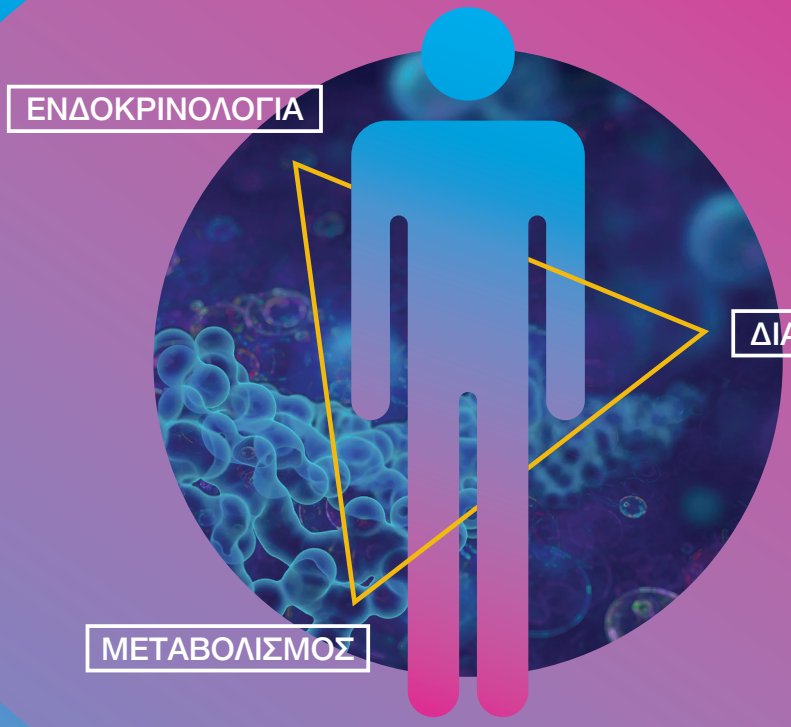

ενδόραμα'21

18-20 ΦΕΒ 2022

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

ΤΟΜΟΣ
ΠΡΑΚΤΙΚΩΝ

ενδόραμα'21

ΠΡΟΓΡΑΜΜΑ

Παρασκευή 18/02/2022

13:00-13:30 Εγγραφές

13:30-16:30 Νέες Τεχνολογίες

16:30-17:30 Λιπίδια
ΠΡΟΕΔΡΟΣ: Γιώργος Ιωαννίδης
ΟΜΙΛΗΤΗΣ: Γενοβέφα Κολοβού

17:30-18:30 Γυναικεία Αναπαραγωγή
ΠΡΟΕΔΡΟΣ: Βασιλική Συρίου
ΟΜΙΛΗΤΗΣ: Νεκταρία Ξήτα

18:30-19:45 Ανδρική Αναπαραγωγή
ΠΡΟΕΔΡΟΣ: Ευτυχία Κούκκου
ΟΜΙΛΗΤΗΣ: Ευαγγελία Μπίλλα

19:45-21:00 Διάλεξη: «Γονιδιακή θεραπεία: παρόν και μέλλον»
ΠΡΟΕΔΡΟΣ: Δημήτρης Παπαχρήστου & Περικλής Δουζδαμπάνης
ΟΜΙΛΗΤΗΣ: Κωνσταντίνος Στρατάκης

21:00-21:30 Πολιτιστικό Ενδόραμα
Το «22 και οι πρόσφυγες από υγιεινής απόψεως»
ΕΙΣΗΓΗΤΗΣ: Αντώνης Λιάκος

Σάββατο 19/02/2022

09:00-10:00 Παιδιατρική Ενδοκρινολογία
ΠΡΟΕΔΡΟΣ: Κωνσταντίνος Στρατάκης
ΟΜΙΛΗΤΗΣ: Μαρία Καράντζα - Χαρώνη

10:00-11:30 Υπόφυση
ΠΡΟΕΔΡΟΣ: Γεώργιος Πιαδίτης
ΟΜΙΛΗΤΗΣ: Γεωργία Ντάλη

11:30-12:30 Ινσουλινο-εξαρτώμενος Σαχαρώδης Διαβήτης
ΠΡΟΕΔΡΟΣ: Ζαδάλλα Μούσλεχ
ΟΜΙΛΗΤΗΣ: Βάια Λαμπαδιάρη

ΠΡΟΓΡΑΜΜΑ

12:30-13:30 Μη Ινσουλινο-εξαρτώμενος Σαχαρώδης Διαβήτης
ΠΡΟΕΔΡΟΣ: Θεόδωρος Αλεξανδρίδης
ΟΜΙΛΗΤΗΣ: Νικόλαος Τεντολούρης

13:30-14:30 Διατροφή
ΠΡΟΕΔΡΟΣ: Μιχάλης Κουτσιλιέρης
ΟΜΙΛΗΤΗΣ: Dan Benardot

14:30-16:00 Ομάδες Εκπαίδευσης Διαβητικού Ελέγχου

16:00-17:00 Επινεφρίδια
ΠΡΟΕΔΡΟΣ: Δήμητρα Βασιλειάδη
ΟΜΙΛΗΤΗΣ: Κρυσταλλένια Αλεξανδράκη

17:00-18:00 Νέα Φάρμακα Ι
ΠΡΟΕΔΡΟΣ: Ιωάννης Αναστάσιος Βατάλας
ΟΜΙΛΗΤΗΣ: Εύα Κασσή

18:00-19:00 Νέα Φάρμακα ΙΙ
ΠΡΟΕΔΡΟΣ: Νικόλαος Καλογερής
ΟΜΙΛΗΤΗΣ: Εμμανουήλ Σουβατζόγλου

19:00-20:00 Μεταβολισμός Οστών
ΠΡΟΕΔΡΟΣ: Χρήστος Κοσμίδης
ΟΜΙΛΗΤΗΣ: Αθανάσιος Αναστασιλάκης

20:00-21:00 Θυροειδής
ΠΡΟΕΔΡΟΣ: Γρηγόρης Ευφραιμίδης
ΟΜΙΛΗΤΗΣ: Γεώργιος Σημαιάκης

Κυριακή 20/02/2022

09:00-11:30 Κλινικό Φροντιστήριο Φοιτητών Ι

11:30-14:00 Κλινικό Φροντιστήριο Φοιτητών ΙΙ

ΟΜΙΛΗΤΕΣ - ΠΡΟΕΔΡΟΙ

Κρυσταλλένια Αλεξανδράκη
Ενδοκρινολόγος Ακαδημαϊκός Υπότροφος, Ιατρική Σχολή, ΕΚΠΑ.

Θεόδωρος Αλεξανδρίδης
Καθηγητής Παθολογίας Ενδοκρινολογίας Διευθυντής Ενδοκρινολογικού Τμήματος Πανεπιστημίου Πατρών

Αθανάσιος Αναστασιλάκης
Ενδοκρινολόγος Επιμελητής του Ενδοκρινολογικού Τμήματος του 424 ΓΣΝΕ

Δήμητρα Α. Βασιλειάδη
Ενδοκρινολόγος-Διευθύντρια Ε.Σ.Υ., Τμήμα Ενδοκρινολογίας και Μεταβολισμού, Διαβητολογικό Κέντρο, Κέντρο Εμπειρογνωμοσύνης Σπανίων Ενδοκρινικών Νοσημάτων, Νοσοκομείο Ευαγγελισμός, Αθήνα

Ιωάννης – Αναστάσιος Βατάλας
Ενδοκρινολόγος-Διαβητολόγος Διδάκτωρ Ιατρικής Σχολής Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών

Περικλής Δουσδαμπάνης
Διδάκτωρ Ιατρικής Σχολής Πατρών, Νεφρολόγος , Διευθυντής Μονάδα Χρόνιας Αιμοκάθαρσης ‘’Κυανούς Σταυρός Πατρών’’, Πρόεδρος Ιατρικής Εταιρείας Δυτικής Ελλάδας & Πελοποννήσου

Γρηγόρης Ευφραιμίδης
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Γιώργος Ιωαννίδης
Ενδοκρινολόγος τ. Διευθυντής του Τμήμα Ενδοκρινολογίας - Διαβητολογικού Κέντρου του ΓΝΑ «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»

