufficient, island city-state in maritime Southeast Asia. The population of Singapore comprises approximately 5.4 million people in 3 ethnic groups—Chinese, Malays, and Indians (18). The country's vaccination drive against coronavirus 2019 started in January 2021 and more than 90% of the eligible population have completed the full regimen (19). The majority of the population received the RNA-based vaccines.

We describe a case series of 12 patients with new-onset or relapsed Graves' disease-related hyperthyroidism after vaccination presenting to a single tertiary endocrinology clinic in Singapore.

Case Series Description

We included all consecutive patients who presented with new onset or exacerbation of hyperthyroidism to our center with a temporal sequence to the vaccine between January and December 2021. All the participants signed an informed consent. The study was approved by our institutional review board (DSRB reference 2021/00960).

Twelve patients presented with Graves' hyperthyroidism after they received the SARS-CoV-2 mRNA vaccines. Six patients had new-onset symptoms, whereas the other 6 had relapses of previously well-controlled conditions. None of the

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Clinical Research Article

New Onset or Deterioration of Thyroid Eye Disease After mRNA SARS-CoV-2 Vaccines: Report of 2 Cases and Literature Review

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Abstract

Context: Occurrence of Graves' disease (GD) has been reported following SARS-CoV-2 vaccine administration, but little is known about thyroid eye disease (TED) after SARS-CoV-2 vaccination.

Objective: We describe 2 cases of TED activation following mRNA SARS-CoV-2 vaccination and review additional cases reported in the literature.

Methods: We report 2 cases of TED activation following SARS-CoV-2 vaccination: 1 case of TED worsening in a patient with GD, and 1 of de novo active TED progressing to dysthyroid optic neuropathy in a patient with a history of Hashimoto hypothyroidism. Our literature search revealed 8 additional reported TED cases associated with SARS-CoV-2 vaccination until June 2022. We review the characteristics, duration, and management of TED following SARS-CoV-2 vaccination in these cases.

Results: Of all 10 reported TED cases following SARS-CoV-2 vaccination, 4 developed new-onset TED and 6 previously stable TED cases experienced significant deterioration. Six patients had known GD and 2 patients had Hashimoto thyroiditis. Two cases progressed to dysthyroid optic neuropathy, 6 had moderate/severe active disease, and 2 had mild disease that did not require treatment. Seven TED cases received teprotumumab and had a favorable response, 2 of whom had prior limited response to initial prednisone or methylprednisolone and tocilizumab therapy.

Conclusion: New diagnosis or deterioration of TED after mRNA SARS-CoV-2 vaccination can occur, with most cases described in patients with underlying autoimmune thyroid disease. Our report raises awareness to this potential complication to promote early recognition and prompt management of TED associated with mRNA SARS-CoV-2 vaccines. Further studies are needed to explore the mechanism, risk factors, prevention, and treatment of TED following mRNA SARS-CoV-2 vaccination.

Key Words: mRNA SARS-CoV-2 vaccine, autoimmune thyroid disease, thyroid eye disease, teprotumumab, Graves' orbitopathy

Abbreviations: CAS, clinical activity score; DON, dysthyroid optic neuropathy; FDA, U.S. Food and Drug Administration; GD, Graves' disease; TED, thyroid eye disease; TSH, thyrotropin (thyroid-stimulating hormone); TSI, thyroid stimulated immunoglobulin.

SARS-CoV-2 vaccination and infection have been linked to a number of autoimmune and inflammatory diseases, including thyroid dysfunction (1-4). Both Graves' disease (GD) and nonthyroidal ocular manifestations have been reported after administration of the SARS-CoV-2 vaccine (5-7). However, little is known about thyroid eye disease (TED) in relation to exposure to SARS-CoV-2 vaccination.

Thyroid eye disease is a debilitating and potentially sight-threatening condition. Approximately 90% of patients with TED have hyperthyroidism and about 10% are euthyroid or hypothyroid (8). Of the patients with GD, up to 40% can develop TED (9). The disease involves an active inflammatory phase that can last 6 to 36 months followed by a stable inactive chronic phase (10). Clinical evaluation of TED patients involves assessment of the activity and severity of their disease. Activity is assessed through the clinical activity score (CAS), which measures inflammatory signs and symptoms, with a score of ≥ 3/7 at presentation or ≥ 4/10 at follow-up, reflecting active disease (11). Severity is determined by the degree of proptosis, diplopia, and soft tissue changes and their impact on quality of life (12). Risk factor control, steroids, and orbital radiation have been the traditional treatments of active moderate/severe TED in the past, while biologics such as tocilizumab and rituximab have been tried with limited success (13-16). The insulin growth factor-1 receptor (IGF-1R), which forms a complex with the thyroid-stimulating hormone (TSH) receptor, has recently been shown to play an important role in the pathogenesis of TED, by mediating activation of orbital fibroblasts in response to TSH receptor stimulating antibodies (17). Teprotumumab, an antagonist of the IGF-1R, has

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Teprotumumab Efficacy, Safety, and Durability in Longer-Duration Thyroid Eye Disease and Re-treatment

OPTIC-X Study

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Purpose: To evaluate teprotumumab safety/efficacy in patients with thyroid eye disease (TED) who were nonresponsive or who experienced a disease flare.

Design: The Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X) is a teprotumumab treatment and re-treatment trial following the placebo-controlled teprotumumab Phase 3 Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC) trial.

Participants: Patients who previously received placebo (n = 37) or teprotumumab (n = 14) in OPTIC.

Methods: OPTIC nonresponders or those who flared (≥2-mm increase in proptosis, ≥2-point increase in clinical activity score [CAS], or both) during follow-up were treated for the first time (previous placebo patients) or re-treated with teprotumumab in OPTIC-X with 8 infusions over 24 weeks.

Main Outcome Measures: Proptosis response and safety. Secondary outcomes included proptosis, CAS, subjective diplopia, and quality-of-life.

Results: Thirty-three of 37 placebo-treated OPTIC patients (89.2%) became proptosis responders (mean ± standard deviation, −3.5 ± 1.7 mm) when treated with teprotumumab in OPTIC-X. The responses were equivalent to the OPTIC study. In these responders, proptosis, CAS of 0 or 1, and diplopia responses were maintained in 29 of 32 patients (90.6%), 20 of 21 patients (95.2%), and 12 of 14 patients (85.7%), respectively, at follow-up week 48. The median TED duration was 12.9 months versus 6.3 months in those treated with teprotumumab in the OPTIC study. Of the 5 OPTIC teprotumumab nonresponders re-treated in OPTIC-X, 2 responded, 1 showed a proptosis reduction of 1.5 mm from OPTIC baseline, and 2 discontinued treatment early. Of the OPTIC teprotumumab responders who experienced flare, 5 of 8 patients (62.5%) responded when re-treated (mean proptosis reduction, 1.9 ± 1.2 mm from OPTIC-X baseline and 3.3 ± 0.7 mm from OPTIC baseline). Compared with published double-masked trials and their integrated follow-up, no new safety signals were identified. Mild hearing impairment was reported; 4 events occurred during the first course of treatment, and 2 events reoccurred after re-treatment.

Conclusions: Patients with TED of longer disease duration responded similarly to those treated earlier in the disease course. Patients with an insufficient initial response or flare may benefit from additional teprotumumab therapy. No new safety risk was identified; however additional postmarketing pharmacovigilance is ongoing. *Ophthalmology 2022;129:438-449 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Thyroid eye disease (TED) is a chronic, debilitating autoimmune disease commonly associated with Graves' disease. Thyroid eye disease presents with varying degrees of orbital inflammation and tissue expansion. Signs and symptoms of early TED include periorbital inflammation, retrobulbar pain, visual disturbance, diplopia, and proptosis. Over time, most patients experience quiescence of the acute inflammatory signs; however, proptosis and diplopia can persist

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GUIDELINES AND STATEMENTS

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Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association

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Thyroid eye disease (TED) remains challenging for clinicians to evaluate and manage. Novel therapies have recently emerged, and their specific roles are still being determined. Most patients with TED develop eye manifestations while being treated for hyperthyroidism and under the care of endocrinologists. Endocrinologists, therefore, have a key role in diagnosis, initial management, and selection of patients who require referral to specialist care. Given that the need for guidance to endocrinologists charged with meeting the needs of patients with TED transcends national borders, and to maximize an international exchange of knowledge and practices, the American Thyroid Association and European Thyroid Association joined forces to produce this consensus statement.

Keywords: thyroid eye disease, consensus statement, American Thyroid Association, European Thyroid Association

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ORIGINAL ARTICLE

WILEY

Development and pilot testing of a conversation aid to support the evaluation of patients with thyroid nodules

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Abstract

Objective: To support patient-centred care and the collaboration of patients and clinicians, we developed and pilot tested a conversation aid for patients with thyroid nodules.

Design, Patient and Measurements: We developed a web-based Thyroid NOdule Conversation aid (TNOC) following a human-centred design. A proof of concept observational pre–post study was conducted (TNOC vs. usual care [UC]) to assess the impact of TNOC on the quality of conversations. Data sources included recordings of clinical visits, post-encounter surveys and review of electronic health records. Summary statistics and group comparisons are reported.

Results: Sixty-five patients were analysed (32 in the UC and 33 in the TNOC cohort). Most patients were women (89%) with a median age of 57 years and were incidentally found to have a thyroid nodule (62%). Most thyroid nodules were at low risk for thyroid cancer (71%) and the median size was 1.4 cm. At baseline, the groups were similar except for higher numeracy in the TNOC cohort. The use of TNOC was associated with increased involvement of patients in the decision-making process, clinician satisfaction and discussion of relevant topics for decision making. In addition, decreased decisional conflict and fewer thyroid biopsies as the next management step were noted in the TNOC cohort. No differences in terms of knowledge transfer, length of consultation, thyroid cancer risk perception or concern for thyroid cancer diagnosis were found.

Conclusion: In this pilot observational study, using TNOC in clinical practice was feasible and seemed to help the collaboration of patients and clinicians.

KEYWORDS
conversation aids, shared decision making, thyroid cancer, thyroid nodules

original reports abstract

Pre-existing Thyroid Autoimmunity and Risk of Papillary Thyroid Cancer: A Nested Case-Control Study of US Active-Duty Personnel

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PURPOSE Thyroid autoimmunity has been associated with differentiated thyroid cancer although multiple potential biases might have influenced the results of previous studies.

METHODS We conducted a case-control study nested within the cohort of US active-duty personnel 1996-2014 to assess the association between thyroid autoimmunity, defined by serology, and thyroid cancer diagnosis. The primary exposure was thyroid peroxidase (TPO) antibody status 7-10 years before the thyroid cancer index date. We also assessed whether diagnosis of thyroid autoimmunity mediated any associations identified and if thyroid cancer features differed by autoimmunity status.

RESULTS Among 451 incident cases of papillary thyroid cancer and matched controls (median age 36 years, 61.4% men), TPO antibody positivity (*v* negative) 7-10 years prediagnosis was associated with thyroid cancer (odds ratio [OR] 1.90 [95% CI, 1.33 to 2.70]). Exploratory analyses suggested an increasing risk of thyroid cancer with higher TPO antibody titer (TPO antibody 550-1,399 IU/mL: OR 2.95 [95% CI, 1.37 to 6.36]; and ≥ 1,400 IU/mL: OR 3.91 [95% CI, 1.66 to 9.24]). Positive TPO antibody status remained associated with thyroid cancer after those with diagnosed autoimmunity were excluded, and the association was not mediated by diagnosis of thyroid autoimmunity. Among the cases with diagnosed autoimmunity, 58% thyroid cancers were ≤ 10 mm diameter.

CONCLUSION Longstanding prior thyroid autoimmunity up to 10 years before thyroid cancer diagnosis was associated with papillary thyroid cancer risk. The results could not be fully explained by diagnosis of thyroid autoimmunity although when autoimmunity had been identified, thyroid cancers were diagnosed at a very early stage.

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BACKGROUND

The incidence of thyroid cancer has risen markedly over recent decades in both women and men[1]; worldwide, it is now the tenth most common cancer diagnosed overall and fifth most common in women.[2] An important reason for more frequent identification of thyroid cancer is where medical investigations detect subclinical disease, which has likely led to overdiagnosis of lesions that might never have caused harm.[3] However, evidence also suggests that there has been a true increase in thyroid cancer incidence, and this, plus scant knowledge of thyroid cancer causes, fuels the continuous search for potential risk factors.[1]

Thyroid autoimmunity was first proposed as a risk factor for papillary thyroid cancer in 1955.[4] The relationship is plausible; chronic tissue inflammation precedes cancer at multiple sites.[5] Thyroid autoimmunity (chiefly Hashimoto's thyroiditis but also Graves' disease) causes chronic thyroid inflammation that is most commonly identified on histology and serology testing for antibodies that target thyroid antigens (eg, thyroid peroxidase [TPO] and thyroglobulin [Tg]).

Most studies support a link between thyroid autoimmunity and thyroid cancer, with meta-analyses suggesting that thyroid autoimmunity doubles the risk of thyroid cancer.[6,7] However, several sources of bias might have influenced the results of these mainly cross-sectional studies. Most studies assessing thyroid autoimmunity via histology and serology are cross-sectional. These are prone to reverse causation, which could occur if thyroid cancer induces an immune response (ie, peritumoral inflammation or autoantibody production). Selection bias is also possible if diagnosis of thyroid autoimmunity leads to thyroid cancer identification and hence selection as a case. Longitudinal studies assessing the risk of thyroid cancer after diagnosis of benign thyroid diseases (including autoimmune thyroid disease) could also be biased if medical surveillance in those known to have autoimmune thyroid disease identifies small, subclinical tumors, whereas similar subclinical tumors remain undiagnosed in those not under medical surveillance.

We aimed to investigate the association between thyroid autoimmunity and differentiated thyroid cancer, using a

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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ORIGINAL ARTICLE

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Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association

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Abstract

Background: The use of ultrasound-guided ablation procedures to treat both benign and malignant thyroid conditions is gaining increasing interest. This document has been developed as an international interdisciplinary evidence-based statement with a primary focus on radiofrequency ablation and is intended to serve as a manual for best practice application of ablation technologies.

ΘΥΡΟΕΙΔΗΣ | ΣΠΥΡΙΔΟΥΛΑ ΜΑΡΑΚΑ

Methods: A comprehensive literature review was conducted to guide statement development and generation of best practice recommendations. Modified Delphi method was applied to assess whether statements met consensus among the entire author panel.