Νίκος Καλογερής
Ενδοκρινολόγος

Μαρία Καράντζα - Χαρώνη
Ενδοκρινολόγος Παίδων, Διευθύντρια, Κλινική Παιδιατρικής – Εφηβικής Ενδοκρινολογίας, «ΜΗΤΕΡΑ»

Εύα Κασσή
Ενδοκρινολόγος, Αναπληρώτρια Καθηγήτρια της Ιατρικής Σχολής του Πανεπιστημίου Αθηνών

Γενοβέφα Κολοβού
Καρδιολόγος, Διευθύντρια Προληπτικής Καρδιολογίας στο Metropolitan Hospital

Χρήστος Κοσμίδης
Ορθοπεδικός, Διδάκτωρ ΕΚΠΑ

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Ενδοκρινολόγος

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Δημήτρης Παπαχρήστου
Ενδοκρινολόγος & Παθολόγος Διαβητολόγος Αναπληρωτής Καθηγητής ΔΠΘ

Γεώργιος Πιαδίτης
Διευθυντής τμήματος Ενδοκρινολογίας, Διαβητολογίας & Μεταβολισμού στο νοσοκομείο Ερρίκος Ντυνάν»

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Βασιλική Συρίου
Ενδοκρινολόγος, Διευθύντρια ΕΣΥ. ΓΝΑ « ΕΛΠΙΣ «

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ΧΟΡΗΓΟΙ

UNI-PHARMA Pharmaceutical Laboratories S.A.
ELPEN
Lilly ΦΑΡΜΑΣΕΡΒ
AstraZeneca
MERCK
ITF Hellas Pharmaceuticals
SOLGAR Since 1947
innovis Future health today
Vita Longa Pharmaceutical Company
sanofi
Η ΕΠΙΣΤΗΜΗ ΤΗΣ ΦΥΣΗΣ
NORMA
Medtronic
Galenica
Epsilon Health
100 Years of Excellence PETSIAVAS A NAME, A HISTORY, A FUTURE
RECORDATI
Roche
novo nordisk
FARAN
InterMed Pharmaceutical Laboratories

ΠΑΙΔΙΑΤΡΙΚΗ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ

ΜΑΡΙΑ ΚΑΡΑΝΤΖΑ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ ΠΑΙΔΩΝ,
ΔΙΕΥΘΥΝΤΡΙΑ, ΚΛΙΝΙΚΗ ΠΑΙΔΙΑΤΡΙΚΗΣ – ΕΦΗΒΙΚΗΣ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑΣ, «ΜΗΤΕΡΑ»

COVID-19 and pediatric endocrinology

1. Precocious Puberty and Covid-19 into Perspective: Potential Increased Frequency, Possible Causes, and a Potential Emergency to Be Addressed

Maria E. Street[1*], Chiara Sartori[1], Cecilia Catellani[1,2] and Beatrice Righi[1]
Division of Pediatric Endocrinology and Diabetology, Unit of Pediatrics, Department of Mother and Child, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

PhD Program in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy Front. Pediatr., 20 September 2021 | https://doi.org/10.3389/fped.2021.734899

A significant increase in precocious puberty, rapidly progressive puberty and precocious menarche has been reported in Italy since the initial lockdown because of the pandemic, and this could represent a new emergency to be addressed during this pandemic. There is a need, therefore, for further understanding and research. Many causes could account for this. Initially, it was thought that the changes in life-style, in screen time, and sleeping habits could be the cause but if considered individually these are insufficient to explain this phenomenon. Likely, changes in central nervous mediators, and an increase in catecholamines could contribute as a trigger, however, these aspects are poorly studied and understood as well as the real perceptions of these children. Finally, staying more indoors has certainly exposed these children to specific contaminants working as endocrine disruptors which could also have had an effect. It would be of utmost importance to compare this phenomenon worldwide with appropriate studies in order to verify what is happening, and gain a new insight into the consequences of the covid-19 pandemic and into precocious puberty and for future prevention.

2. Characteristics of hospitalized children with SARS-CoV-2 in the New York City metropolitan area

Verma S, Lumba R, Dapul HM, Gold-von Simson G, Phoon CK, Lighter JL, Farkas JS, Vinci A, Noor A, Raabe VN, Rhee D, Rigaud M, Mally PV, Randis TM, Dreyer B, Ratner AJ, Manno CS, Chopra A

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Hosp Pediatr. 2021 Jan;11(1):71–78.doi: 10.1542/hpeds.2020-001917.

https://pubmed.ncbi.nlm.nih.gov/33033078/

In a cohort of 82 children (0–21 years) who were hospitalized for severe SARS-CoV-2 associated respiratory illness, obesity was the strongest risk factor for the outcome of critical care. Already during the first COVID-19 wave, it was shown that obesity is a major risk factor for severe COVID-19 infection

in adults and caused the age at disease manifestation to shift towards younger ages . Recent findings give insights into the underlying mechanism that links obesity to severe COVID-19 infection:

1. Obesity leads to respiratory dysfunction, characterised by increased airway resistance, reduced gas exchange and lung volume and muscle strength, and decreased diaphragmatic excursions . Transdifferentiation of pulmonary lipofibroblasts into myofibroblasts may contribute to the development of pulmonary fibrosis and thus aggravate the severity of COVID-19 associated lung disease .

2. Insulin resistance and chronic subclinical inflammation associated with obesity lead to an increased vulnerability to infection-related lung failure .

3. The expression of angiotensin converting enzyme 2 (the functional receptor of SARS-CoV-2) is upregulated in adipocytes from patients with obesity, making adipose tissue a potential target organ and viral reservoir .

4. Leptin links metabolism to the immune response by signaling via the Jak/STATand Akt pathways. Increased circulating leptin levels seen in obesity lead to compromised systemic immune response. Leptin is also an important mediator of pulmonary immunity and elevated leptin levels worsen the pulmonary defense against infection (5). Leptin may also increase systemic inflammation via paracrine effects on T cells (6). In a mouse model, administration of antileptin antibody decreased pro-inflammatory events and improved lung pathology and survival .

Based on clinical observations and pathophysiological findings, specific recommendations for prevention and care of patients with obesity and COVID-19 disease have recently been published

Congenital Hypothyroidism

3. Congenital hypothyroidism: A 2020-2021 consensus guidelines update-An ENDO-European Reference Network initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology

van Trotsenburg P, Stoupa A, Le´ger J, Rohrer T, Peters C, Fugazzola L, Cassio A, Heinrichs C, Beauloye V, Pohlenz J, Rodien P, Coutant R, Szinnai G, Murray P, Barte´s B, Luton D, Salerno M, de Sanctis L, Vigone M, Krude H, Persani L, Polak M Thyroid. 2021:387–419. doi:10.1089/thy.2020.0333.

These updated ENDO-European Reference Network (ENDO-ERN), European Society for Paediatric Endocrinology (ESPE) and European Society for Endocrinology (ESE) guidelines for congenital hypothyroidism will serve as comprehensive review of the literature providing recommendations to all aspects of the disease.

The first Consensus Guidelines for congenital hypothyroidism of ESPE were published in 2014 [1]. This revised version of the guidelines was realized by a panel of paediatric and adult endocrinologists, obstetricians, and a representative of patient organisations. They give an update on all recommendations in the light of new evidence and knowledge from the literature between 2013 and 2020 according to the GRADE (grading of recommendations, assessment, development, and evaluation) system. The evidence section for each recommendation provides detailed discussion of the current available literature and questions that remain and need further clinical research. The main chapters comprise neonatal screening, diagnostic criteria, substitutive treatment, outcome, genetics, and antenatal diagnosis and cover all aspects of primary congenital hypothyroidism. Major innovations are the integration of recommendations for central congenital hypothyroidism and a comprehensive update on known and new genetic forms of congenital hypothyroidism.

4. Newborn screening TSH values less than 15 mIU/L are not associated with long-term hypothyroidism or cognitive impairment

West R, Hong J, Derraik JGB, Webster D, Heather NL, Hofman PL
J Clin Endocrinol Metab. 2020; 105:dgaa415. doi:10.1210/clinem/dgaa415.

The optimal cut-off for neonatal screening has long been a matter of debate. The optimal balance between optimal detection of cases and increase of false positive patients is difficult to define. Also, in the most recent guidelines for congenital hypothyroidism (see previous paper in this chapter 3.7), no precise cut-off was recommended, as screening approaches differ considerably [1].

West et al. addressed this open question by a retrospective study. They analysed the long-term neurodevelopmental outcome of 96 healthy individuals who passed routine neonatal screening according to the 15 mU/l TSH cut-off. They had a neonatal screening TSH of 8–14 mU/l. At age 6–12 years, these individuals and 76 siblings were investigated by Wechsler Intelligence Scale for Children. The study was powered to detect differences of 5 IQ points or more between cases and siblings.
Lower mid-childhood IQ showed a mild correlation with increasing TSH levels !15 mU/l. However, if IQ was compared between cases and siblings, no difference was detected over the whole TSH-range of 8–14 mU/l. The authors conclude that there was no clinically relevant long-term negative effect when screening cut-off is 15 mU/l. They argue against lowering the neonatal screening cut-off to below15 mU/l.

This study is of importance in a field where long-term data are scarce. The study was well designed and limitations discussed in detail. As also discussed by the authors, it is noteworthy that 80% (53/67) of cases with available siblings included had a TSH of 8–11 mU/l, while only 20% (13/67) of cases with siblings had a TSH value between 12–14 mU/l rendering the data more robust in the lower range of TSH values below %11 mU/l, where 12-14 case-sibling pairs could be compared for each additional unit of TSH. Nevertheless, these data add information on a TSH range, where also previous studies included only few cases. [2]. Ultimately, only prospective studies of treated versus untreated patients will provide robust evidence for the optimal TSH screening cut-off.

5. Cognitive and motor outcome in patients with early-detected central congenital hypothyroidism compared with siblings

Naafs JC, Marchal JP, Fliers E, Verkerk PH, Luijten MAJ, Boelen A, van Trotsenburg ASP, Zwaveling-Soonawala N J Clin Endocrinol Metab. 2021;106:e1231–e1239. doi:10.1210/clinem/dgaa901.

The results of this study are a robust argument to implement neonatal screening for central congenital hypothyroidism (CCH) worldwide. Only few countries, such as the Netherlands, screen for CCH. Neurodevelopmental outcome data are scarce for CCH compared to primary congenital hypothyroidism (PCH) not only because of the lack of widely established screening but also due to lower incidence (CCH 1:16,000 vs. PCH 1:2500-1:3000) .

Naafs et al. present a large cohort of well phenotyped patients with CCH, all detected by neonatal screening and treated early [2]. They compared full scale intelligence quotient (FSIQ) in patients with isolated CCH (iCCH, nZ35), CCH in the context of multiple pituitary hormone deficiencies (MPHD, nZ52) and patient siblings (nZ52). They found no significant difference in FSIQ between iCCH patients and siblings. However, patients with CCH in the context of MPHD, compared to iCCH and siblings, showed a significantly lower mean FSIQ (-7.5, and -7.9 points, respectively), most pronounced in the subgroup of performance IQ. So far, data on neurodevelopmental outcome in clinically detected and late treated CCH and MPHD patients are lacking for comparison. But the cost-effectiveness of neonatal screening for CCH has already been shown more than a decade ago also in the Netherlands.

Thyroid clinical studies

6. Randomised trial of block and replace vs. dose titration thionamide in young people with thyrotoxicosis

Wood CL, Cole M, Donaldson M, Dunger DB, Wood R, Morrison N, Matthews JNS, Pearce SHS, Cheetham TD Eur J Endocrinol. 2020;183:637–645. doi:10.1530/EJE-20-0617.

This study provides for the first time clear evidence that the block and replace (BR) strategy (combination of carbimazole plus levothyroxine) is not superior to the carbimazole dose titration (DT) strategy for treatment of paediatric Graves' disease.

Wood et al. present the first randomized controlled multicentre trial of patients with Graves' diseases in the paediatric age group comparing treatment stability of DT vs. BR. Each patient (nZ82) was randomized shortly after diagnosis and treated for three years. The authors found no difference between DT and BR in percentage of TSH or FT4 levels in or outside the reference range during the study period. However, 3/40 patients on BR vs. 0/41 on DT developed neutropenia.

These data are important, providing for the first-time clear evidence that BR therapy has no advantage on long term biochemical stability compared to DT, although BR is still widely used by paediatric endocrinologists [1]. These data strengthen the current guidelines of the American Thyroid Association and European Thyroid Association (ATA and ETA) [2,3] which do not recommend BR because of its higher carbimazole dose and therefore increased risk of drug-related side effects, as shown by a meta-analysis in adult patients

Growth Hormone Therapy: Safety

7. Long-term safety of growth hormone treatment in childhood: two Large observational studies: nordiNet IOS and ANSWER

Sa¨vendahl L, Polak M, Backeljauw P, Blair JC, Miller BS, Rohrer TR, Hokken-Koelega A, Pietropoli A, Kelepouris N, Ross J Karolinska Institutet, Karolinska University Hospital, Solna, Sweden.
lars.savendahl@ki.se

J Clin Endocrinol Metab. 2021 May 13;106(6):1728–1741.
doi:10.1210/clinem/dgab080. PMID: 33571362

This report gathered data from two large observational studies (NordiNet International Outcome Study and ANSWER Program) aimed at assessing the incidence of adverse drug reactions (ADRs), serious adverse events (SAEs), and their relation with rhGH dose. The whole study cohort included 37,702 subjects, with O130,000 patient-years follow-up. As in previous studies, subjects were stratified into different risk groups according to underlying diagnosis: low-risk (68.4%; comprising isolated GHD, SGA children, and ISS); intermediate-risk (27.5%; multiple pituitary hormone deficiencies, Turner and other syndromes), and high-risk (4.1%, malignancies and syndromes with high risk of malignancy).

As expected, the incidence of adverse events was lowest in the low-risk group. The most frequent ADRs and SAEs included “nervous system disorders” (such as headache) and “musculoskeletal and connective tissue disorders” (such as arthralgia and scoliosis). Among the low-risk group, the incidence of SAEs was significantly higher in SGA children. Perhaps counter-intuitively, GH dose was inversely associated with AE incidence rates. This finding is likely explained by the practice to prescribe lower GH doses to patients considered at higher risk of AEs. No case of cerebral hemorrhage and no increase in mortality risk was observed.

It has to be pointed out that this study reports with events occurring during GH treatment, whereas SAGhE analyzed events occurring in young adults who had received GH treatment during childhood. The lack of long-term follow-up limits the potential of this study to capture the risk of developing non communicable diseases (eg, diabetes, cardio-vascular morbidity, neoplasms or neurodegenerative diseases).

8. Long-term mortality after childhood growth hormone treatment: the SAGhE cohort study

Sa¨vendahl L, Cooke R, Tidblad A, Beckers D, Butler G, Cianfarani S, Clayton P, Coste J, Hokken-Koelega ACS, Kiess W, Kuehni CE, Albertsson-Wikland K, Deodati A, Ecosse E, Gausche R, Giacomozzi C, Konrad D, Landier F, Pfaeffle R, Sommer G, Thomas M, Tollerfield S, Zandwijken GRJ, Carel JC, Swerdlow AJ
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SAGhE is a large independent European consortium including eight different countries (Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and the UK) which was set up to evaluate the long-term safety of rhGH in a large cohort (O24 000) of young adult patients treated during childhood (1). In this report, overall and cause-specific mortality was assessed by comparison to general population data to calculate standardized mortality ratios (SMR). Patients were subdivided into different risk groups: 1) low-risk, further subdivided in group 1a (isolated GHD, idiopathic short stature (ISS) or mild skeletal dysplasia) and group 1b (small for gestational age (SGA); 2) intermediate-risk, including multiple pituitary hormone deficiencies and specific syndromes (Turner, Noonan, Down, etc.), and 3), high-risk, history of malignancies or chronic renal failure. The follow-up was O400 000 patient-years (to age 25 years).

In group 1a, all-cause mortality was not significantly increased. In group 1b, mortality risk was significantly increased (SMR 1.5, 95%CI 1.1–1.9) although this result was mainly driven by the French sub-cohort. Mortality risk was also significantly increased in the intermediate and high-risk groups. Notably, mortality from diseases of the circulatory and hematological systems was increased in all risk groups.