Results: A review of the current state of ultrasound-guided ablation procedures for the treatment of benign and malignant thyroid conditions is presented. Eighteen best practice recommendations in topic areas of preprocedural evaluation, technique, postprocedural management, efficacy, potential complications, and implementation are provided.

Conclusions: As ultrasound-guided ablation procedures are increasingly utilized in benign and malignant thyroid disease, evidence-based and thoughtful application of best practices is warranted.

KEYWORDS

international consensus, radiofrequency ablation, thermal ablation, thyroid ablation, ultrasound-guided ablation

1 | INTRODUCTION

There is growing global interest in ultrasound (US)-guided ablation procedures for treating benign and malignant thyroid conditions. These procedures are performed by surgeons, radiologists, and endocrinologists, and clinical practice guidelines have recently been published by several representative professional societies.[1–5] Given this multidisciplinary and international development, there is a pressing need to identify best clinical practices. The standardization of terminology and reporting criteria has been emphasized as a critical component of this process.[6,7]

This document has been developed as an interdisciplinary international statement primarily addressing radiofrequency ablation (RFA), as this technology has garnered significant recent interest and is associated with robust literature. Laser thermal ablation (LTA) and ethanol ablation are well-established practices also associated with significant evidence. Other emerging technologies, including microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) are gaining in popularity and warrant evaluation.

With the increasing use of ablation technologies across a variety of clinical settings, it is important to define criteria for the candidacy of patients undergoing these procedures. Such criteria permit assessment of efficacy and promote the judicious use of evolving technologies. This document will address use of ablation technologies in benign and malignant conditions which have accrued adequate evidence and received sufficient attention in the literature; such benign conditions include nodules with compressive symptoms, cosmetic disturbance, or autonomously functioning thyroid nodules. Malignant conditions include recurrent thyroid malignancy (in the thyroid remnant or in lymph nodes) and small, low-risk primary thyroid cancers.

Importantly, an established skill set in the performance of US and US-guided procedures is a prerequisite for the safe application of US-guided ablation technologies. This document does not supplant this essential foundational experience, but rather is intended to serve as a resource to reduce variation in practice, support delivery of highest quality care, and promote responsible global dissemination of these technologies.[8] Collectively, the recommendations provided are intended to offer a manual for best practice application of ablation technologies.

2 | BACKGROUND

2.1 | Principles of thermal ablation

All thermal ablation techniques are based upon the destruction of tissue in extreme hyperthermic conditions. The primary mechanism of cell death is coagulation necrosis. Below 40°C, cellular damage is reversible without long term effect.[9,10] Between 50 and 60°C, irreversible injury is induced, occurring more rapidly as temperature increases. Fixed ablation techniques often seek to maintain temperatures in this range for 4–6 min. Beyond 60°C, protein denaturation and cellular membrane disruption result in near immediate tissue necrosis, and is the premise for the moving shot technique used in RFA.[9,10] Above 100–110°C, tissue vaporization and carbonization occur, creating gas around the electrode that

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REVIEW and SCHOLARLY DIALOG

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Serum Thyroglobulin Measurement Following Surgery Without Radioactive Iodine for Differentiated Thyroid Cancer: A Systematic Review

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Background: The utility of serum thyroglobulin (Tg) measurement following partial thyroidectomy or total/near-total thyroidectomy without radioactive iodine (RAI) for differentiated thyroid cancer is unclear. This systematic review examines the diagnostic accuracy of serum Tg measurement for persistent, recurrent, and/or metastatic cancer in these situations.
Methods: Ovid MEDLINE, Embase, and Cochrane Central were searched in October 2021 for studies on Tg measurement following partial thyroidectomy or total/near-total thyroidectomy without or before RAI. Quality assessment was performed, and evidence was synthesized qualitatively.
Results: Thirty-seven studies met inclusion criteria. Four studies ($N=561$) evaluated serum Tg measurement following partial thyroidectomy, five studies ($N=751$) evaluated Tg measurement following total/near-total thyroidectomy without RAI, and 28 studies ($N=7618$) evaluated Tg measurement following total or near-total thyroidectomy before RAI administration. Following partial thyroidectomy, Tg measurement was not accurate for diagnosing recurrence or metastasis, or estimates were imprecise. Following total/near-total thyroidectomy without RAI, evidence was limited due to few studies with very low rates of recurrence or metastasis, but indicated that Tg levels were usually stable and low.

For Tg measurements before RAI administration, diagnostic accuracy for metastatic disease or persistence varied, although sensitivity appeared high (but specificity low) at a cutoff of >1 to 2.5 ng/mL. However, applicability to patients who do not undergo RAI is uncertain because patients selected for RAI are likely to represent a higher risk group. The evidence was very low quality for all scenarios. All studies had methodological limitations, and there was variability in the Tg thresholds evaluated, patient populations, outcomes assessed, and other factors.
Conclusions: Very limited evidence suggests low utility of Tg measurement for identifying recurrent or metastatic disease following partial thyroidectomy. Following total/near-total thyroidectomy, Tg levels using a cutoff of 1–2.5 ng/mL might identify patients at low risk for persistent or metastatic disease. Additional research is needed to clarify the role of Tg measurement in these settings, determine optimal Tg thresholds, and determine appropriate measurement intervals.

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REVIEWS and SCHOLARLY DIALOG

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Active Surveillance Versus Thyroid Surgery for Differentiated Thyroid Cancer: A Systematic Review

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Background: Active surveillance has been proposed as an appropriate management strategy for low-risk differentiated thyroid cancer (DTC), due to the typically favorable prognosis of this condition. This systematic review examines the benefits and harms of active surveillance vs. immediate surgery for DTC, to inform the updated American Thyroid Association guidelines.
Methods: A search on Ovid MEDLINE, Embase, and Cochrane Central was conducted in July 2021 for studies on active surveillance vs. immediate surgery. Studies of surgery vs. no surgery for DTC were assessed separately to evaluate relevance to active surveillance. Quality assessment was performed, and evidence was synthesized narratively.
Results: Seven studies (five cohort studies [$N=5432$] and two cross-sectional studies [$N=538$]) of active surveillance vs. immediate surgery, and seven uncontrolled treatment series of active surveillance ($N=1219$) were included. One cross-sectional study was rated fair quality, and the remainder were rated poor quality. In patients with low risk (primarily papillary), small (primarily ≤1 cm) DTC, active surveillance, and immediate surgery were associated with similar, low risk of all-cause or cancer-specific mortality, distant metastasis, and recurrence after surgery. Uncontrolled treatment series reported no cases of mortality in low-risk DTC managed with active surveillance. Among patients managed with active surveillance, rates of tumor growth were low; rates of subsequent surgery varied and primarily occurred due to patient preference rather than tumor progression. Four cohort studies ($N=88,654$) found that surgery associated with improved all-cause or thyroid cancer mortality compared with nonsurgical management, but findings were potentially influenced by patient age and tumor risk category and highly susceptible to confounding by indication; eligibility for, and receipt of, active surveillance; and timing of surgery was unclear.
Conclusions: In patients with small low-risk (primarily papillary) DTC, active surveillance and immediate surgery may be associated with similar mortality, risk of recurrence, and other outcomes,

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but methodological limitations preclude strong conclusions. Studies of no surgery vs. surgery are difficult to interpret due to clinical heterogeneity and potential confounding factors and are unsuitable for assessing the utility of active surveillance. Research is needed to clarify the benefits and harms of active surveillance and determine outcomes in nonpapillary DTC, larger (>1 cm) cancers, and older patients.

Keywords: differentiated thyroid cancer, active surveillance, systematic review, surgery

Introduction

Thyroid cancer accounts for more than 90% of endocrine system malignancies, with an estimated 44,280 cases in 2021 (1). It is the most common cancer among adolescents and young adults (2,3) and the seventh-most common among women overall (1). More than 95% of thyroid cancers are classified as differentiated thyroid cancer (DTC), primarily of a papillary (70–90%) or follicular (10–20%) subtype (4). Localized DTC is associated with a highly favorable prognosis, with a 5-year survival rate of nearly 100% for papillary and 98% for follicular cancers (5). Worldwide, the incidence of thyroid cancer nearly tripled from 1975 to 2009 (6). Although some studies indicate stable thyroid cancer mortality (suggesting increased identification of subclinical indolent cancers) (7,8), other data indicate increased mortality (9).

The standard primary treatment for DTC has been surgery (total thyroidectomy or lobectomy). However, surgery is associated with potential morbidity, including the need for thyroid hormone treatment, hypoparathyroidism, and recurrent laryngeal nerve injury. To avoid surgical morbidity and potential overtreatment, active surveillance has been proposed as an alternative to immediate surgery for small low-risk DTC (8,10). Active surveillance refers to close monitoring of the primary cancer without performing initial surgery or other more intensive treatments (8). In active surveillance, patients may be offered surgery with curative intent when progression occurs. This differs from watchful waiting, which usually involves less intensive observation and symptom management in persons typically not candidates for curative treatment.

A 2015 American Thyroid Association guideline stated that surgery is ''generally recommended'' for DTC, but noted active surveillance as an alternative for very low-risk tumors (e.g., small papillary microcarcinoma without evidence of metastases or local invasion and favorable cytology), high surgical risk, short life expectancy, or other significant health conditions (11). Given the availability of new evidence, the American Thyroid Association commissioned a systematic review on active surveillance for DTC, to inform updated guidelines.

Methods

This review was conducted using a prespecified protocol and followed published methods for conducting effectiveness and comparative effectiveness reviews (12). In conjunction with the American Thyroid Association Differentiated Adult Thyroid Cancer Guidelines Task Force, we developed the Key Questions for this review. Patient representatives were not involved in the development of the Key Questions, although we sought to address important health outcomes as well as patient-reported outcomes, including impacts on quality of life.

(1) In adult patients with DTC, what are the effects of active surveillance versus thyroid surgery on risk of recurrence, mortality (all-cause or thyroid cancer), and other outcomes (subsequent surgery, lymph node or distant metastasis, quality of life, and harms [e.g., vocal cord paralysis, hypoparathyroidism, receipt of thyroid hormone replacement])?
(2) In adult patients with DTC, what are the effects of no surgery versus surgery on risk of recurrence, mortality, and other outcomes?

Key Question 1 addresses studies that directly compared active surveillance versus immediate thyroid surgery in patients with DTC. In these studies, active surveillance involved close monitoring for cancer progression and symptoms. Key Question 2 was a secondary comparison addressing studies of no surgery versus surgery. In these studies, there was no clear active surveillance protocol, and reasons for not undergoing surgery or timing of surgery were unreported. However, these studies were addressed as a secondary Key Question to assess the relevance and limitations for informing outcomes of active surveillance. For both Key Questions, we examined how outcomes varied in groups defined by patient age and tumor size.

Search strategies

We searched the Cochrane Central Register of Controlled Trials, Elsevier Embase®, and Ovid MEDLINE® (through July 2021). Search strategies are shown in Supplementary Appendix SA1. Searches were supplemented by reference list review of relevant articles.

Study selection

Abstracts and full-text articles were evaluated using prespecified eligibility criteria. The population was adults with DTC of any size. The main comparison (Key Question 1) was active surveillance versus immediate thyroid surgery (lobectomy or total thyroidectomy). Active surveillance was defined as close monitoring without surgery in patients eligible for surgery with curative intent. Because we anticipated few studies of active surveillance versus immediate surgery, we also included uncontrolled treatment series of patients undergoing active surveillance.

As a secondary comparison (Key Question 2), we also included cohort studies of no surgery versus surgery. Such studies lack information regarding eligibility for, or receipt of, active surveillance, reasons for not performing surgery, and intended intitial treatment, with high potential

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ΔΙΟΝΥΣΗΣ ΧΑΡΤΟΥΜΠΕΚΗΣ

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EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

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recommendations were provided for both PCSK9 mAbs in the 2017 ACC nonstatin ECDP.

The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (denoted as the 2018 AHA/ACC/multisociety cholesterol guideline in this document) continued to endorse the net clinical benefits of statin therapy in the 4 main patient management groups, the importance of the appropriate intensity of statin therapy, achieving expected percent reductions in LDL-C, and the role of the clinician-patient discussion and shared decision-making. However, there were a number of key modifications or refinements of recommendations from the 2013 ACC/AHA cholesterol guideline:

- Patients with ASCVD were categorized into 1 of 2 groups: not at very high risk or at very high risk. Very high-risk patients have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (see **Table 1**). Based on evidence from IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), FOURIER, and ODYSSEY Outcomes, this very high-risk group of patients has demonstrated cardiovascular benefits from the addition of ezetimibe, evolocumab, and alirocumab.[5-9]
- Consistent with expert guidance provided in the 2017 ACC nonstatin ECDP, [6] the 2018 AHA/ACC/multisociety cholesterol guideline recommends use of an LDL-C threshold of ≥70 mg/dL (1.8 mmol/L) to consider the addition of nonstatin therapy to maximally tolerated statin therapy in patients with ASCVD.[7]
- Ezetimibe is recommended as the initial nonstatin therapy in patients with clinical ASCVD who are receiving maximally tolerated statin therapy and have an LDL-C level ≥70 mg/dL.[7]
- In patients with clinical ASCVD who are judged to be at very high risk and are being considered for PCSK9 mAb therapy, maximally tolerated LDL-C-lowering therapy should include maximally tolerated statin therapy and ezetimibe.[7]
- The 2018 AHA/ACC/multisociety cholesterol guideline includes the following value statement: "At mid-2018 list prices, PCSK9 mAbs have a low cost value (>$150,000 per quality-adjusted life year [QALY]) compared with good cost value (<$50,000 per QALY)."[7]
- In patients with primary severe hypercholesterolemia LDL-C ≥190 mg/dL, recommendations are provided for the addition of ezetimibe, PCSK9 mAbs, or bile acid sequestrants (BAS) (see Section 5.2).[7]
- In primary prevention patients at borderline or intermediate risk of ASCVD by the Pooled Cohort Equation (PCE), the clinician-patient risk discussion should include risk-enhancing factors that may confer a higher risk state and may support a decision to initiate or intensify statin therapy (see **Table 2**). Risk-enhancing factors are useful for further personalizing the initial risk estimate based on patient-specific factors that are not considered in the PCE and may carry greater lifetime risk. Several risk-enhancing factors may also be specific targets of therapy beyond the risk factors in the PCE.[7]
- In adults without diabetes and with LDL-C levels ≥70 to 189 mg/dL at a 10-year ASCVD risk of 7.5% to <20%, if the decision about statin therapy is uncertain, it is recommended to consider measuring coronary artery calcification.[7]
  - If the coronary artery calcium (CAC) score is 0 AU, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (diabetes, family history of premature coronary heart disease, cigarette smoking);
  - If the CAC score is 1 to 99 AU and less than the 75th percentile for the age/sex/race group, it is reasonable to initiate statin therapy for patients ≥55 years of age;
  - If the CAC score is 100 AU or higher or in the 75th percentile or higher for the age/sex/race group, it is reasonable to initiate statin therapy.

TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease

TABLE 2 Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
■ **Family history of premature ASCVD** (men aged <55 years; women aged <65 years)
■ **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL [4.1-4.8 mmol/L); non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L]*
■ **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes the diagnosis
■ **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
■ **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
■ **History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia**
■ **High-risk races/ethnicities** (eg, South-Asian ancestry)
■ **Lipids/biomarkers:** Associated with increased ASCVD risk ■ **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL) ■ If measured: 1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) 2. **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a). 3. **Elevated apoB ≥130 mg/dL:** A relative indication for its measurement would be triglycerides ≥200 mg/dL. A level ≥130 mg/dL corresponds to LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor 4. **ABI** <0.9

*Optimally, 3 determinations. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; AIDS = acquired immunodeficiency syndrome; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); RA = rheumatoid arthritis.

The 2018 AHA/ACC/multisociety cholesterol guideline recommendations significantly refine personalization of risk assessment in primary prevention, more accurately characterize the risk of recurrent ASCVD events in secondary prevention, and carefully guide clinicians in matching the intensity of LDL-C-lowering therapies, both statin and nonstatin therapies, to the patient's level of risk.

Since publication of the 2018 AHA/ACC/multisociety cholesterol guideline, 3 additional nonstatin therapies—bempedoic acid, evinacumab, and inclisiran—have received FDA approval for management of hypercholesterolemia. While awaiting ongoing cardiovascular outcomes trials and subsequent revision of evidence-based guidelines, the ACC recognized that clinicians, patients, and payers may seek more specific recommendations on when to use newer nonstatin therapies if the response to statin therapy, ezetimibe, and/or PCSK9 mAbs is deemed inadequate.

1.1. Rationale for Expert Consensus Decision Pathway

In 2021, the ACC convened this writing committee to address current gaps in care for LDL-C lowering to reduce ASCVD risk. This effort relies extensively on the evidence base established by the 2013 ACC/AHA and 2018 AHA/ACC/multisociety cholesterol guidelines and attempts to provide further recommendations for clinicians and patients regarding use of newer nonstatin therapies. It should be noted that this process did not involve formal systematic reviews, grading of evidence, or synthesis of evidence. The goal was to provide practical guidance for clinicians and patients in situations not covered by the 2018 AHA/ACC/multisociety cholesterol guideline until such time as the next round of guidelines can formally review recent scientific evidence and cardiovascular outcomes trials of newer agents for ASCVD risk reduction are completed. Specifically, the ACC convened this writing committee to answer the following questions regarding the use of nonstatin therapies:

1. In what patient populations should newer nonstatin therapies be considered?
2. In what situations should newer nonstatin therapies be considered; that is, when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?
3. If newer nonstatin therapies are to be added, which therapies should be considered and in what order to maximize patient benefit and preference?

1.1.1. Newer Nonstatin Therapies

Bempedoic acid is a small molecule that inhibits ATP-citrate lyase, an enzyme in the cholesterol synthesis pathway that is upstream of the rate-limiting enzyme HMG CoA reductase.[10] This results in up-regulation of the LDL receptor with improved clearance of LDL and reduction in blood LDL-C levels. Bempedoic acid is administered orally as a prodrug and is activated by very-long-chain acyl-CoA synthetase-1, an enzyme present in liver cells, but not muscle cells. This has been considered a possible advantage in patients with statin-associated muscle symptoms. The CLEAR Tranquility (Evaluation of the Efficacy and Safety of Bempedoic Acid [ETC-1002] as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C) and CLEAR Serenity (Evaluation of the Efficacy and Safety of Bempedoic Acid in Patients With Hyperlipidemia and Statin Intolerant) trials have demonstrated that monotherapy with bempedoic acid 180 mg daily in patients with statin-associated muscle symptoms on no statin therapy reduced LDL-C levels by approximately 24.5% compared with placebo.[11-13] In patients with ASCVD, heterozygous familial hypercholesterolemia (HeFH), or multiple cardiovascular risk factors, bempedoic acid added to statin therapy resulted in an additional

TABLE 3 Strategies and Nonstatin Agents Considered for Management of LDL-Related ASCVD Risk

Strategy/Agent	Comments
Referral to another clinician	
Referral to lipid specialist	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, baseline LDL-C ≥190 mg/dL, or intolerance to at least 2 (preferably 3) statin therapies with 1 attempt at the lowest FDA-approved dose and a trial of an alternative statin therapy regimen (eg, every-other-day dosing) ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction ■ **Considerations in referring:** Lipid specialists may be available for virtual visits for patients in some rural or remote locations
Referral to RD/RDN	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, or baseline LDL-C ≥190 mg/dL ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction
Nonstatin agents that may be used to manage LDL-related ASCVD risk	
Ezetimibe[34]	■ **Mechanism of action:** Inhibits NPC1L1 protein; reduces cholesterol absorption in small intestine. ■ **FDA-approved indication(s):** As adjunct to diet to: 1) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with primary hyperlipidemia, either alone or in combination with statin therapy; 2) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) ↓ TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; and 4) ↓ sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia) ■ **Dose:** 10 mg orally daily, with or without food. Take either ≥2 h before or ≥4 h after BAS, if used in combination ■ **Mean % reduction in LDL-C (per PI):** Monotherapy—18%; combination therapy with statin therapy (incremental reduction)—25% ■ **Contraindication:** History of hypersensitivity to this medication. ■ **Warnings/precautions:** 1. Not recommended in patients with moderate/severe hepatic impairment. 2. Persistent elevations in hepatic transaminases may occur with concomitant statin therapy. Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy. 3. Cases of myopathy and rhabdomyolysis have been reported when ezetimibe was used alone or in combination with statin therapy. ■ **Adverse effects:** Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities. In combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use ■ **Drug-drug interactions:** Cyclosporine, fibrates, BAS ■ **CV outcomes trials:** IMPROVE-IT[8] (The addition of ezetimibe to moderate-intensity statin therapy in patients with recent ACS resulted in incremental lowering of LDL-C and reduced the primary composite endpoint of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years); SHARP[35] (Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years) ■ **Other prescribing considerations:** Generally well tolerated. Generic available
PCSK9 mAb (alirocumab,[36] evolocumab[37])	■ **Mechanism of action:** Human mAb to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C ■ **FDA-approved indication(s):** ***Alirocumab and evolocumab:*** 1) ↓ LDL-C in adults with primary hyperlipidemia (including HeFH) as adjunct to diet, either alone or in combination with other lipid-lowering therapies ***Alirocumab:*** 1) ↓ risk of MI, stroke, and unstable angina requiring hospitalization in adults with ASCVD; 2) ↓ LDL-C in adults with HoFH as adjunct to other LDL-C–lowering therapies ***Evolocumab:*** 1) ↓ risk of MI, stroke, and coronary revascularization in adults with ASCVD; 2) ↓ LDL-C in pediatric patients (aged ≥10 years) with HeFH as adjunct to diet and other LDL-C–lowering therapies; 3) ↓ LDL-C in adults and pediatric patients (aged ≥10 years) with HoFH as adjunct to diet and other LDL-C–lowering therapies ■ **Dose and route of administration:** ***Alirocumab:*** Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD or primary hyperlipidemia: initiate 75 mg SC every 2 weeks. If more LDL-C reduction needed, may ↑ dose to 150 mg every 2 weeks. Alternative starting dose is 300 mg SC every 4 weeks. For the 300-mg dose, administer 2 (150-mg) injections consecutively at 2 different injection sites. In adults with HeFH undergoing LDL apheresis or adults with HoFH, administer 150 mg SC every 2 weeks ***Evolocumab:*** Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD, adults with primary hypercholesterolemia, including with established clinical ASCVD or HeFH, or in pediatric patients (aged ≥10 years) with HeFH, administer 140 mg SC every 2 weeks or 420 mg SC once monthly in abdomen, thigh, or upper arm. In adults or pediatric patients (aged ≥10 years) with HoFH, administer 420 mg SC once monthly; if more LDL-C reduction is needed after 12 weeks, may ↑ dose to 420 mg every 2 weeks. In adults or pediatric patients (age ≥10 years) with HoFH on LDL apheresis, may initiate 420 mg SC every 2 weeks to correspond with apheresis schedule; evolocumab should be given after apheresis is complete. To administer 420-mg dose, either use the prefilled single-dose on-body infuser or give 3 (140-mg) injections consecutively within 30 min.

Continued on the next page

TABLE 3 Continued

Strategy/Agent	Comments
	■ **Mean % LDL-C reduction (per PI):** ***Alirocumab:*** when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 mg SC every 2 weeks ↓ LDL-C by an additional 45% and 58%, respectively, when added to maximally tolerated statin therapy. ***Evolocumab:*** 140 mg every 2 weeks and 420 mg SC every 4 weeks, ↓ LDL-C by an additional 64% and 58%, respectively. ■ **Contraindication:** History of hypersensitivity to the medication. ■ **Warnings/precautions:** Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. ■ **Adverse effects:** ***Alirocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, injection site reactions, influenza; in patients with ASCVD: noncardiac chest pain, nasopharyngitis, myalgia. No evidence of increase in cognitive adverse effects observed in ODYSSEY Outcomes or CANTAB.[9,38] ***Evolocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions; in patients with ASCVD: diabetes, nasopharyngitis, upper respiratory tract infection. No evidence of an increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS.[5,39] ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions identified for alirocumab or evolocumab ■ **CV outcomes trials:** ***Alirocumab:*** ODYSSEY Outcomes[9] in 18,600 post-ACS (4-52 weeks) patients on evidence-based statin therapy; Demonstrated that addition of alirocumab reduced the primary endpoint of CHD death, MI, ischemic stroke, or hospitalization for UA. ***Evolocumab:*** FOURIER[5] in 27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization, or hospitalization for unstable angina. ■ **Other prescribing considerations:** Robust LDL-C reduction, cost, SC administration at home, may require prior authorization. ***Evolocumab:*** Advise latex-sensitive patients that the needle covers on the products contain latex.
Bempedoic acid[40]	■ **Mechanism of action:** ACL inhibitor; inhibits cholesterol synthesis in the liver; increases LDL receptor density. Bempedoic acid and its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 180 mg orally once daily, with or without food. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—17%-18%. ■ **Contraindication:** none ■ **Warnings/precautions:** 1) May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs, as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2) Discontinue immediately if the patient experiences rupture of a tendon. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17] ■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[17] ■ **Drug-drug interactions:** Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials not completed. CLEAR Outcomes trial completion expected later in 2022. ■ **Other prescribing considerations:** cost; pill burden; requires prior authorization
Bempedoic acid and ezetimibe[41]	■ **Refer to section on ezetimibe for information specific to this agent.** ■ **Mechanism of action:** See the mechanisms of action for bempedoic acid and ezetimibe included in this table. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 1 tablet (180 mg bempedoic acid/10 mg ezetimibe) orally, once daily, with or without food. Swallow whole. Take either ≥2 hours before or ≥4 hours after BAS, if used in combination. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—38%. ■ **Contraindication:** History of hypersensitivity to ezetimibe. ■ **Warnings/precautions:** 1. May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2. Discontinue immediately if the patient experiences tendon rupture. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17]

Continued on the next page

TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremities, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, influenza. Consider alternative therapy if history of tendon disorder or rupture; discontinue immediately if tendon rupture occurs. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[42] ■ **Drug-drug interactions:** Cyclosporine; fibrates. Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials for bempedoic acid not completed. Completion of CLEAR Outcomes trial expected later in 2022. CV outcomes trial will not be required for fixed-dose combination of ezetimibe and bempedoic acid. ■ **Prescribing considerations:** ↓ LDL-C within the range of moderate-intensity statin therapy; cost; requires prior authorization
Inclisiran[43]	■ **Mechanism of action:** siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician. ■ **Mean % reduction in LDL-C (per PI):** 48%-52% ■ **Contraindications (per PI):** None ■ **Warnings/precautions (per PI):** None ■ **Adverse effects:** Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions (per PI):** None ■ **CV outcomes trials:** CV outcomes trials not yet completed. ORION-4 currently in progress with estimated completion in 2026. VICTORION-2P currently in progress with estimated completion in 2027. ■ **Other prescribing considerations:** robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization.
BAS[44,45]	■ **Mechanism of action:** Nonabsorbed, lipid-lowering polymer that binds bile acids in the intestine and impedes their reabsorption. As the bile acid pool ↓, the hepatic enzyme cholesterol 7-α-hydroxylase is up-regulated, which ↑ conversion of cholesterol to bile acids. This causes ↑ demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme HMG-CoA reductase and ↑ numbers of hepatic LDL receptors. These compensatory effects result in ↑ clearance of LDL particles from the blood, in turn resulting in ↓ serum LDL-C levels. Serum TG levels may ↑ or remain unchanged. ■ **FDA-approved indication(s):** ***Colesevelam:*** As an adjunct to diet and exercise to 1) ↓ LDL-C in adults with primary hyperlipidemia; 2) ↑ glycemic control in adults with type 2 diabetes; 3) ↓ LDL-C in boys and post-menarchal girls (aged 10-17 years) with HeFH who are unable to reach LDL-C targets after an adequate trial of diet therapy and lifestyle modifications. ***Cholestyramine, colestipol:*** ↓ LDL-C with primary hyperlipidemia, as adjunct to diet ■ **Dose and route of administration:** ***Colesevelam:*** Tablets: 6 tablets orally once daily or 3 tablets orally twice daily; take tablets with a meal and liquid. Suspension: one 3.75-g packet orally daily, or one 1.875-g packet orally twice daily; mix powder with 8 ounces of water, fruit juice, or soft drink; take with meal. 3.75 g is equivalent to 6 tablets. 1.875 g is equivalent to 3 tablets; ***Cholestyramine:*** 8-16 g/day orally, divided into 2 doses; **Colestipol:** 2-16 g/day orally, given once or in divided doses ■ **Mean % LDL reduction (per PI):** ***Colesevelam:*** Monotherapy—15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy—additional 10%-16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg). ***Cholestyramine:*** Monotherapy—10.4% vs placebo. ***Colestipol:*** not provided in PI. In dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively[46] ■ **Contraindications (per PI):** ***Colesevelam:*** TG >500 mg/dL; history of hypertriglyceridemia-induced pancreatitis; bowel obstruction. ***Cholestyramine:*** History of serious hypersensitivity to this medication. ***Colestipol:*** Complete biliary obstruction, history of serious hypersensitivity to this medication. ■ **Warnings/precautions:** May ↑ TG and cause acute pancreatitis, monitor TG, discontinue if signs and symptoms of acute pancreatitis occur; may cause GI obstruction, avoid with gastroparesis, other GI motility disorders, and history of major GI tract surgery with risk for bowel obstruction; may cause vitamin K or fat-soluble vitamin deficiencies, oral vitamins should be given ≥4 hours before this medication; may decrease absorption of other medications, other medications should be given ≥4 hours before this medication. Some products contain phenylalanine, which may be harmful to patients with phenylketonuria.

Continued on the next page

TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Constipation, dyspepsia, and nausea. ■ **Use during pregnancy/lactation:** Considered safe to use ■ **Drug-drug interactions:** In general, BAS may decrease absorption of other medications; it is a good practice for all other medications to be given ≥4 hours before BAS. Concomitant use of BAS is known to decrease absorption of cyclosporin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan, phenytoin, sulfonylureas, thyroid replacement therapy, warfarin; give these medications ≥4 hours before BAS. For patients on warfarin, monitor INR frequently during BAS initiation and then periodically. Cholestyramine may increase exposure to metformin; monitor glycemic control. ■ **CV outcomes trials:** In LRC-CPPT, 3,806 asymptomatic middle-aged men with primary hypercholesterolemia were randomized to cholestyramine resin vs placebo for an average of 7.4 years. The cholestyramine group experienced a 19% reduction in risk ($P < 0.05$) of the primary endpoint—definite CHD death and/or definite nonfatal MI. The effects of colesevelam and colestipol on cardiovascular morbidity and mortality have not been determined ■ **Considerations in prescribing:** Pill burden; inconvenience in preparation of oral suspension preparations; drug interactions, GI side effects; exacerbation of hypertriglyceridemia; orally administered, colesevelam lowers HbA_{1c} 0.5% in diabetes; CV outcomes data not available for all products
Agents that may be used to treat HoFH under care of a lipid specialist	
Evinacumab[21]	■ **Mechanism of action:** Human monoclonal antibody that binds to and inhibits ANGPTL3. Promotes VLDL processing and clearance upstream of LDL formation ■ **FDA-approved indication(s):** ↓ LDL-C in adults and pediatric patients (aged ≥12 years) with HoFH as adjunct to other LDL-C–lowering therapies ■ **Dose and route of administration:** 15 mg/kg administered by healthcare professional as IV infusion once monthly (every 4 weeks). See PI for preparation and administration instructions. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with other lipid-lowering therapies (incremental reduction)—49%. ■ **Contraindication:** History of serious hypersensitivity to this medication. ■ **Warnings/precautions:** 1. Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. 2. May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥5 months following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-833-385-3392). ■ **Adverse effects:** nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions have been identified ■ **CV outcomes trials:** The effect of evinacumab on CV morbidity and mortality has not been determined ■ **Other prescribing considerations:** See prescribing information for complete preparation and administration instructions. Robust LDL-C reduction; cost, IV administration, requires prior authorization
Lomitapide[47]	■ **Mechanism of action:** Directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits synthesis of chylomicrons and VLDL and leads to ↓ LDL-C ■ **FDA-approved indications:** ↓ LDL-C, TC, apoB, and non-HDL-C in patients with HoFH, as adjunct to a low-fat diet and other lipid-lowering treatments (including LDL apheresis, where available) ■ **Dose and route of administration:** Initiate 5 mg orally once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, up to the maximum recommended dose of 60 mg daily ■ **Mean % LDL reduction (per PI):** Mean and median percent changes in LDL-C from baseline when added to baseline lipid-lowering therapy were −40% and −50%, respectively ■ **Black box warnings:** 1. May cause elevations in liver transaminases; measure ALT, AST, alkaline phosphatase, total bilirubin before initiating this medication; during treatment, adjust dose if ALT or AST ≥3 times the upper limit of normal; discontinue this medication for clinically significant liver toxicity. 2. Increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Hepatic steatosis associated with lomitapide may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Because of the risk of hepatotoxicity, lomitapide is only available through the REMS program ■ **Contraindications:** 1) Pregnancy; 2) concomitant use with strong/moderate CYP3A4 inhibitors; 3) moderate/severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests. ■ **Warnings/precautions:** 1) May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥2 weeks following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-877-902-4099).

Continued on the next page

TABLE 3 Continued

Strategy/Agent	Comments
	■ **Adverse effects:** Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** 1. CYP3A4 inhibitors increase exposure to lomitapide. Strong/moderate CYP3A4 inhibitors are contraindicated with lomitapide. Avoid grapefruit juice. 2. Do not exceed 30 mg daily of lomitapide when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives. 3. Increases plasma concentration of warfarin; monitor INR regularly, especially with lomitapide dose adjustment. 4. Increased systemic exposure to simvastatin and lovastatin exposure with lomitapide. Limit statin dose when coadministered due to myopathy risk. 5. Consider dose reduction of P-glycoprotein substrates because of possible increased absorption with lomitapide. 6. Separate lomitapide dosing with BAS by at least 4 hours. ■ **CV outcomes trials:** The effect of lomitapide on CV morbidity and mortality has not been determined ■ **Considerations in prescribing:** Cost, oral administration, requires strict adherence to low-fat diet and gradual dose escalation to reduce GI side effects, requires daily doses of specific vitamins (Vitamin E 400 IU, linoleic acid ≥200 mg, alpha-linolenic acid ≥210 mg, eicosapentaenoic acid ≥110 mg, docosahexaenoic acid ≥80 mg); requires monitoring of transaminase levels, long-term consequences of hepatic steatosis unknown, prescriber training, REMS program
LDL apheresis	■ **Mechanism of action:** Selectively removes apo B-containing lipoproteins, producing an acute reduction in LDL-C. ■ **FDA approved indication:** Patients with FH unresponsive to pharmacologic and dietary management who are either functional homozygotes with an LDL-C >500 mg/dL, functional heterozygotes with no known CV disease but an LDL-C >300 mg/dL, or functional heterozygotes with known cardiovascular disease and LDL-C >200 mg/dL ■ **Dose and route of administration:** Extracorporeal technique performed weekly or biweekly ■ **Mean % LDL-C reduction:** With weekly or biweekly treatment, average LDL-C can ↓ to ∼50-60% of the original levels. LDL-C increases after each apheresis session but does not return to the original level ■ **Adverse effects:** Problems with venous access; transient hypotension, fatigue; bleeding; hypocalcemia; iron deficiency due to regular phlebotomy for diagnostic purposes; heparin allergy; and bradykinin syndrome (especially with ACEi) ■ **Drug-drug interactions:** ACEi should not be used with dextran sulfate method owing to risk of bradykinin syndrome ■ **CV outcomes trials:** Limited due to ethical considerations in RCTs of very high-risk patients with HoFH, but it is reasonable to assume reductions in CV disease events are proportional to the degree of LDL-C lowering ■ **Considerations in prescribing:** Cost, extracorporeal technique, inconvenient, locations not readily available in some regions, time-consuming, robust reduction in LDL-C

↑ = increase; ↓ = decrease; ACEi = angiotensin-converting enzyme inhibitor; ACL = adenosine triphosphate-citrate lyase; ACS = acute coronary syndrome; ACSVl1 = acyl-CoA synthetase-1; ALT = alanine transaminase; apoB = apolipoprotein B-100; ASCVD = atherosclerotic cardiovascular disease; ANGPTL3 = Angiopoietin-like 3; AST = aspartate aminotransferase; BAS = bile acid sequestrant; CANTAB = Cambridge Neuropsychological Test Automated Battery; CHD = coronary heart disease; CKD = chronic kidney disease; CLEAR Outcomes = Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant With Bempedoic Acid [ETC-1002] or Placebo; CV = cardiovascular; CYP3A4 = Cytochrome P450 3A4; EBBINGHAUS = Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects; FDA = Food and Drug Administration; FH = familial hypercholesterolemia; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GI = gastrointestinal; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IMPROVE-IT = IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; mAb = monoclonal antibody; MI = myocardial infarction; NPC1L1 = Niemann-Pick C1 like 1; ODYSSEY = Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; ORION-4 = A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; PI = prescribing information; RD/RDN = registered dietician/registered dietician nutritionist; REMS = Risk Evaluation and Mitigation Strategy; SC = subcutaneous; SHARP = Study of Heart and Renal Protection; siRNA = synthetic small interfering ribonucleic acid; TC = total cholesterol; TG = triglycerides; UA = unstable angina; VICTORION-2P = A Randomized, Double-blind, Placebo-controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease; VLDL = very low-density lipoprotein

of special circumstances for subpopulations with comorbidities, and then updated the strategies to create a clinical pathway or algorithm that could be followed by clinicians for each patient scenario. All issues were discussed, and all algorithms were finalized with full consensus of the writing committee members.

Persistent or severe hypertriglyceridemia: The writing committee did not directly consider or recommend adjunctive approaches for persistent or severe hypertriglyceridemia (lifestyle modifications, prescription omega-3 fatty acids, fibric acid derivatives) because these were recently addressed in detail in the 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia (denoted in this document as the 2021 ACC ECDP on management of hypertriglyceridemia).[48] Clinicians are referred to that ECDP, as needed, at the appropriate point in each algorithm.

TABLE 4 Factors to Consider in the Clinician–Patient Discussion

Potential for additional ASCVD risk reduction from addition of nonstatin therapy to evidence-based statin therapy to lower LDL-C	■ Percentage LDL-C reduction achieved with evidence-based statin therapy (if <50% and not on maximally tolerated statin, should increase statin therapy first and reinforce lifestyle modifications) *and* whether patient is above LDL-C threshold for consideration of nonstatin therapies ■ For patients with ASCVD, patient's status as very high risk or not very high risk on evidence-based statin therapy (see Table 1)* ■ For patients without ASCVD or baseline LDL-C ≥190 mg/dL, patient's baseline predicted 10-year ASCVD risk prestatin and presence of risk-enhancing factors (see Table 2)† ■ Available scientific evidence of ASCVD risk reduction (and magnitude of benefit) when nonstatin therapy is added to evidence-based statin therapy‡ ■ Additional desired % LDL-C lowering beyond that achieved on evidence-based statin therapy§ ■ Mean percentage LDL-C lowering expected with proposed nonstatin therapy when added to evidence-based statin therapy‖
Potential for clinically significant adverse events or drug–drug interactions from addition of nonstatin therapy to evidence-based statin therapy for lowering LDL-C	■ See Table 3
Cost considerations	■ Potential out-of-pocket cost of therapy to the patient (eg, insurance plan coverage, pharmacy or medical benefit, copayment, availability of assistance programs).
Patient preferences and considerations	■ Patient's perception of benefit from addition of nonstatin therapy ■ Convenience of nonstatin therapy (eg, route, setting [home or medical office], and frequency of administration, pill burden, storage) ■ Potential of nonstatin therapy to jeopardize adherence to other evidence-based therapies ■ Cost of nonstatin therapy ■ Anticipated life expectancy, comorbidities, and impact of therapy on quality of life

*For example, in the Treating to New Targets trial, patients with CHD who received 10 mg of atorvastatin daily had a 5-year event rate of 10.9%, and those who received 80 mg of atorvastatin daily had a 5-year event rate of 8.7%. These numbers (and similar rates from other trials) may inform the number-needed-to-treat. Additional consideration of comorbidities and other poorly controlled or well-controlled risk factors will increase or decrease risk accordingly. See Table 1 for criteria for defining patients at very high risk.
†Use the Pooled Cohort Equations to estimate 10-y ASCVD risk. See Table 1 for criteria for defining patients at very high risk.
‡Such evidence exists for ezetimibe from the IMPROVE-IT study, with a 6% relative/2% absolute risk reduction in a composite ASCVD endpoint over 7 years when added to a moderate-intensity statin. Evidence from FOURIER and ODYSSEY Outcomes demonstrate 2% absolute/15% relative ASCVD risk reduction. Data are lacking for addition of BAS to statins, bempedoic acid, inclisiran, and evinacumab. Niacin preparations have been associated with no benefit and potential for significant harms when added to statin therapy.
§For example, patients on maximally tolerated statin therapy with LDL-C ≥130 mg/dL may receive more benefit from the addition of a nonstatin therapy than those with on-statin LDL-C of 80 mg/dL.
‖For example, when added to statins, ezetimibe may lower LDL-C an additional 20%-25% on average; PCSK9 inhibitors may lower LDL-C an additional 60% on average. For each 40-mg/dL reduction in LDL-C using safe and evidence-based therapies, there appears to be an approximate 20% relative risk reduction in ASCVD. This number, combined with the baseline absolute risk, may inform the number-needed-to-treat.
ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

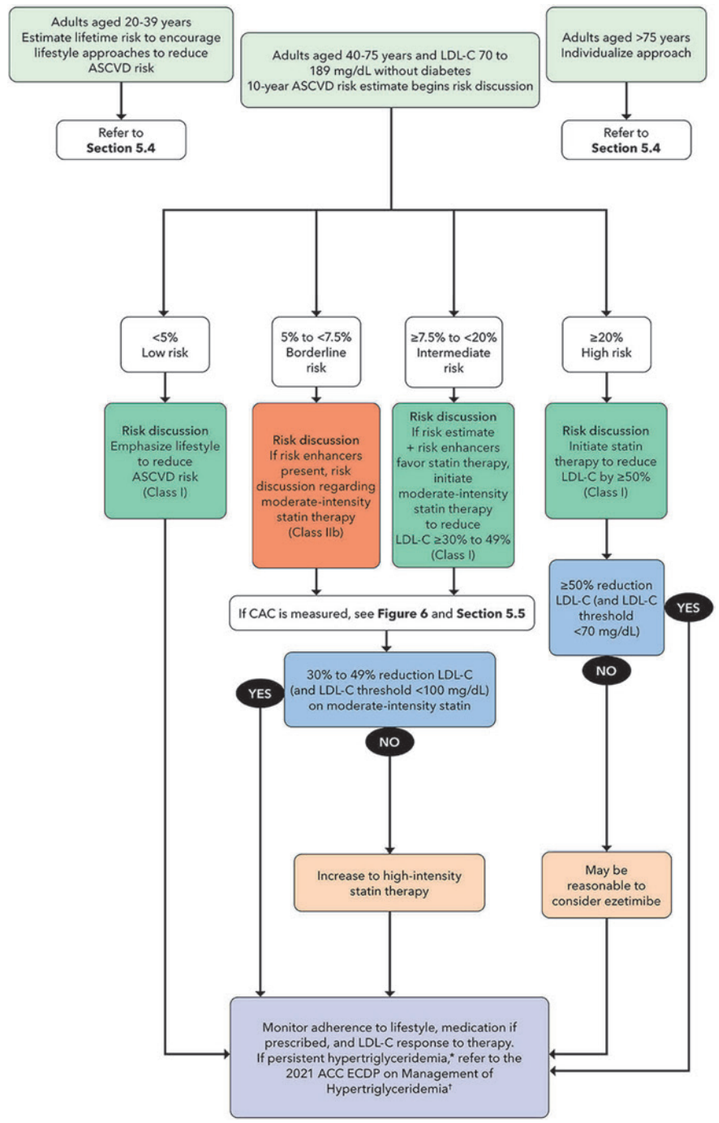
3. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation, specific assumptions and definitions were adopted by the writing committee in the development of this document.