This large long-term independent study confirms earlier data from post-marketing surveillance studies indicating no significant effect of childhood rhGH therapy on overall mortality in patients with isolated growth hormone deficiency or idiopathic short stature. Whether the increased mortality observed in subjects born SGA should be attributed to rhGH treatment during childhood is open to debate, as it may be due to their inherent cardiometabolic risk or to the genetic cause underlying small size at birth (4). Consistent with this, mortality was not associated with mean daily or cumulative doses of rhGH for any of the risk groups.

Overall, these data are reassuring, however prolonged long-term surveillance of patients treated with rhGH in childhood is still needed as mortality from cardiovascular and hematological diseases in all treated groups was higher than the general population.

9. Association of childhood growth hormone treatment with long-term cardiovascular morbidity

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This nationwide population-based study assessed the long-term risk of cardiovascular events in patients who had received rhGH therapy during childhood and adolescence. The study cohort comprised 3.408 subjects treated under the GHD, SGA or ISS indications, and 50 036 age-, sex-, and region-based matched controls. Median follow-up was 14.9 years (to age 25 years) with a total of 795 125 person-years. Patients in each diagnostic group had a significant higher risk for cardiovascular events than controls (hazard ratio 1.69; 95% CI, 1.30–2.19), especially women (HR, 2.95; 95%CI, 1.31–3.20) and those treated for SGA (HR, 1.97, %CI, 1.28- 3.04). The increased risk was found in all treated groups and was associated with longer therapy duration and cumulative rhGH dose. The most common severe cardiovascular events were ischemic heart disease, cardiomyopathy and stroke.

GH has pleiotropic effects on the cardiovascular system. Acromegaly, a pathological model of exposure to high GH concentrations, is characterized by an increased cardiovascular mortality (2). The results of this study are consistent with previous data from French SAGhE cohort showing higher cerebrovascular mortality (3) and a higher risk of hemorrhagic stroke in subjects receiving rhGH for GHD, SGA and ISS indications during childhood (4). The authors wondered whether the observed increased cardiovascular risk might have been caused by discontinuation of rhGH treatment in adulthood in GHD patients rather than treatment during childhood. However, a further analysis of data from patients who continued therapy after completion of growth confirmed the increased cardiovascular morbidity.

These results are consistent with those reported by the SAGHE consortium. It should be noted that neither of these study designs can separate effects of rhGH therapy from risks related to the underlying condition. However, they further suggest the need of a long-term close cardiovascular monitoring in children treated with rhGH, especially in women and those treated for the SGA indication.

10. Longitudinal study on metabolic health in adults SGA during 5 years after GH with or without 2 years of GnRHa treatment

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doi:10.1210/clinem/dgaa287. PMID: 32436961

The aim of this longitudinal study was to investigate the potential long-term adverse effects of combined GnRHa/GH treatment on metabolic and bone health in short SGA children. Reassuring data are found at 5 years after cessation of GH therapy.

Children born small for gestational age (SGA) have weight and/or length at birth less than -2 SDS for gestational age. Approximately 10% of SGA children do not catch-up their growth retardation and have permanent short stature. Growth Hormone (GH) treatment is effective in improving the growth outcome of SGA children especially when therapy is started well before the onset of puberty. In children born SGA with predicted adult height less than -2.5 S.D., the combined therapy with GH plus 2-years gonadotropin releasing hormone analogues (GnRHa) has been suggested to postpone puberty and eventually increase adult height (3). Therapy with GnRH analogues may affect fat deposition, BMI and bone density as shown in retrospective studies conducted in children with central precocious puberty.

In this study, insulin sensitivity and b-cell function (by frequently sampled intravenous glucose tolerance tests, FSIGT), blood pressure, serum lipid levels, body composition and bone mineral density (by dual-energy x-ray absorptiometry (DXA) scans), were assessed during the 5 years after cessation of GH therapy in SGA young adults who were treated during childhood with the combination of GHCGnRHa (nZ112) compared to those treated with GH alone (nZ251) and 145 age-matched adults born appropriate for gestational age (AGA). In the GH treated group, a subgroup (nZ95) was randomly assigned to treatment with either GH 1 or 2 mg/m2/day (w 0.033 or 0.067 mg/kg/d).

At 5 years after discontinuation of GH therapy, the three groups showed no significant differences in fat mass, FSIGT results, blood pressure, serum lipid levels and bone mineral density. Total fat mass and trunk fat were lower, and lean body mass was higher in those treated with 2 mg GH/m^2/day, compared to 1 mg GH/m^2/day, whereas FSIGT results, limb fat, blood pressure, serum lipid levels, and bone density were similar in both GH-dose groups.

This further elegant study from the Rotterdam team shows that combined GnRHa/GH therapy is not associated with long-term adverse effects on metabolism, body composition and bone mineralization markers. However, the efficacy of the combined GH/GnRHa therapy has to be tested in a larger group of short SGA children before being transferred to clinical practice. Moreover, it has to be pointed out that the available metabolic markers are a surrogate of the real cardiometabolic status. In this regard, two recent studies reporting an increased long-term cardiovascular morbidity and mortality in SGA young adults treated with GH during childhood raises concern about a potential, likely IGF1-mediated, adverse effect on endothelial function, whose detection may elude the standard metabolic assessment .

Novel Treatments for Rare Skeletal Disorders

11. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial

Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, Ullot Font R, Harmatz P, Rutsch F, Bober MB, Polgreen LE, Ginebreda I, Mohnike K, Charrow J, Hoernschemeyer D, Ozono K, Alanay Y, Arundel P, Kagami S, Yasui N, White KK, Saal HM, Leiva-Gea A, Luna-Gonza´lez F, Mochizuki H, Basel D, Porco DM, Jayaram K, Fisheleva E, Huntsman Labed A, Day J
Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, VIC, Australia Lancet. 2020 Sep 5;396(10252):684–692.
Abstract: https://pubmed.ncbi.nlm.nih.gov/32891212/

In brief: Activating mutations in FGFR3 inhibit endochondral ossification in achondroplasia resulting in disproportionate extreme short stature. In this randomised, double-blind, phase 3, placebo-controlled trial, once-daily subcutaneous treatment with vosoritide, a C-type natriuretic peptide-analogue, was found to increase the rate of linear growth in children with achondroplasia.

Comment: Achondroplasia is characterised by extreme, disproportionate short stature with macrocephaly and several complications including foramen magnum stenosis with cervico-medullary compression, hydrocepha lus, obstructive sleep apnea. There is an increased risk of sudden death in infancy. Mortality is increased from birth to 4 years of age as well as in the fourth and fifth decades of life.

The condition is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 gene (FGFR3) that constitutively activates the mitogen-activated protein kinase (MAPK)–extracellular signal regulated kinase pathway in chondrocytes. C-type natriuretic peptide (CNP) acts on the natriuretic peptide receptor 2 (NPR2) and is a potent stimulator of endochondral ossification at the level of the growth plate. CNP stimulates growth, at least in part, by inhibiting FGFR3-mediated MAPK signalling. Vosoritide is a recombinant C-type natriuretic peptide analogue with an extended half-life.

A previous phase 2 and dose-finding study of daily subcutaneous vosoritide treatment in children (5 to 14 years of age) with achondroplasia demonstrated that the dose-dependent increase in growth rate appeared to level off at a positive effect of approximately 1.5 cm/year that was maintained up to 42 months of treatment.

In this phase 3, randomized, double-blind, placebo-controlled, 52-week trial (NCT03197766), the efficacy and safety of daily subcutaneous injections of vosoritide (15.0 mg/kg) was compared to placebo in 121 children (age range, 5 to !18 years) with achondroplasia. Two patients in the vosoritide group discontinued their participation after 2 and 6 days due to pain from injection and fear of needles, respectively. The remaining 119 participants completed the study and enrolled in the extension study. All 121 randomized patients were included in the efficacy analyses.