1. The writing committee endorses the evidence-based approaches to ASCVD risk reduction in adults enumerated in the 2018 AHA/ACC/multisociety cholesterol guideline.[7]
2. The algorithms herein begin with the assumption that the patient is in 1 of the 4 evidence-based patient management groups identified in the 2018 AHA/ACC/multisociety cholesterol guideline:
   a. Adults aged ≥20 years with clinical ASCVD on statin therapy for secondary prevention;
   b. Adults aged ≥20 years with LDL-C ≥190 mg/dL (not due to secondary modifiable causes) on statin therapy for primary prevention;
   c. Adults aged 40-75 years without ASCVD, but with diabetes and LDL-C <190 mg/dL, on statin therapy for primary prevention; and
   d. Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70 to 189 mg/dL and an estimated 10-year risk for ASCVD ≥7.5%, on statin therapy for primary prevention.

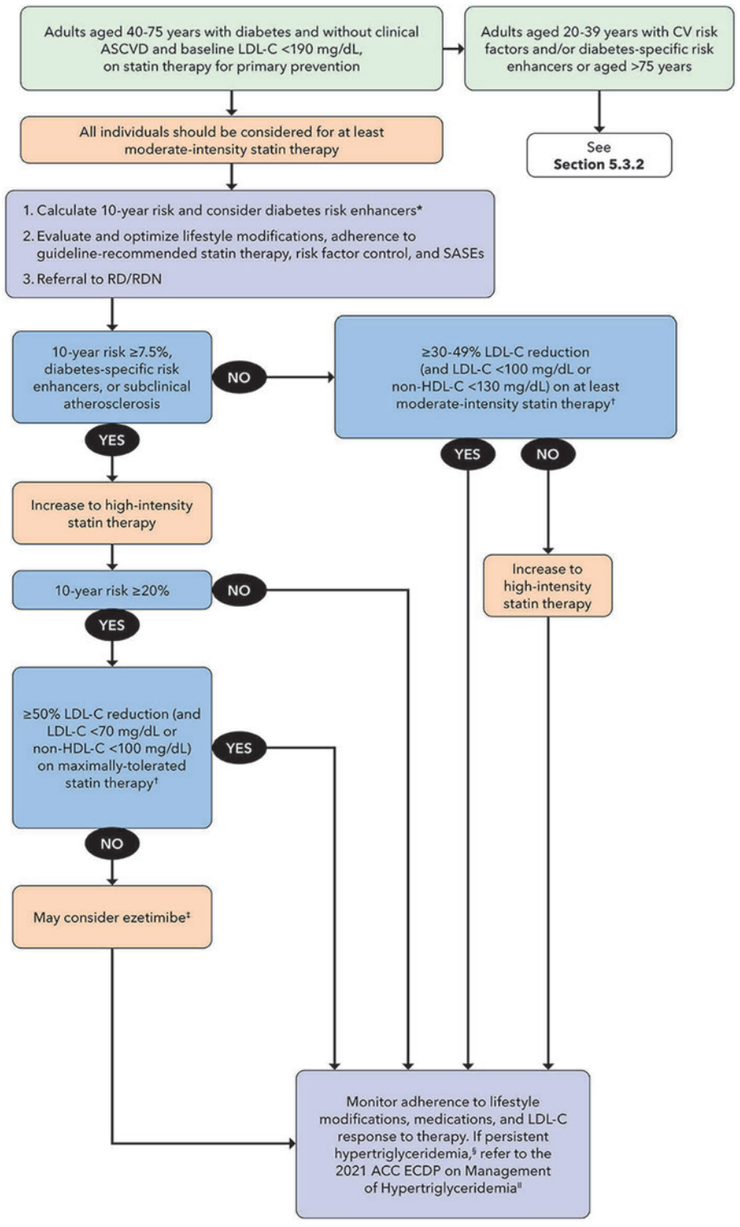
   Patients not in 1 of these 4 patient management groups who may be at elevated risk for ASCVD events (patients with heart failure, patients on maintenance hemodialysis, women considering pregnancy or already pregnant, and patients with previous organ transplantation) are considered in a separate section and should receive individualized care in the context of shared decision-making between the clinician and patient (see Section 5.7).
3. These algorithms assume that the patient is currently taking the maximally tolerated dose of statin therapy or has attempted to take statin therapy as a result of shared decision-making and that the clinician and patient are trying to determine whether additional therapy is needed to further reduce ASCVD risk. If a patient has a less-than-anticipated LDL-C response to the statin dose, additional clinical approaches are

FIGURE 5 Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)



Adapted from Grundy et al.[7] *Fasting triglycerides ≥150 mg/dL following a minimum of 4-12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia †Refer to 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993.
ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; ECDP = Expert Consensus Decision Pathway; LDL-C = low-density lipoprotein cholesterol

FIGURE 4 Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention



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JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Roger Chou, MD; Amy Cantor, MD, MPH; Tracy Dana, MLS; Jesse Wagner, MA; Azrah Y. Ahmed, BA; Rongwei Fu, PhD; Maros Ferencik, MD, PhD, MCR

IMPORTANCE A 2016 review for the US Preventive Services Task Force (USPSTF) found use of statins for primary prevention of cardiovascular disease (CVD) was associated with reduced mortality and cardiovascular outcomes.

OBJECTIVE To update the 2016 review on statins for primary prevention of CVD to inform the USPSTF

DATA SOURCES Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (to November 2021); surveillance through May 20, 2022.

STUDY SELECTION Randomized clinical trials on statins vs placebo or no statin and statin intensity in adults without prior cardiovascular events; large cohort studies on harms.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES All-cause and cardiovascular mortality, myocardial infarction, stroke, composite cardiovascular outcomes, and adverse events.

RESULTS Twenty-six studies were included: 22 trials (N = 90 624) with 6 months to 6 years of follow-up compared statins vs placebo or no statin, 1 trial (n = 5144) compared statin intensities, and 3 observational studies (n = 417 523) reported harms. Statins were significantly associated with decreased risk of all-cause mortality (risk ratio [RR], 0.92 [95% CI, 0.87 to 0.98]; absolute risk difference [ARD], −0.35% [95% CI, −0.57% to −0.14%]), stroke (RR, 0.78 [95% CI, 0.68 to 0.90]; ARD, −0.39% [95% CI, −0.54% to −0.25%]), myocardial infarction (RR, 0.67 [95% CI, 0.60 to 0.75]; ARD, −0.85% [95% CI, −1.22% to −0.47%]), and composite cardiovascular outcomes (RR, 0.72 [95% CI, 0.64 to 0.81]; ARD, −1.28% [95% CI, −1.61% to −0.95%]); the association with cardiovascular mortality was not statistically significant (RR, 0.91 [95% CI, 0.81 to 1.02]; ARD, −0.13%). Relative benefits were consistent in groups defined by demographic and clinical characteristics, although data for persons older than 75 years were sparse. Statin therapy was not significantly associated with increased risk of serious adverse events (RR, 0.97 [95% CI, 0.93 to 1.01]), myalgias (RR, 0.98 [95% CI, 0.86 to 1.11]), or elevated alanine aminotransferase level (RR, 0.94 [95% CI, 0.78 to 1.13]). Statin therapy was not significantly associated with increased diabetes risk overall (RR, 1.04 [95% CI, 0.92 to 1.19]), although 1 trial found high-intensity statin therapy was significantly associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). Otherwise, there were no clear differences in outcomes based on statin intensity.

CONCLUSIONS AND RELEVANCE In adults at increased CVD risk but without prior CVD events, statin therapy for primary prevention of CVD was associated with reduced risk of all-cause mortality and CVD events. Benefits of statin therapy appear to be present across diverse demographic and clinical populations, with consistent relative benefits in groups defined by demographic and clinical characteristics.

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Comparative effectiveness of statins on non-high density lipoprotein cholesterol in people with diabetes and at risk of cardiovascular disease: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE
To compare the efficacy of different statin treatments by intensity on levels of non-high density lipoprotein cholesterol (non-HDL-C) for the prevention of cardiovascular disease in people with diabetes.

DESIGN
Systematic review and network meta-analysis.

DATA SOURCES
Medline, Cochrane Central Register of Controlled Trials, and Embase from inception to 1 December 2021.

REVIEW METHODS
Randomised controlled trials comparing different types and intensities of statins, including placebo, in adults with type 1 or type 2 diabetes mellitus were included. The primary outcome was changes in levels of non-HDL-C, calculated from measures of total cholesterol and HDL-C. Secondary outcomes were changes in levels of low density lipoprotein cholesterol (LDL-C) and total cholesterol, three point major cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, and death related to cardiovascular disease), and discontinuations because of adverse events. A bayesian network meta-analysis of statin intensity (low, moderate, or high) with random effects evaluated the treatment effect on non-HDL-C by mean differences and 95% credible intervals. Subgroup analysis of patients at greater risk of major cardiovascular events was compared with patients at low or moderate risk. The confidence in network meta-analysis (CINeMA) framework was applied to determine the certainty of evidence.

RESULTS
In 42 randomised controlled trials involving 20 193 adults, 11 698 were included in the meta-analysis. Compared with placebo, the greatest reductions in levels of non-HDL-C were seen with rosuvastatin at high (−2.31 mmol/L, 95% credible interval −3.39 to −1.21) and moderate (−2.27, −3.00 to −1.49) intensities, and simvastatin (−2.26, −2.99 to −1.51) and atorvastatin (−2.20, −2.69 to −1.70) at high intensity. Atorvastatin and simvastatin at any intensity and pravastatin at low intensity were also effective in reducing levels of non-HDL-C. In 4670 patients at greater risk of a major cardiovascular events, atorvastatin at high intensity showed the largest reduction in levels of non-HDL-C (−1.98, −4.16 to 0.26, surface under the cumulative ranking curve 64%). Simvastatin (−1.93, −2.63 to −1.21) and rosuvastatin (−1.76, −2.37 to −1.15) at high intensity were the most effective treatment options for reducing LDL-C. Significant reductions in non-fatal myocardial infarction were found for atorvastatin at moderate intensity compared with placebo (relative risk=0.57, confidence interval 0.43 to 0.76, n=4 studies). No significant differences were found for discontinuations, non-fatal stroke, and cardiovascular deaths.

CONCLUSIONS
This network meta-analysis indicated that rosuvastatin, at moderate and high intensity doses, and simvastatin and atorvastatin, at high intensity doses, were most effective at moderately reducing levels of non-HDL-C in patients with diabetes. Given the potential improvement in accuracy in predicting cardiovascular disease when reduction in levels of non-HDL-C is used as the primary target, these findings provide guidance on which statin types and intensities are most effective by reducing non-HDL-C in patients with diabetes.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42021258819.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In people with diabetes, statins are the basis of primary and secondary prevention of cardiovascular disease by reducing plasma levels of low density lipoprotein cholesterol (LDL-C), but evidence is lacking on the comparative effectiveness of statins on non-high density lipoprotein cholesterol (non-HDL-C)

Non-HDL-C is thought to be more strongly associated with the risk of cardiovascular disease than LDL-C in statin users, and therefore might be a better tool for assessing the risk of cardiovascular disease and the effects of treatment

Guidelines from the National Institute for Health and Care Excellence for adults with diabetes recommend that non-HDL-C should replace LDL-C as the primary target for reducing the risk of cardiovascular disease when taking lipid lowering agents

WHAT THIS STUDY ADDS

Rosuvastatin, given at moderate and high intensity doses, and simvastatin and atorvastatin, given at high intensity doses, were the most effective treatments in patients with diabetes, reducing concentrations of non-HDL-C by 2.20-2.31 mmol/L over 12 weeks

In patients at high risk of major cardiovascular events (secondary prevention), atorvastatin at high intensity doses showed the largest reduction in non-HDL-C (~2.0 mmol/L)

These findings can guide decision making for clinicians and support policy guidelines for the management of lipid levels, with non-HDL-C as a primary target, in patients with diabetes

ESC European Society of Cardiology

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SPECIAL ARTICLE
Miscellaneous

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

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Listen to the audio abstract of this contribution.

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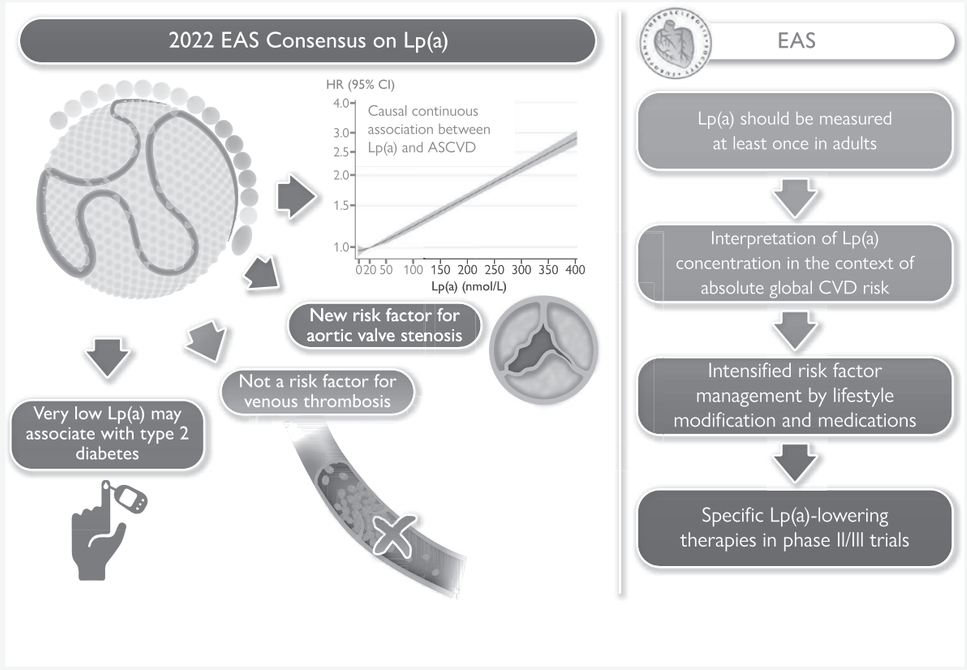
ΛΙΠΙΔΙΑ | ΔΙΟΝΥΣΗΣ ΧΑΡΤΟΥΜΠΕΚΗΣ

Graphical Abstract



Key points from the 2022 Lp(a) consensus statement. Current evidence demonstrates a causal continuous association in different ethnicities between Lp(a) concentration and cardiovascular outcomes including aortic valve stenosis, but not for venous thrombotic events. A meta-analysis of prospective studies shows that very low Lp(a) levels are associated with increased risk of diabetes mellitus. For clinical practice, Lp(a) should be measured at least once in adults and results interpreted in the context of a patient's absolute global cardiovascular risk, with recommendations on intensified early risk factor management by lifestyle modification. The statement also reviews currently available and future possibilities to specifically lower Lp(a).

Abstract

This 2022 European Atherosclerosis Society lipoprotein(a) [Lp(a)] consensus statement updates evidence for the role of Lp(a) in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis, provides clinical guidance for testing and treating elevated Lp(a) levels, and considers its inclusion in global risk estimation. Epidemiologic and genetic studies involving hundreds of thousands of individuals strongly support a causal and continuous association between Lp(a) concentration and cardiovascular outcomes in different ethnicities; elevated Lp(a) is a risk factor even at very low levels of low-density lipoprotein cholesterol. High Lp(a) is associated with both microcalcification and macrocalcification of the aortic valve. Current findings do not support Lp(a) as a risk factor for venous thrombotic events and impaired fibrinolysis. Very low Lp(a) levels may associate with increased risk of diabetes mellitus meriting further study. Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the oxidized phospholipids carried by Lp(a). This panel recommends testing Lp(a) concentration at least once in adults; cascade testing has potential value in familial hypercholesterolaemia, or with family or personal history of (very) high Lp(a) or premature ASCVD. Without specific Lp(a)-lowering therapies, early intensive risk factor management is recommended, targeted according to global cardiovascular risk and Lp(a) level. Lipoprotein apheresis is an option for very high Lp(a) with progressive cardiovascular disease despite optimal management of risk factors. In conclusion, this statement reinforces evidence for Lp(a) as a causal risk factor for cardiovascular outcomes. Trials of specific Lp(a)-lowering treatments are critical to confirm clinical benefit for cardiovascular disease and aortic valve stenosis.

Keywords Lipoprotein(a) • Cardiovascular risk • Aortic stenosis • Clinical guidance • Testing • Treatment • Consensus • Model of care

The NEW ENGLAND JOURNAL of MEDICINE

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Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

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ABSTRACT

BACKGROUND

High triglyceride levels are associated with increased cardiovascular risk, but whether reductions in these levels would lower the incidence of cardiovascular events is uncertain. Pemafibrate, a selective peroxisome proliferator–activated receptor α modulator, reduces triglyceride levels and improves other lipid levels.

METHODS

In a multinational, double-blind, randomized, controlled trial, we assigned patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia (triglyceride level, 200 to 499 mg per deciliter), and high-density lipoprotein (HDL) cholesterol levels of 40 mg per deciliter or lower to receive pemafibrate (0.2-mg tablets twice daily) or matching placebo. Eligible patients were receiving guideline-directed lipid-lowering therapy or could not receive statin therapy without adverse effects and had low-density lipoprotein (LDL) cholesterol levels of 100 mg per deciliter or lower. The primary efficacy end point was a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes.

RESULTS

Among 10,497 patients (66.9% with previous cardiovascular disease), the median baseline fasting triglyceride level was 271 mg per deciliter, HDL cholesterol level 33 mg per deciliter, and LDL cholesterol level 78 mg per deciliter. The median follow-up was 3.4 years. As compared with placebo, the effects of pemafibrate on lipid levels at 4 months were –26.2% for triglycerides, –25.8% for very-low-density lipoprotein (VLDL) cholesterol, –25.6% for remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins after lipolysis and lipoprotein remodeling), –27.6% for apolipoprotein C-III, and 4.8% for apolipoprotein B. A primary endpoint event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup. The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with a higher incidence of adverse renal events and venous thromboembolism and a lower incidence of nonalcoholic fatty liver disease.

CONCLUSIONS

Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. (Funded by the Kowa Research Institute; PROMINENT ClinicalTrials.gov number, NCT03071692.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Das Pradhan can be contacted at apradhan@bwh.harvard.edu and Dr. Ridker can be contacted at pridker@bwh.harvard.edu or at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Ave., Boston, MA 02215.

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

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CME at NEJM.org

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

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ABSTRACT

BACKGROUND

Lipoprotein(a) is a presumed risk factor for atherosclerotic cardiovascular disease. Olpasiran is a small interfering RNA that reduces lipoprotein(a) synthesis in the liver.

METHODS

We conducted a randomized, double-blind, placebo-controlled, dose-finding trial involving patients with established atherosclerotic cardiovascular disease and a lipoprotein(a) concentration of more than 150 nmol per liter. Patients were randomly assigned to receive one of four doses of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) or matching placebo, administered subcutaneously. The primary end point was the percent change in the lipoprotein(a) concentration from baseline to week 36 (reported as the placebo-adjusted mean percent change). Safety was also assessed.

RESULTS

Among the 281 enrolled patients, the median concentration of lipoprotein(a) at baseline was 260.3 nmol per liter, and the median concentration of low-density lipoprotein cholesterol was 67.5 mg per deciliter. At baseline, 88% of the patients were taking statin therapy, 52% were taking ezetimibe, and 23% were taking a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor. At 36 weeks, the lipoprotein(a) concentration had increased by a mean of 3.6% in the placebo group, whereas olpasiran therapy had significantly and substantially reduced the lipoprotein(a) concentration in a dose-dependent manner, resulting in placebo-adjusted mean percent changes of –70.5% with the 10-mg dose, –97.4% with the 75-mg dose, –101.1% with the 225-mg dose administered every 12 weeks, and –100.5% with the 225-mg dose administered every 24 weeks (P<0.001 for all comparisons with baseline). The overall incidence of adverse events was similar across the trial groups. The most common olpasiran-related adverse events were injection-site reactions, primarily pain.

CONCLUSIONS

Olpasiran therapy significantly reduced lipoprotein(a) concentrations in patients with established atherosclerotic cardiovascular disease. Longer and larger trials will be necessary to determine the effect of olpasiran therapy on cardiovascular disease. (Funded by Amgen; OCEAN[a]-DOSE ClinicalTrials.gov number, NCT04270760.)

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*A list of the OCEAN(a)-DOSE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Polypill Strategy in Secondary Cardiovascular Prevention

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ABSTRACT

BACKGROUND

A polypill that includes key medications associated with improved outcomes (aspirin, angiotensin-converting–enzyme [ACE] inhibitor, and statin) has been proposed as a simple approach to the secondary prevention of cardiovascular death and complications after myocardial infarction.

METHODS

In this phase 3, randomized, controlled clinical trial, we assigned patients with myocardial infarction within the previous 6 months to a polypill-based strategy or usual care. The polypill treatment consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary composite outcome was cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent revascularization. The key secondary end point was a composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke.

RESULTS

A total of 2499 patients underwent randomization and were followed for a median of 36 months. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 (12.7%) in the usual-care group (hazard ratio, 0.76; 95% confidence interval [CI], 0.60 to 0.96; P=0.02). A key secondary-outcome event occurred in 101 patients (8.2%) in the polypill group and in 144 (11.7%) in the usual-care group (hazard ratio, 0.70; 95% CI, 0.54 to 0.90; P=0.005). The results were consistent across prespecified subgroups. Medication adherence as reported by the patients was higher in the polypill group than in the usual-care group. Adverse events were similar between groups.

CONCLUSIONS

Treatment with a polypill containing aspirin, ramipril, and atorvastatin within 6 months after myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events than usual care. (Funded by the European Union Horizon 2020; SECURE ClinicalTrials.gov number, NCT02596126; EudraCT number, 2015-002868-17.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fuster can be contacted at vfuster@cnic.es or at Centro Nacional de Investigaciones Cardiovasculares, Melchor Fernández Almagro 3, Madrid 28029, Spain.

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

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 11, 2022

ORIGINAL INVESTIGATIONS

Effect of Pelacarsen on Lipoprotein(a) Cholesterol and Corrected Low-Density Lipoprotein Cholesterol

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ABSTRACT

BACKGROUND Laboratory methods that report low-density lipoprotein cholesterol (LDL-C) include both LDL-C and lipoprotein(a) cholesterol [Lp(a)-C] content.

OBJECTIVES The purpose of this study was to assess the effect of pelacarsen on directly measured Lp(a)-C and LDL-C corrected for its Lp(a)-C content.

METHODS The authors evaluated subjects with a history of cardiovascular disease and elevated Lp(a) randomized to 5 groups of cumulative monthly doses of 20-80 mg pelacarsen vs placebo. Direct Lp(a)-C was measured on isolated Lp(a) using LPA4-magnetic beads directed to apolipoprotein(a). LDL-C was reported as: 1) LDL-C as reported by the clinical laboratory; 2) LDL-C_{corr} = laboratory-reported LDL-C − direct Lp(a)-C; and 3) LDL-$C_{corrDahlén}$ = laboratory LDL-C − [Lp(a) mass × 0.30] estimated by the Dahlén formula.

RESULTS The baseline median Lp(a)-C values in the groups ranged from 11.9 to 15.6 mg/dL. Compared with placebo, pelacarsen resulted in dose-dependent decreases in Lp(a)-C (2% vs −29% to −67%; $P = 0.001$-<0.0001). Baseline laboratory-reported mean LDL-C ranged from 68.5 to 89.5 mg/dL, whereas LDL-C_{corr} ranged from 55 to 74 mg/dL. Pelacarsen resulted in mean percent/absolute changes of −2% to −19%/−0.7 to −8.0 mg/dL ($P = 0.95$-0.05) in LDL-C_{corr}, −7% to −26%/−5.4 to −9.4 mg/dL ($P = 0.44$-<0.0001) in laboratory-reported LDL-C, and 3.1% to 28.3%/0.1 to 9.5 mg/dL ($P = 0.006$-0.50) increases in LDL-$C_{corrDahlén}$. Total apoB declined by 3%-16% ($P = 0.40$-<0.0001), but non-Lp(a) apoB was not significantly changed.

CONCLUSIONS Pelacarsen significantly lowers direct Lp(a)-C and has neutral to mild lowering of LDL-C_{corr}. In patients with elevated Lp(a), LDL-C_{corr} provides a more accurate reflection of changes in LDL-C than either laboratory-reported LDL-C or the Dahlén formula. (J Am Coll Cardiol 2022;79:1035-1046) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on JACC.org.

Approximately 60 years since its discovery, lipoprotein(a) [Lp(a)] is now accepted as a genetic, independent, and likely causal risk factor for cardiovascular disease.[1-3] Lp(a) is a risk factor in primary prevention settings,[4,5] as well as in patients on statins and those enrolled in PCSK9 inhibitor trials.[6,7] In particular, alirocumab provides significant risk reduction in recurrent events

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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The Journal of Clinical Investigation

REVIEW SERIES: NEW THERAPEUTIC TARGETS IN CARDIOVASCULAR DISEASES
Series Editor: Daniel P. Kelly

Addressing dyslipidemic risk beyond LDL-cholesterol

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Despite the success of LDL-lowering drugs in reducing cardiovascular disease (CVD), there remains a large burden of residual disease due in part to persistent dyslipidemia characterized by elevated levels of triglyceride-rich lipoproteins (TRLs) and reduced levels of HDL. This form of dyslipidemia is increasing globally as a result of the rising prevalence of obesity and metabolic syndrome. Accumulating evidence suggests that impaired hepatic clearance of cholesterol-rich TRL remnants leads to their accumulation in arteries, promoting foam cell formation and inflammation. Low levels of HDL may associate with reduced cholesterol efflux from foam cells, aggravating atherosclerosis. While fibrates and fish oils reduce TRL, they have not been uniformly successful in reducing CVD, and there is a large unmet need for new approaches to reduce remnants and CVD. Rare genetic variants that lower triglyceride levels via activation of lipolysis and associate with reduced CVD suggest new approaches to treating dyslipidemia. Apolipoprotein C3 (APOC3) and angiopoietin-like 3 (ANGPTL3) have emerged as targets for inhibition by antibody, antisense, or RNAi approaches. Inhibition of either molecule lowers TRL but respectively raises or lowers HDL levels. Large clinical trials of such agents in patients with high CVD risk and elevated levels of TRL will be required to demonstrate efficacy of these approaches.

Introduction

Imagine a 60-year-old patient with metabolic syndrome (obesity, hypertension, insulin resistance, and dyslipidemia) who is taking a statin and has an LDL-cholesterol (LDL-C) level of 70 mg/dL but also has elevated triglycerides (TGs; 200 mg/dL) and low HDL-cholesterol (HDL-C; 30 mg/dL). What could be approaches to reduce atherosclerotic cardiovascular disease (CVD) risk in this patient? Approaches could first include further efforts to reduce LDL-C by maximizing the dose of potent statins, adding the cholesterol absorption inhibitor ezetimibe, or suppressing the LDL-R–regulating protein PCSK9 with monoclonal antibodies. While each of these treatments reduces CVD risk, they do not very consistently reduce TG levels and they still leave a substantial residue of CVD events (1–3). Treatment options for further lowering TGs might include fibrates or fish oils; however, the evidence for a beneficial effect of fibrates is not compelling (4), and while some fish oils may reduce CVD (5), the underlying mechanisms and impact remain uncertain. Although low HDL-C is associated with increased CVD risk, there are currently no effective drugs for targeting low HDL, and the whole idea of raising HDL-C has been called into question (6). Thus, beyond LDL-C, there are no optimal current treatment options to address dyslipidemia, as exemplified by this typical patient with metabolic syndrome.

A major theme of this Review is that lowering levels of TG-rich lipoproteins (TRLs) by activation of lipolysis and enhanced hepatic clearance of cholesterol-rich TRL remnants is likely to be beneficial for CVD (Figure 1). Activation of lipolysis leads to reduction in the levels of atherogenic TRL as well as increased levels of HDL: both effects may reduce atherosclerosis. While diet, exercise, and weight loss can have an important role in lowering TGs and raising HDL-C (7–10), the emphasis here will be on treatments using novel technologies to target new pathways that have been uncovered through genetic studies.