After 52 weeks of treatment, the annualized growth velocity was 1.57 cm/year higher in the vosoritide compared to the placebo group (95% CI 1.22–1.93; P!0.0001) and slightly better at 1.71 cm/year (95% CI 1.40–2.01) if adjusted for baseline growth velocity. In addition, all subgroup analyses (sex, age, tanner stage, height z-score, baseline growth velocity) indicated a positive effect of vosoritide. This study demonstrates that vosoritide is efficacious in increasing the growth velocity in children with achondroplasia and supports previous studies indicating that is safe. Further studies with earlier start and longer duration of treatment are needed to determine the total amount of height gain that can be accomplished with this treatment and possible effects on other important complications of the condition.

Bone- Translational highlights

12. Hormonal regulation of biomineralization

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Nat Rev Endocrinol. 2021 May;17(5):261–275
Abstract: https://pubmed.ncbi.nlm.nih.gov/33727709/

In brief: This article systematically reviews the current advances in the understanding of mineral metabolism with focus on the regulation of mineralization in skeletal tissue and inhibition of mineralization in non-skeletal tissue. This is mandatory reading for any aspiring endocrinologist.

Comment: Mineralization of the skeleton and teeth are critically important to allow ambulation and feeding. Inhibition of this process is equally important to prevent ectopic mineralization of soft tissues and organs, which is disabling and potentially lethal. The review is well-structured as it presents the current understanding of the complex regulation of the physiological and pathological aspects of the mineralization process. The roles and regulation of calcium and inorganic phosphate, dietary intake of minerals as well as the balance between activators and inhibitors of mineralization are discussed. The major regulators of biomineralization include parathyroid hormone (PTH), the vitamin D system, vitamin K, fibroblast growth factor 23 (FGF23) and phosphatase enzymes, and their respective roles in the mineralization process are discussed in detail. In addition, alternative regulatory mechanisms that control mineral delivery, skeletal metabolism and biomineralization in the fetus, the neonate, and in the mother during pregnancy and lactation are also discussed.

Puberty

13. Phase 3 trial of a small-volume subcutaneous 6-month duration leuprolide acetate treatment for central precocious puberty

Klein KO, Freire A, Gryngarten MG, Kletter GB, Benson M, Miller BS, Dajani TS, Eugster EA, Mauras N

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https://academic.oup.com/jcem/article/105/10/e3660/5879679

In brief: This phase 3 multi-centre, open-label, single-arm study explores the efficacy, pharmacokinetics and safety of 6-monthly 45-mg subcutaneous leuprolide acetate in 59 patients with central precocious puberty (CPP). Six-monthly leuprolide acetate appears to be a promising treatment to suppress pubertal hormones and

progression of secondary sexual features. Comment: CPP is classically treated with GnRH agonists. Available treatments include intramuscular leuprolide acetate injections, intramuscular triptorelin injections and subcutaneous histrelin acetate implants .

This phase 3 study evaluated the pharmacokinetics, safety and efficacy of 6-monthly 45-mg subcutaneous leuprolide acetate. Fifty-nine patients (57 girls and 2 boys) received 2 injections of leuprolide acetate and were evaluated at weeks 0, 24 and 48. Post-stimulation LH was suppressed (!4 IU/L) in 87% and 88% of children at weeks 24 and 48, respectively. Growth velocity regressed in O50% of patients at weeks 24 and 48, and average bone age advancement slightly but significantly regressed. Breast development regressed in almost all girls (55/57) and genital development regressed from G3 to G2 after 2 injections in both treated boys. An initial burst release of leuprolide was reported between 1 and 6 hours post-injection, followed by stable levels from weeks 12 to 44. Injections were well tolerated and

no withdrawal was reported. Two serious adverse effects were documented (wheezing and rash) but considered unrelated.

Although short in duration, this first phase 3 study indicates that a 6-monthly leuprolide acetate treatment represents a promising treatment to suppress pubertal hormones and progression of secondary signs of sexual maturation. Such a convenient administration might improve feasibility and adherence.

Gender Dysphoria- Basic Research

14. Behavioral and neurobiological effects of GnRH agonist treatment in mice - potential implications for puberty suppression in transgender individuals

Anacker C, Sydnor E, Chen BK, LaGamma CC, McGowan JC, Mastrodonato A, Hunsberger HC, Shores R, Dixon RS, McEwen BS, Byne W, Meyer-Bahlburg HFL, Bockting W, Ehrhardt AA, Denny CA

Neuropsychopharmacology. 2021 Apr;46(5):882–890.
doi:10.1038/s41386-020-00826-1. PMID: 32919399.

This mouse study addresses the question of the psychological effects of treatment with the GnRH analogue (GnRHa) leuprolide. Six-week-old, i.e. early-pubertal, male and female mice were injected daily with leuprolide (20 mg) or saline for 6 weeks. The mice were subjected to a number of behavioral tests, and hormonal stress response was assessed. The effects on reproductive function, social and affective behaviour, cognition, and brain activity were studied.

A main focus has previously been the effects of GnRHa on bone mineral density in adolescents receiving GnRHa in the context of gender dysphoria. Neuropsychiatric and neurobiological effects, other than halting puberty and possibly alleviating the stress of gender dysphoria and allowing for thorough psychological assessment, have been increasingly discussed, as GnRH receptors are particularly abundant in the hippocampus and the limbic system.

These data show for the first time that GnRH agonist treatment after puberty onset has sex-specific effects on social and affective behavior, stress regulation, and neural activity in mice. More specifically, increased hyperlocomotion, changes in social preference, and increased neuroendocrine stress responses were seen in male mice, while increased hyponeophagia and despair-like behaviour (reactions responsive to antidepressant treatment) were noted in females. In addition, corticosterone response was increased in male but not female mice on exposure to a new situation.

The authors discuss the possibility that increased signs of depression in adolescents with gender dysphoria who are treated with GnRHa may not be readily detectable due to a decrease in depressive symptoms related to the physical changes of the treatment. Although mice and humans differ particularly with regards to hormonal effects in the brain, this study raises further questions about the eventual neuropsychological off-target effects of GnRH agonists as used in adolescents with gender dysphoria.

Obesity and Weight regulation

15. Maternal obesity interrupts the coordination of the unfolded protein response and heat shock response in the postnatal developing hypothalamus of male offspring in mice

Chen N, Zhang Y, Wang M, Lin X, Li J, Li J, Xiao X
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doi:10.1016/j.mce.2021.111218. PMID: 33636254

This study used a high fat and high sucrose diet to generate obese mice. The offspring of these mice showed activation of the unfolding protein response and the heat-shock response in the hypothalamus as early as weaning. This was associated with malformed paraventricular nucleus axonal projections and defective leptin signaling. Intriguingly early inhibition of hypothalamic ER stress in the offspring failed to improve the metabolic outcome but worsened it. A key molecule (called heat shock protein 70 (HSP70)) was altered in the early postnatal developing hypothalamus which might lead to permanent unfolded protein response activation later in life.

Maternal overnutrition and obesity are risk factors for later development of childhood obesity and type 2 diabetes mellitus. The underlying mechanisms involved in the development of childhood obesity following maternal obesity are unknown but might involve changes in the feeding center of the hypothalamus. In the hypothalamus, there are two key neuronal subtypes (anorexigenic and orexigenic) which impinge on the paraventricular nucleus which regulates feeding behavior. Leptin plays a key role in regulating this whole circuit. In mice models of obesity, endoplasmic recticulum (ER) stress is noted in the hypothalamus early in the neonatal period with defective changes in the paraventricular neuronal projections. ER stress is controlled by the unfolding protein response and the heat-shock response which is a cellular protective mechanism activated by different stressors where chaperon proteins prevent cellular stress response by protein folding and re-folding and by activating autophagy.

These observations suggest that developmental exposure to a maternal obesogenic environment may lead to an imbalance in the unfolded protein and heat shock responses in the postnatal developing hypothalamus. This imbalance might lead to defects in obesity programming of the offspring.