Trends in residual risk

CVD, including myocardial infarction and stroke, is the leading cause of death in the United States and accounts for 28% of overall mortality (11). CVD risk factors include age, sex, hypertension, diabetes, smoking, body mass index, and increased levels of LDL-C or TGs or reduced HDL-C levels (1, 12). Current therapies for prevention of ischemic events focus on controlling risk factors, as well as suppressing thrombosis in at-risk individuals, and this approach has contributed to decades of improvement in CVD mortality (13). This trend has stalled in recent years, in part because of the rise of obesity, diabetes, and their associated dyslipidemias. The metabolic syndrome has become more prevalent in all sociodemographic groups in the United States, and now occurs in more than one-third of adults (14).

Both fasting and nonfasting TG levels associate with CVD risk. In a European population, 27% of adults had nonfasting TGs greater than 176 mg/dL, a level that was associated with an approximately 1.9-fold increase in risk of CVD (15). In individuals with TGs greater than 580 mg/dL, the risk was increased even further to 5.1-fold for myocardial infarction and 3.2-fold for

Conflict of interest: ART is on the scientific advisory board and is a cofounder of Staten Biotechnology and has consulted for Amgen, Commonwealth Serum Laboratories, the Medicines Company, AstraZeneca, and Foresite Labs. IJG has received laboratory support and consulting fees from Arrowhead Pharmaceuticals and has consulted for Ionis Pharmaceuticals/Akcea Therapeutics.

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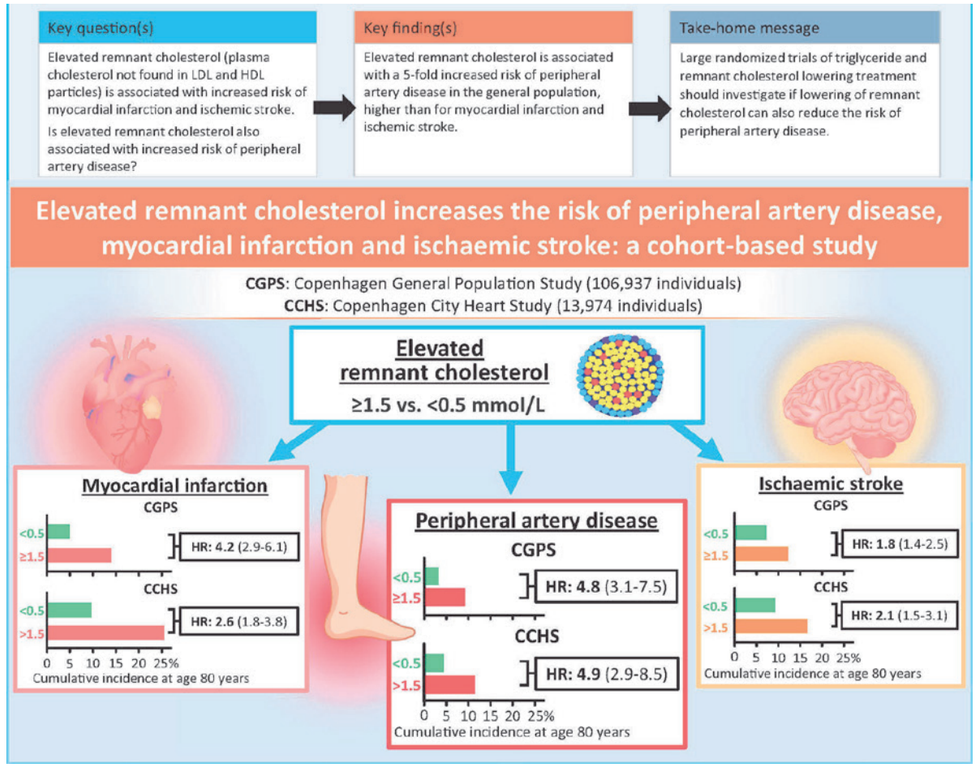
Graphical Abstract Comparison of risk of peripheral artery disease, myocardial infarction, and ischaemic stroke as a function of ...



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Stroke

CLINICAL AND POPULATION SCIENCES

Remnant Cholesterol Variability and Incident Ischemic Stroke in the General Population

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BACKGROUND: Studies have demonstrated that remnant cholesterol is correlated with the risk of ischemic stroke. However, it is unknown whether visit-to-visit variability in remnant cholesterol concentration affects ischemic stroke. We sought to examine the role of remnant cholesterol variability in the subsequent development of ischemic stroke in the general population.

METHODS: We performed a post hoc analysis including eligible participants from the Kailuan Study cohort who underwent 3 health examinations and were free of atrial fibrillation, myocardial infarction, stroke, cancer, or known lipid-medication use from 2006 to 2010. Participants were followed up until the end of 2017. Variability was quantified as variability independent of the mean, average real variability, and SD. Multivariate analysis was performed using the Fine and Gray competing risk model to estimate subhazard ratios assuming death as a competing risk.

RESULTS: The final study cohort comprised 38 556 participants. After a median follow-up of 7.0 years, 1058 individuals were newly diagnosed with ischemic stroke. After adjusting for age (time scale), sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes, family history of cardiovascular disease, body mass index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and mean remnant cholesterol, the highest quartile (quartile 4) of variability independent of the mean of remnant cholesterol was associated with an increased ischemic stroke risk compared with the lowest quartile (quartile 1), (subhazard ratio, 1.27 [95% CI, 1.06–1.53]). For each 1-SD increase in variability independent of the mean of remnant cholesterol, the risk increased by 9% (subhazard ratio, 1.09 [95% CI, 1.03–1.16]). The association was also significant using average real variability and SD as indices of variability.

CONCLUSIONS: Greater remnant cholesterol variability was associated with a higher risk of ischemic stroke in the general population.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular disease ■ cholesterol ■ ischemic stroke ■ lipids ■ lipoprotein

Remnant plasma cholesterol is emerging as a measure for the prediction of cardiovascular or cerebrovascular disease risk.[1–4] The measure may explain—in part—the significant residual cardiovascular risk among statin-treated individuals, even in the context of aggressive treatment to reach LDL (low-density lipoprotein) cholesterol targets. The term remnant cholesterol describes the cholesterol in triglyceride-rich lipoproteins, composed of very low-density lipoproteins and intermediate-density lipoproteins in the fasting state, and these 2 lipoproteins together with chylomicron remnants in the nonfasting state.[5]

See related article, p 1942

The Copenhagen General Population Study and the Copenhagen City Heart Study have reported an association

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Stroke is available at www.ahajournals.org/journal/str

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NICE National Institute for Health and Care Excellence

NICE guidance

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides

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Research

JAMA Internal Medicine | Original Investigation

Association of Statin Therapy Initiation With Diabetes Progression
A Retrospective Matched-Cohort Study

Ishak A. Mansi, MD; Matthieu Chansard; Ildiko Lingvay, MD, MPH, MSCS; Song Zhang, PhD; Ethan A. Halm, MD, MPH, MBA; Carlos A. Alvarez, PharmD, MSc, MSCS

IMPORTANCE Statin therapy has been associated with increased insulin resistance; however, its clinical implications for diabetes control among patients with diabetes is unknown.

OBJECTIVE To assess diabetes progression after initiation of statin use in patients with diabetes.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective matched-cohort study using new-user and active-comparator designs to assess associations between statin initiation and diabetes progression in a national cohort of patients covered by the US Department of Veterans Affairs from fiscal years 2003-2015. Patients included were 30 years or older; had been diagnosed with diabetes during the study period; and were regular users of the Veterans Affairs health system, with records of demographic information, clinical encounters, vital signs, laboratory data, and medication usage.

INTERVENTIONS Treatment initiation with statins (statin users) or with H2-blockers or proton pump inhibitors (active comparators).

MAIN OUTCOMES AND MEASURES Diabetes progression composite outcome comprised the following: new insulin initiation, increase in the number of glucose-lowering medication classes, incidence of 5 or more measurements of blood glucose of 200 mg/dL or greater, or a new diagnosis of ketoacidosis or uncontrolled diabetes.

RESULTS From the 705 774 eligible patients, we matched 83 022 pairs of statin users and active comparators; the matched cohort had a mean (SD) age of 60.1 (11.6) years; 78 712 (94.9%) were men; 1715 (2.1%) were American Indian/Pacific Islander/Alaska Native, 570 (0.8%) were Asian, 17 890 (21.5%) were Black, and 56 633 (68.2 %) were White individuals. Diabetes progression outcome occurred in 55.9% of statin users vs 48.0% of active comparators (odds ratio, 1.37; 95% CI, 1.35-1.40; $P < .001$). Each individual component of the composite outcome was significantly higher among statin users. Secondary analysis demonstrated a dose-response relationship with a higher intensity of low-density lipoprotein-cholesterol lowering associated with greater diabetes progression.

CONCLUSIONS AND RELEVANCE This retrospective matched-cohort study found that statin use was associated with diabetes progression, including greater likelihood of insulin treatment initiation, significant hyperglycemia, acute glycemic complications, and an increased number of prescriptions for glucose-lowering medication classes. The risk-benefit ratio of statin use in patients with diabetes should take into consideration its metabolic effects.

Supplemental content

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NEWS & VIEWS

DIABETES

Statins and diabetes mellitus progression: a fly in the ointment?

Niki Katsiki and Dimitri P. Mikhailidis

Statins might exert diabetogenic effects, potentially increasing insulin resistance and worsening glucose control. However, patients with diabetes mellitus are at high or very high cardiovascular risk and, thus, statin use is strongly recommended. Adding ezetimibe to statins might be helpful in achieving lipid targets and reducing cardiovascular risk without adversely affecting glucose metabolism.

Refers to Mansi, I. A. et al. Association of statin therapy initiation with diabetes progression: a retrospective matched-cohort study. *JAMA Intern. Med.* https://doi.org/10.1001/jamainternmed.2021.5714 (2021).

In a recent retrospective matched-cohort study, Mansi et al.[1] assessed the effect of statin initiation on glycaemic control in patients with diabetes mellitus (diabetes mellitus type was not specified) covered by the US Department of Veterans Affairs (from 2003 to 2015). In brief, 83,022 pairs of patients using statins or an active comparator drug (that is, proton pump inhibitors (PPIs) or H2 blockers) were analysed (mean age 60.1 years old, 94.9% men and 68.2% white participants). Statin users were significantly more prone to diabetes mellitus progression (defined as new diagnosis of ketoacidosis or uncontrolled diabetes mellitus, increased number of antidiabetic drugs, ≥5 measurements of fasting blood glucose (FBG) ≥200 mg dl^{-1} or insulin initiation) compared with patients who used active comparators (OR 1.37, 95% CI 1.35–1.40; $P < 0.001$)[1]. Furthermore, the rate of each of these primary-outcome components was statistically significantly higher in patients who used statins than in those using active comparators. In secondary analyses, a dose–response association was identified between statin use and the risk of the study outcomes. Finally, among patients with no comorbidities at baseline ($n = 187,518$), patients treated with statins had an even greater (than in the overall cohort) risk of diabetes mellitus progression (OR 1.56, 95% CI 1.52–1.60; $P < 0.001$) versus those using active comparators[1].

These findings highlight a potential negative effect of statins on insulin resistance and glycaemic control. In this context, statin use (long-term and at high doses) has previously been linked to new-onset diabetes mellitus, especially in high-risk populations[2]. However, statins offer an overall benefit in terms of preventing vascular events in patients with diabetes mellitus[2]. Therefore, statin use is recommended for patients with diabetes mellitus by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[2].

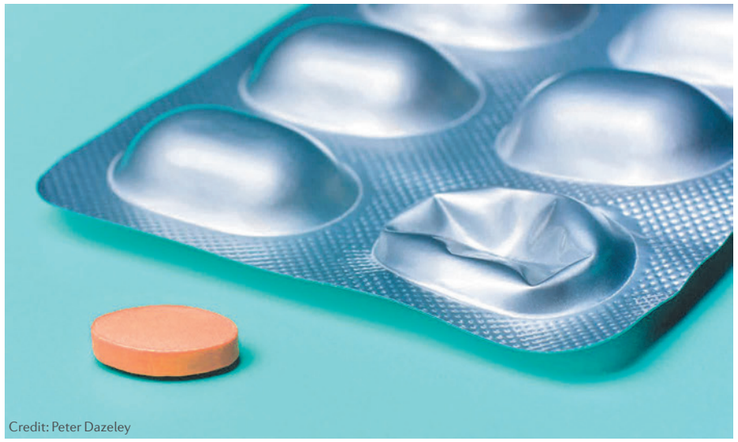
Mansi et al.[1] did not evaluate the effects of each statin on diabetes mellitus progression; thus, more research is required to clarify whether different statins (for example, lipophilic versus hydrophilic) have different effects on glucose metabolism. Furthermore, they could not ascertain whether the outcomes were due to statin use or due to a reduction in levels of LDL cholesterol[1]. In this context, the addition of ezetimibe could be helpful, both in achieving LDL cholesterol targets and minimizing the potential risk of statin-induced diabetes mellitus progression by allowing the administration of lower statin doses. Ezetimibe inhibits cholesterol absorption in the intestine, whereas statins inhibit cholesterol production mainly in the liver[3]. Indeed, a previous meta-analysis reported that ezetimibe did not affect FBG

> These findings highlight a potential negative effect of statins on insulin resistance and glycaemic control

(six studies, $n = 734$) or HbA_{1c} (six studies, $n = 342$) compared with placebo; similar results were observed when ezetimibe was added to a statin[3]. In the same meta-analysis, ezetimibe plus a low-dose statin was shown not to change FBG (six studies, $n = 521$) or HbA_{1c} (six studies, $n = 526$) compared with high-dose statin[3]. These ezetimibe-related neutral effects on glycaemic indexes were observed both in patients with and without diabetes mellitus[3]. Ezetimibe was also shown to improve glycaemic index values and insulin sensitivity[4]. Also, the ezetimibe plus statin combination versus statin monotherapy statistically significant decreased the incidence of vascular events in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) in patients with type 2 diabetes mellitus[5].

Of note, small but significant increases have been observed in FBG (weighted mean difference (WMD) 1.88 mg dl^{-1}, 95% CI 0.91–2.68; $P < 0.001$) and HbA_{1c} (WMD 0.032%, 95% CI 0.011–0.050; $P < 0.001$) following treatment with PCSK9 inhibitors for 78 weeks compared with placebo, as reported in a meta-analysis (20 randomized controlled trials, $n = 68,123$)[6]. More data are needed on the effects of these lipid-lowering drugs on glucose metabolism in the long-term.