16. Structure reveals the activation mechanism of the MC4 receptor to initiate satiation signalling

Israeli H, Degtjarik O, Fierro F, Chunilal V, Gill AK, Roth NJ, Botta J, Prabahar V, Peleg Y, Chan LF, Ben-Zvi D, McCormick PJ, Niv Y, Shalev-Benami M Weizmann Institute of Science, Rehovot, Israel.danny.ben-zvi@mail.huji.ac.il.Science 2021;372(6544): 808–814https://doi.org/10.1126/science.abf7958

Isreali et al. describe the molecular structure of the melanocortin 4 receptor (MC4R) complexed with its effector G protein (Gs alpha) and setmelanotide, a pharmacological agonist of MC4R. MC4R is a known key element in body weight regulation, connecting response to leptin with inhibition of hunger and food intake. Targeted deletion of Mc4r in mice induces weight gain (1), and heterozygous loss- of-function mutations in MC4R are frequently found in obese children as well as adults (2, 3). Thus, targeting MC4R pharmacologically is a major focus in the development of weight loss therapies. Setmelanotide is the first US FDA-approved MC4R agonist for treatment of obesity due to genetically based deficiencies of pro-opiomelanocortin (POMC), proprotein subtilisin/kexin type 1 (PCSK1), and leptin receptor LEPR. The current study contributes important data to our understanding of MC4R signalling. Although a recent publication describes the crystal structure of MC4R bound to an antagonist, and thus provides data about the structure of the inactive receptor , the architecture of active MC4R had not been described so far. Using single-particle cryogenic electron microscopy, the authors were able to analyse conformational changes and to display crucial amino acids mediating activation of the receptor. This information may be helpful in modelling of pathogenic MC4R mutations and to identify those patients with MC4R defects that would potentially benefit from setmelanotide treatment.

17. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials

Cle´ment K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, De Waele K, Farooqi IS, Gonneau-Lejeune J, Gordon G, Kohlsdorf K, Poitou C, Puder L, Swain J, Stewart M, Yuan G,Wabitsch M, Ku¨hnen P; Setmelanotide POMC and LEPR

Phase 3 Trial Investigators Lancet Diabetes Endocrinol. 2020 Dec;8(12):960–970.

https://pubmed.ncbi.nlm.nih.gov/33137293/

This article reports the results of two single-arm, open-label, multicentre, phase 3 trials of the MC4R agonist, setmelanotide, in patients with severe obesity due to pro-opiomelanocortin (POMC) deficiency or leptin receptor (LEPR) deficiency.

Mean % change in bodyweight after˜1 year was -25 ·6 % in patients with POMC deficiency and -12·5% in those with LEPR deficiency.

Melanocortin 4 receptor (MC4R) is a key component of the leptin-melanocortin pathway and plays an important role in the regulation of appetite and body weight. Severe early-onset obesity can be caused by biallelic variants in genes that affect MC4R signalling. These trials were conducted in 10 hospitals in North America (Canada and the USA) and Europe (Belgium, France, Germany, the Netherlands, and UK). The POMC trial (NCT02896192) Included individuals aged 6 + years with obesity caused by POMC deficiency, defined as homozygous or compound heterozygous variants in POMC or PCSK1. The LEPR trial (NCT03287960) included individuals aged 6+ years with obesity caused by LEPR deficiency, defined as homozygous or compound heterozygous variants in LEPR. In both trials, setmelanotide produced significant weight loss and reduction in hunger scores in after w1 year of treatment. Setmelanotide was well tolerated in all individuals, and no new safety concerns were observed. Patients in both groups reported injection site reactions.

Effectiveness was greater in POMC patients than in LEPR patients. The primary outcome, weight loss of 10+ %, was observed in 80% of POMC and 45% of LEPR patients, and this was also reflected in mean % changes in bodyweight (-25·6% vs -12·5%, respectively). Furthermore, all POMC patients reported skin hyperpigmentation compared to 36% of LEPR patients. The authors comment on the potentially different aspects of POMC and LEPR deficiency. They posit that setmelanotide as an MC4R agonist is potentially able to completely restore signalling in POMC obesity. By contrast, in LEPR, setmelanotide might only partially restore signalling, given that apart from POMC neurons LEPR is also expressed on agouti-related peptide-positive neurons.

In the POMC trial, nausea was reported in 5 participants and vomiting in 3 participants. Five serious adverse events (depression, major depression, acute adrenocortical insufficiency, pneumonia, and pleurisy) were reported in 4 participants but none was considered to be related to setmelanotide. No treatment emergent adverse events led to study drug withdrawal or death. In addition, 1 participant reported suicidal ideation at baseline but not at w1 year. Another participant developed suicidal ideation at w1 year. In the LEPR trial, nausea and vomiting were reported in 4 participants that both resolved without sequelae. Four serious adverse events (cholecystitis, suicidal ideation, gastric banding reversal, and road traffic accident leading to death) were reported in 3 participants; none was considered to be related to setmelanotide. One participant discontinued the trial because of grade 1 hypereosinophilia, which was considered to be possibly related to setmelanotide and resolved following discontinuation. In both studied groups, no treatment-related cardiovascular adverse events were reported, and there was no evidence that setmelanotide was associated with changes in blood pressure or heart rate. No cases of suicidal ideation and behaviour were reported at either baseline or at˜1 year.

18. Human MC4R variants affect endocytosis, trafficking and dimerization revealing multiple cellular mechanisms involved in weight regulation

Brouwers B, de Oliveira EM, Marti-Solano M, Monteiro FBF, Laurin SA, Keogh JM, Henning E, Bounds R, Daly CA, Houston S Ayinampudi V, Wasiluk N, Clarke D, Plouffe B, Bouvier M, Babu MM, Farooqi IS, Mokrosin´ski J University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre,Wellcome-MRC Institute of Metabolic Science, Cambridge CB2 0QQ, UK. isf20@cam.ac.uk. J Cell Rep. 2021 Mar 23;34(12):108862. doi: 10.1016/j.celrep.2021.108862.https://pubmed.ncbi.nlm.nih.gov/33761344/

This study demonstrates that MC4R variants found in humans affect receptor endocytosis, trafficking and dimerization and thus reveal multiple cellular mechanisms involved in weight regulation. The findings contribute to our understanding of the complex mechanisms that lie behind the melanocortin 4 receptor's (MC4R) pivotal role in weight regulation. Stimulation of MC4R, a G-protein coupled receptor, is considered to be one of the key factors that reduces appetite and regulates energy homeostasis and body weight. It was previously shown that the binding of pro-opiomelanocortin (POMC) derived melanocyte-stimulating hormone (MSH) to the MC4R leads to increased production of cyclic AMP (cAMP) . We are aware of several G-protein related pathways that can be 'drugged' and meanwhile MC4R is a prime target for anti-obesity drugs . Informed by the recently published 3D structure of the MC4R novel therapeutic methods to target MC4R can be more efficiently investigated and developed. These authors aimed to investigate the cellular functioning and trafficking of MC4R by looking at effects of several naturally occurring MC4R variants when experimentally expressed in HEK293 cells, which do not endogenously express MC4R. 48 rare MC4R variants from previously published large cohorts (minor allele frequency [MAF], <1%) and 2 more common variants (MAF 1-2%) that have previously been associated with obesity protection were studied. To quantitatively assess and monitor the intracellular and extracellular interaction/signalization of different MC4R pathways, such as plasma membrane (PM) expression, b- arrestin recruitment, G-a interaction, MAPK mitogen activated protein kinases)/ERK (extracellular signal-regulated kinases) phosphorylation, homodimerization and early (recycling) or late (degradation) endocytosis, enhanced bystander bioluminescence resonance energy transfer (ebBRET) sensors were applied. The effects of these 50 MC4R variants were functionally categorized as either gain of function (GOF) and/or loss of function (LOF) for each of their respective cellular interaction pathways. Interestingly, some pathways might be able to regulate MC4R activity independent of cAMP production. 19 MC4R variants previously shown to be similar to WT or to have none/or limited effects on cAMP production (O85% of WT cAMP production) are shown here to impair one or more pathways. Based on these results, there are obviously novel ways to target MC4R. As an example, targeting the homodimerization process with an allosteric modulator might be an option similar to several experimental therapies that are currently under investigation for central nervous system disorders. By dissecting mechanisms that regulate MC4R with naturally occurring human variants, this study expands our knowledge of MC4R functionality. We believe that further human as well as transgenic animal and cell model studies are needed to further examine the relevance of these new mechanisms. A recent study has shown the interaction between setmelanotide and several naturally occurring human MC4R variants by using cryogenic electron microscopy and thereby helps to better understand the core functioning of MC4R

19. Loss-of-function mutations in the melanocortin 4 receptor in a UK birth cohort

Wade KH, Lam BYH, Melvin A, Pan W, Corbin LJ, Hughes DA, Rainbow K, Chen JH, Duckett K, Liu X, Mokrosin´ski J, Mo¨rseburg A, Neaves S, Williamson A, Zhang C, Farooqi IS, Yeo GSH, Timpson NJ, O'Rahilly S Medical Research Council (MRC) Integrative Epidemiology Unit (IEU), University of Bristol, Bristol, UK.n.j.timpson@bristol.ac.uk.Nat Med, 2021 Jun;27(6):1088–1096.doi: 10.1038/s41591-021-01349-y.https://pubmed.ncbi.nlm.nih.gov/34045736/

This paper reports the high prevalence of MC4R loss-of-function (LoF) variants in a normal population and their large impact on longitudinally assessed anthropometric traits from birth to young adult life.

This is the first study to examine the prevalence of all non-synonymous MC4R variants in a large sample (5724 persons) of a representative birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC examined over 75% of all children born in the larger Bristol area between 1990-1992, thus these data provide an accurate estimate of true prevalence in a (mainly white) European population. Obesity is one of the most important non-communicable diseases and has finally now been acknowledged by EU commission as a disease in its own right. In contrast to polygenic obesity, monogenic obesity is much rarer. However, the prevalence reported here, 1 in 337, means that LoF MC4R variants can no longer be termed a rare disease. The longitudinal characterization of participants in ALSPAC, provides a unique possibility to compare the development of anthropometric traits between MC4R LoF variant carriers (nZ17) to non-LoF variant carriers (nZ5707). They identify a large and stable influence of LoF MC4R variants on BMI, weight and body fat from 5 years onwards. Interestingly, in contrast to previous studies by the same authors, no evidence for reduced systolic blood pressure or increased adult height was found after adjusting for age, sex and BMI. Rare, non-synonymous wild-type like variant carriers (nZ21) did not differ from wildtype or synonymous, common variant carriers. However, there is no individual analysis for wild-type like carriers offered and LoF was primarily defined as reduced cAMP generation upon MC4R stimulation in a heterologous cell system expressing the MC4R variant, although other MC4R signalling pathways have been described. As for some of the here listed wild-type like variants, debates exist on their possible pathogenetic effects. A more detailed analysis would have been welcomed. In conclusion, LoF MC4R variants conferring a reproducible risk for increased adiposity seem to be more frequent than previously assumed; hence a generous screening approach should be advocated, especially since some variants seem to be rescuable by synthetic MC4R activators, such as Setmelanotide.

20. Obesity treatment effect in Danish children and adolescents carrying melanocortin-4 receptor mutations

Trier C, Hollensted M, Schnurr TM, Lund MAV, Nielsen TRH, Rui G, Andersson EA, Svendstrup M, Bille DS, Gjesing AP, Fonvig CE, Frithioff-Bøjsøe C, Balslev-Harder M, Quan S, Gamborg M, Pedersen O, A¨ngquist L, Holm JC, Hansen T Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. torben.hansen@sund.ku.dk. Int J Obes (Lond). 2021;45(1):66–76. https://doi.org/10.1038/s41366-020-00673-6

This study investigated the influence of MC4R variants on treatment effectiveness in a large cohort undergoing an outpatient treatment program. Carriers of MC4R loss-of-function (LoF) variants showed a lack of improvement in BMI, in contrast to non LoF carriers. As we learn that MC4R LoF variants are more common than expected (their impact gains importance, not only on the natural course of BMI, but also on treatment success. The validated treatment program of the Children's Obesity Clinic (TCOC) in Denmark shows on average a sustained BMI SDS reduction by 0.2-0.3 , which is comparable to other European outpatient programs, such as Obeldicks light . Remarkably, in this large study (nZ1209), of the roughly 80% of patients who could be evaluated after a treatment period of on average 1 year (0.5–4.0 years), the 2.5% carriers of MC4R LoF variants (nZ24) did not reduce their BMI-SDS – in contrast to non LoF carriers (nZ982). Other treatment approaches, including Obeldicks, had actually found that wildtype MC4R variant carriers show the same BMI SDS reduction as LoF variant carriers, but are unable to uphold treatment success. One possible explanation for these divergent observations may be a more extensive treatment approach in former studies. One challenge of this study was the definition LoF in MC4R variants. While some variants show consistently reduced ability to generate cAMP upon MC4R stimulation in a heterologous cell system expressing the MC4R variant, for others, results vary both on cAMP generation and other measures such as activation of extracellular signal-regulated kinase (ERK) 1/2 or receptor cell surface expression. Hence variants considered here to be functionally relevant have been viewed in other studies as wild-type like (1). Nonetheless, this study shows that knowledge on the genetic background can give both treatment centres and families more realistic expectation about treatment outcomes and may also pave the way for patient-tailored treatment approaches.

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Obesity-Associated *GNAS* Mutations and the Melanocortin Pathway

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• DOI: 10.1056/NEJMoa2103329

Background: *GNAS* encodes the Gαs (stimulatory G-protein alpha subunit) protein, which mediates G protein-coupled receptor (GPCR) signaling. *GNAS* mutations cause developmental delay, short stature, and skeletal abnormalities in a syndrome called Albright's hereditary osteodystrophy. Because of imprinting, mutations on the maternal allele also cause obesity and hormone resistance (pseudohypoparathyroidism).

Methods: We performed exome sequencing and targeted resequencing in 2548 children who presented with severe obesity, and we unexpectedly identified 22 *GNAS* mutation carriers. We investigated whether the effect of *GNAS* mutations on melanocortin 4 receptor (MC4R) signaling explains the obesity and whether the variable clinical spectrum in patients might be explained by the results of molecular assays.

Results: Almost all *GNAS* mutations impaired MC4R signaling. A total of 6 of 11 patients who were 12 to 18 years of age had reduced growth. In these patients, mutations disrupted growth hormone-releasing hormone receptor signaling, but growth was unaffected in carriers of mutations that did not affect this signaling pathway (mean standard-deviation score for height, -0.90 vs. 0.75, respectively; P = 0.02). Only 1 of 10 patients who reached final height before or during the study had short stature. *GNAS* mutations that impaired thyrotropin receptor signaling were associated with developmental delay and with higher thyrotropin levels (mean [±SD], 8.4±4.7 mIU per liter) than those in 340 severely obese children who did not have *GNAS* mutations (3.9±2.6 mIU per liter; P = 0.004).

Conclusions: Because pathogenic mutations may manifest with obesity alone, screening of children with severe obesity for *GNAS* deficiency may allow early diagnosis, improving clinical outcomes, and melanocortin agonists may aid in weight loss. *GNAS* mutations that are identified by means of unbiased genetic testing differentially affect GPCR signaling pathways that contribute to clinical heterogeneity. Monogenic diseases are clinically more variable than their classic descriptions suggest. (Funded by Wellcome and others.)

Adrenals

21. GWAS for autoimmune Addison's disease identifies multiple risk loci and highlights AIRE in disease susceptibility

Eriksson D, Røyrvik EC, Aranda-Guille´n M, Berger AH, Landegren N, Artaza H, Hallgren A˚, Grytaas MA, Stro¨m S, Bratland E, Botusan IR, Oftedal BE, Breivik L, Vaudel M, Helgeland Ø, Falorni A, Jørgensen AP, Hulting AL, Svartberg J, Ekwall O, Fougner KJ,Wahlberg J, Nedrebø BG, Dahlqvist P; Norwegian Addison Registry Study Group; Swedish Addison Registry Study Group, Knappskog PM, Wolff ASB, Bensing S, Johansson S, Ka¨mpe O, Husebye ES Nat Commun. 2021 Feb 11; 12(1):959. https://pubmed.ncbi.nlm.nih.gov/33574239/