PPIs and H2 blockers were the active comparators of statins in the Mansi et al. study[1]. PPIs were not associated with clinically important effects on glucose and insulin metabolism in patients with type 2 diabetes mellitus in a meta-analysis published in 2020 (REF.[7]). However, another meta-analysis published in 2021 (seven studies, $n = 342$) reported significant decreases in HbA_{1c} (WMD −0.36%, 95% CI −0.68 to −0.05; $P = 0.025$) and FBG (WMD −10.0 mg dl^{-1}, 95% CI −19.4 to −0.6; $P = 0.037$) with PPI addition to standard therapy in patients with type 2 diabetes mellitus[8]. Data on H2 blockers and glycaemic control in patients with diabetes mellitus are lacking. However, H2-receptor signalling has been suggested to affect glucose



Credit: Peter Dazeley

(and lipid) metabolism via peripheral actions in the liver and skeletal muscle[9]. Therefore, more evidence is needed to elucidate the effects of PPIs and H2 blockers on diabetes mellitus progression. This information will provide a better interpretation of the results of the Mansi et al. study[1].

In the Mansi et al. study[1], approximately 77% of the overall cohort had no known cardiovascular disease at baseline. However, this population might have had subclinical atherosclerosis or other target-organ damage (for example, microalbuminuria, left ventricular hypertrophy, diabetic neuropathy or retinopathy), and thus have been at very high cardiovascular risk according to the ESC–EAS guidelines[2]. In such patients, intensive statin therapy is mandatory to minimize cardiovascular risk (with a LDL cholesterol goal of <55 mg dl^{-1}; 1.4 mmol l^{-1})[2]. It follows that patients with diabetes mellitus should be screened for the presence of these comorbidities and glycaemic control should also be monitored after initiation of statins[10].

> Statins are recommended, despite the possibility of impairing glucose metabolism

Overall, achieving LDL cholesterol goals in patients with diabetes mellitus is compulsory, as these patients are at high or very high cardiovascular risk. Therefore, statins are recommended, despite the possibility of impairing glucose metabolism. The addition of ezetimibe might be promising both in terms of counteracting the adverse effects of high-dose statins on insulin sensitivity and achieving further cardiovascular risk reduction. More research is needed to elucidate the effects of both statins and PCSK9 inhibitors on glycaemic control. Future trials should look at the overall cost of treating patients with diabetes mellitus with statins as well as the long-term effects of any loss in glycaemic control.

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Competing interests
N.K. has given talks, attended conferences and participated in trials sponsored by Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Novartis, Novo Nordisk, Sanofi, Servier, Viatris and Vianex. D.P.M. has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk.

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HEPATOLOGY COMMUNICATIONS, VOL. 6, NO. 4, 2022

Pcsk9 Deletion Promotes Murine Nonalcoholic Steatohepatitis and Hepatic Carcinogenesis: Role of Cholesterol

George N. Ioannou [1-3] Sum P. Lee,[2] Peter S. Linsley,[4] Vivian Gersuk,[4] Matthew M. Yeh,[2,5] Yen-Ying Chen,[5,6,*] Yi-Jen Peng,[5,7] Moumita Dutta,[8] Gabby Mascarinas,[8] Bruk Molla,[8] Julia Yue Cui,[8] and Christopher Savard[1-3]

Proprotein convertase subtilisin/kexin type 9 (Pcsk9) binds to hepatic low-density lipoprotein receptor (LDLR) and induces its internalization and degradation. Pcsk9 inhibition increases LDLR expression by hepatocytes, which causes increased uptake of circulating LDL, thereby reducing plasma LDL-cholesterol. However, by increasing the uptake of LDL by the liver, Pcsk9 inhibition increases the exposure of the liver to cholesterol, which may result in higher risk of steatohepatitis and ever carcinogenesis. We compared *Pcsk9*-/- knockout (KO) mice and appropriate wild-type (WT) controls of the same strain assigned to a high-fat (15%, wt/wt) diet for 9 months supplemented with 0.25%, 0.5%, or 0.75% dietary cholesterol. *Pcsk9* KO mice on a high-fat, high-cholesterol diet exhibited higher levels of hepatic free cholesterol loading and hepatic cholesterol crystallization than their WT counterparts. *Pcsk9* KO mice developed crown-like structures of macrophages surrounding cholesterol crystal-containing lipid droplets and hepatocytes, exhibited higher levels of apoptosis, and developed significantly more hepatic inflammation and fibrosis consistent with fibrosing steatohepatitis, including 5-fold and 11-fold more fibrosis at 0.5% and 0.75% dietary cholesterol, respectively. When injected with diethylnitrosamine, a hepatic carcinogen, early-in-life *Pcsk9* KO mice were more likely to develop liver cancer than WT mice. *Conclusion: Pcsk9* KO mice on high-cholesterol diets developed increased hepatic free cholesterol and cholesterol crystals and fibrosing steatohepatitis with a higher predisposition to liver cancer compared with WT mice. Future studies should evaluate whether patients on long-term treatment with anti-PSCK9 monoclonal antibodies are at increased risk of hepatic steatosis, steatohepatitis or liver cancer, while accounting for concurrent use of statins. (*Hepatology Communications* 2022;6:780-794).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein secreted primarily by the liver; it binds to hepatic low-density lipoprotein receptor (LDLR) and induces its internalization and degradation. Thus, PCSK9 reduces the expression of LDLR by hepatocytes and increases plasma LDL-cholesterol. Conversely, inhibition of PCSK9 increases LDLR expression by hepatocytes, which causes increased uptake of circulating LDL, thereby reducing plasma LDL-cholesterol. Accordingly, *Pcsk9* knockout mice have hypocholesterolemia, with high levels of hepatic LDLR protein and lower levels of LDL-cholesterol.(1) In humans, gain-of-function mutations in PCSK9 lead to extremely

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ER, endoplasmic reticulum; HMW, high molecular weight; HOMA-IR, Homeostasis Model Assessment–Insulin Resistance; LDLR, low-density lipoprotein receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; Pcsk9, proprotein convertase subtilisin/kexin type 9; TUNEL, terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling.

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Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial

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Summary

Introduction Whether long-term treatment with the twice-yearly, siRNA therapeutic inclisiran, which reduces hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9), results in sustained reductions in LDL cholesterol with an acceptable safety profile is not known. The aim of this study was to assess the effect of long-term dosing of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol.

Methods ORION-3 was a 4-year open-label extension study of the placebo-controlled, phase 2 ORION-1 trial, conducted at 52 sites across five countries. Patients with prevalent atherosclerotic cardiovascular disease or high-risk primary prevention and elevated LDL cholesterol despite maximally tolerated statins or other LDL-lowering treatments, or with documented statin intolerance, who had completed the ORION-1 trial were eligible. Patients receiving inclisiran in ORION-1 received twice-yearly 300 mg subcutaneous inclisiran sodium throughout ORION-3 (inclisiran-only arm), whereas patients receiving placebo in ORION-1 first received subcutaneous evolocumab 140 mg every 2 weeks until day 360 thereafter transitioning to inclisiran twice-yearly for the remainder of ORION-3 study (switching arm). The primary efficacy endpoint was the percentage change in LDL cholesterol with inclisiran from the start of ORION-1 through to day 210 of the open label extension phase in the inclisiran-only arm (approximately 570 days of total inclisiran exposure in the modified intention-to-treat population). Secondary and exploratory endpoints included changes in LDL-C cholesterol and PCSK9 concentrations levels up to day 1440 (4 years) in each arm, and safety. ORION-3 is registered with ClinicalTrials.gov, NCT03060577.

Findings Of the original ORION-1 cohort of 497 patients, 290 of 370 patients allocated to drug continued into the inclisiran-only arm and 92 of 127 patients allocated to placebo entered the switching-arm in the ORION-3 extension study conducted between March 24, 2017, and Dec 17, 2021. In the inclisiran-only arm, LDL cholesterol was reduced by 47·5% (95% CI 50·7–44·3) at day 210 and sustained over 1440 days. The 4-year averaged mean reduction of LDL-C cholesterol was 44·2% (95% CI: 47·1–41·4), with reductions in PCSK9 ranging from 62·2% to 77·8%. Adverse events at the injection site were reported in 39 (14%) of 284 patients in the inclisiran-only arm and 12 (14%) of 87 patients in the switching arm. The incidence of treatment-emergent serious adverse events possibly related to the study drug was 1% (three of 284) in the inclisiran-only arm and 1% (one of 87) in the switching arm.

Interpretation Twice-yearly inclisiran provided sustained reductions in LDL cholesterol and PCSK9 concentrations and was well tolerated over 4 years in the extension study. This is the first prospective long-term study to assess repeat hepatic exposure to inclisiran.

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Introduction

Lowering LDL cholesterol is an established, effective, pharmacological approach to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Current guidelines recommend risk-based LDL cholesterol goals with the aim of maintaining lower LDL cholesterol concentrations long term for those patients at greatest risk of future ASCVD-related events.[1–3] Statin monotherapy results in only 20–40% of very high-risk patients achieving new, lower, recommended LDL cholesterol goals, meaning that those not at goal will not only be required to use combination therapies, but also to be adherent to the additional medication prescribed.[1,3] Injectable therapies directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged, which further reduce LDL cholesterol concentrations, with two approaches currently available. The most common regimen used globally are monoclonal antibodies (mAbs) that bind circulating PCSK9. These require subcutaneous injections every 2 weeks,

HDL cholesterol levels and susceptibility to COVID-19

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Summary

Background Host cell-membrane cholesterol, an important player in viral infections, is in constant interaction with serum high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C). Low serum lipid levels during hospital admission are associated with COVID-19 severity. However, the effect of antecedent serum lipid levels on SARS-CoV-2 infection risk has not been explored.

Methods From our retrospective cohort from the Arkansas Clinical Data-Repository, we used log-binomial regression to assess the risk of SARS-CoV-2 infection among the trajectories of lipid levels during the 2 years antecedent to COVID-19 testing, identified using group-based-trajectory modelling. We used mixed-effects linear regression to assess the serum lipid level trends followed up to the time of, and 2-months following COVID-19 testing.

Findings Among the 11001 individuals with a median age of 59 years (IQR 46-70), 1340 (12.2%) tested positive for COVID-19. The highest trajectory for antecedent serum HDL-C was associated with the lowest SARS-CoV-2 infection risk (RR 0.63, 95%CI 0.46-0.86). Antecedent serum LDL-C, total cholesterol (TC), and triglycerides (TG) were not independently associated with SARS-CoV-2 infection risk. In COVID-19 patients, serum HDL-C (-7.7, 95%CI -9.8 to -5.5 mg/dL), and LDL-C (-6.29, 95%CI -12.2 to -0.37 mg/dL), but not TG levels, decreased transiently at the time of testing.

Interpretation Higher antecedent serum HDL-C, but not LDL-C, TC, or TG, levels were associated with a lower SARS-CoV-2 infection risk. Serum HDL-C, and LDL-C levels declined transiently at the time of infection. Further studies are needed to determine the potential role of lipid-modulating therapies in the prevention and management of COVID-19.

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Keywords: SARS-CoV-2; Risk; LDL; Total cholesterol; Triglycerides

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Introduction

The burden of Coronavirus disease-2019 (COVID-19) continues to remain high worldwide[1] and is currently the most common cause of death due to a single infectious agent.[2] There is a persistent need to understand the host factors that can lead to increased susceptibility

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A global lipid map reveals host dependency factors conserved across SARS-CoV-2 variants

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A comprehensive understanding of host dependency factors for SARS-CoV-2 remains elusive. Here, we map alterations in host lipids following SARS-CoV-2 infection using non-targeted lipidomics. We find that SARS-CoV-2 rewires host lipid metabolism, significantly altering hundreds of lipid species to effectively establish infection. We correlate these changes with viral protein activity by transfecting human cells with each viral protein and performing lipidomics. We find that lipid droplet plasticity is a key feature of infection and that viral propagation can be blocked by small-molecule glycerolipid biosynthesis inhibitors. We find that this inhibition was effective against the main variants of concern (alpha, beta, gamma, and delta), indicating that glycerolipid biosynthesis is a conserved host dependency factor that supports this evolving virus.

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RESEARCH ARTICLE

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Wireless Non-Invasive Monitoring of Cholesterol Using a Smart Contact Lens

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Herein, a wireless and soft smart contact lens that enables real-time quantitative recording of cholesterol in tear fluids for the monitoring of patients with hyperlipidemia using a smartphone is reported. This contact lens incorporates an electrochemical biosensor for the continuous detection of cholesterol concentrations, stretchable antenna, and integrated circuits for wireless communication, which makes a smartphone the only device required to operate this lens remotely without obstructing the wearer's vision. The hyperlipidemia rabbit model is utilized to confirm the correlation between cholesterol levels in tear fluid and blood and to confirm the feasibility of this smart contact lens for diagnostic application of cholesterol-related diseases. Further in vivo tests with human subjects demonstrated its good biocompatibility, wearability, and reliability as a non-invasive healthcare device.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of premature deaths globally, and, according to the World Health Organization (WHO), they accounted for 38% of the deaths. in 2019.[1] Hyperlipidemia, a strong risk factor of CVDs, generally refers to elevations of cholesterol concentrations caused by genetic or environmental factors, including unhealthy diets.[2] The cholesterol concentrations are maintained consistently by the homeostasis of cholesterol essential for the metabolic functions of the human body.[3] However, excessive cholesterol due to the breakdown of the homeostasis can cause apoptosis resulting in necrotic cores which form the plaques.[4] The limited blood flow by the accumulation of plaques in an artery can induce CVDs. Hyperlipidemia can be diagnosed when the total cholesterol concentration of blood exceeds the threshold of 240 mg dL^{-1} (6.2 mM). For diagnosing hyperlipidemia, the standard methods for blood cholesterol quantification are the isotope-dilution mass spectrometry and the modified Abell–Kendall method, which are conducted in hospitals and laboratories. Although cholesterol tests are recommended every 4–6 years for healthy individuals, individuals aged 35 and older with increased risk for CVDs should have cholesterol tests more frequently, as hyperlipidemia shows no symptoms and cholesterol levels can be affected gradually by life patterns or daily diet.

Wearable healthcare devices that can monitor various physiological signals of the human body have been developed vigorously due to the increase in the awareness of wellness, which refers to the state of being in good health, and due to the

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