The authors report a genome-wide association study (GWAS) of autoimmune Addison's disease (AAD) in 1223 cases (defined as autoimmune adrenal failure plus positive serum autoantibodies against 21-hydroxylase) and 4097 healthy controls. Patients with APS-1 were identified and excluded. They identified 9 genome-wide significant genomic loci and explained 35–41% of the additive genetic heritability of AAD. Autoimmune Addison's disease (AAD) is the most common cause of primary adrenal failure in the Western world. It requires lifelong steroid hormone replacement therapy and is fatal if untreated. Autoimmunity is often apparent from the presence of other associated autoimmune diseases, and is confirmed by the presence of autoantibodies against the adrenal enzyme, 21-hydroxylase. Besides the major risk locus at the HLA region, they identified risk variants in or near: PTPN22, CTLA4, LPP, BACH2, SH2B3, SIGLEC5, UBASH3A, and AIRE. Of these, in 5 loci an association has previously been described (PTPN22, CTLA4, HLA, AIRE, and BACH2), while 4 loci were novel (LPP, SH2B3, SIGLEC5, and UBASH3A). Of note, they found AAD associations with two LD-independent protein-coding variants in AIRE: one novel (rs74203920) and one previously reported (rs2075876) . These associations underline the importance of AIRE expression to maintain immune tolerance. The authors offer the interesting example of Down syndrome, where AIRE gene duplication potentially leads to altered expression in the thymus (affecting homeostasis and function of thymic epithelial cells that affect thymic selection processes), impaired central tolerance and increased risks of autoimmune diseases. This study also identified risk loci in genes involved in antigen presentation and recognition, and hence in thymocyte maturation. The authors hypothesize that AAD with positive 21-hydroxylase antibodies has a rather homogenous disease etiology with relatively low polygenicity compared to other diseases, explaining at least in part the high heritability estimates. The study highlights the importance of the complex network of antigen presentation and immunomodulation that underlie autoimmune disease development. These findings underscore the importance of future studies in identifying and developing preventive treatment strategies.

Oncology

22. Health outcomes in offspring born to survivors of childhood cancers following assisted reproductive technologies.

Sommerha¨user G, Borgmann-Staudt A, Astrahantseff K, Baust K, Calaminus G, Dittrich R, Ferna´ndez-Gonza´lez MJ, Ho¨lling H, Ko¨nig CJ, Schilling R, Schuster T, Lotz L, Balcerek M.anja.borgmann@charite.de J Cancer Surviv. 2021; 15: 259–272. https://pubmed.ncbi.nlm.nih.gov/32844376/

Long-term treatment effects are possible reasons for reduced fertility and adverse pregnancy outcomes in childhood cancer survivors (CCS) . This observational study reports perinatal and health outcomes of offspring born to CCS using assisted reproductive technologies (ART). CCS were almost 2-fold more likely to use ART compared to the general population (4.6% vs. 2.6%). Among offspring born to CCS, multiple sibling births and low birth weight were significantly more common following ART than after spontaneous conception. The high prevalence of multiple sibling births after ART in CCS was similar to the 34% reported in the general population. ART did not increase the prevalence of childhood cancer or congenital malformations in offspring born to CCS. A mildly increased prevalence of moderate preterm births (32 to 37 gestational weeks) in the offspring of CCS was detected. The differences in perinatal outcomes were completely explained by differences in multiple sibling birth and other known confounders. Patients included in this study were treated between 1980 and 1999, before the implementation of the guidelines for fertility preservation. Only few patients cryopreserved oocytes/sperm prior to cancer treatment. Most CCS (58.7%) were treated in the 1980s, with higher doses of radiation and alkylating agents than used now. These findings appear particularly reassuring for current patients treated with less toxic protocols. The results are also reassuring because only a mild increase of moderate preterm birth was demonstrated in survivor offspring and most medical consequences occur in severely preterm infants. In this study, the prevalence of childhood cancer and congenital malformations, whether conceived by ART or spontaneous conception, was not higher in CCS offspring than in the general population. A meta-analysis published in 2013, had reported a slightly elevated overall cancer risk in children born after ART. Fertility impairment and potential epigenetic defects in the gametes, rather than the ART procedure itself, were supposed to be the main predisposing factors (2). The study has some limitations. The recruitment based on previous surveys identifying CCS with biological children (required by the German Society for Pediatric Oncology and Hematology to reduce the study burden for survivors) potentially caused a selection bias. The questionnaire-based setting reduces data accuracy by recall bias. Moreover, factors as maternal age, body mass index, infections or other maternal diseases, which clearly influence pregnancy outcome and perinatal events, were not analyzed.

Diabetes

23. Analysis of overlapping genetic association in type 1 and type 2 diabetes

Jamie RJ Inshaw, Carlo Sidore, Francesco Cucca, M Irina Stefana, Daniel JM Crouch, Mark I McCarthy, Anubha Mahajan, John A Todd Diabetologia. 2021 Jun;64(6):1342–1347. doi: 10.1007/s00125-021-05428-0. https://pubmed.ncbi.nlm.nih.gov/33830302/

By studying data from very large-scale genome-wide association studies (GWAS) in European ancestry individuals, the authors compared genetic signals that confer risk of type 1 (T1DM) and type 2 diabetes (T2DM). Only 5 signals were associated with both T1DM and T2DM (‘colocalised signals’). At 4 of these signals, variants that increased risk of T1DM decreased the risk of T2DM: (1) chromosome 16q23.1, near the CTRB1/BCAR1 genes; (2) 11p15.5, near Insulin and IGF2; (3) 4p16.3, near TMEM129 and (4) 1p31.3, near PGM1. Only one signal showed directionally concordant effects, increasing the risks of both T1DM and T2DM: 9p24.2, near GLIS3. It is remarkable that, despite the knowledge of w60 genomic regions associated with T1DM and O200 associated with T2DM, there is so little overlap in the genetic risk factors for these two forms of diabetes. Some have hoped that established treatments for T2DM (e.g. metformin) might also have obvious benefits for patients with T1DM. It was even hypothesised that both forms of diabetes shared a common genetic make-up but were exposed to different in utero and postnatal environments. With that in mind, it seems even more striking that, of the handful of cases of genetic overlap identified, most of the risk variants have directionally opposing effects on T1DM and T2DM. These findings suggest that biological studies of one condition could still shed some insights onto the other. However and unfortunately, the findings cast doubt on the effectiveness of developing common treatments that would benefit both diseases.

ΓΥΝΑΙΚΕΙΑ ΑΝΑΠΑΡΑΓΩΓΗ

ΝΕΚΤΑΡΙΑ ΞΗΤΑ

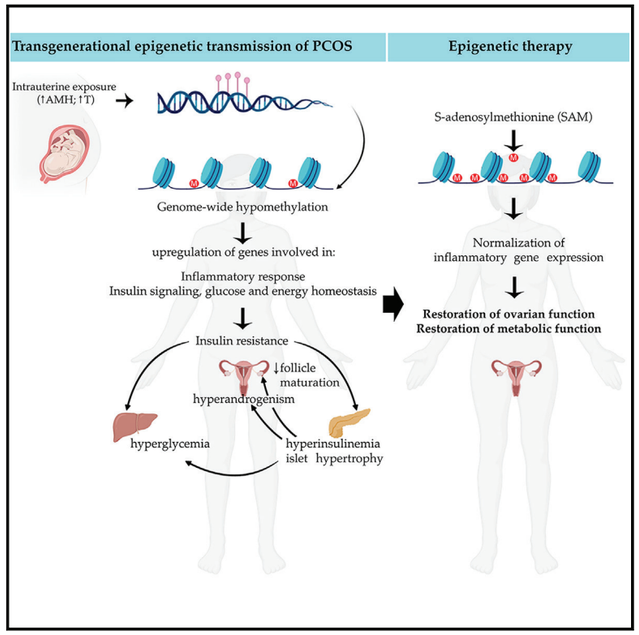
ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ, ΔΙΔΑΚΤΩΡ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΙΩΑΝΝΙΝΩΝ

Cell Metabolism

Article

Polycystic ovary syndrome is transmitted via a transgenerational epigenetic process

Graphical abstract



Highlights

- Transmission of PCOS traits in mice occurs via an altered DNA methylation landscape
- Metabolic- and inflammatory-related pathways are dysregulated in models of PCOS
- Common hypomethylation signatures occur in a mouse model of PCOS and in humans
- Identification of a novel epigenetic-based therapeutic strategy for PCOS

Authors

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In Brief

Polycystic ovary syndrome (PCOS) is the most common female reproductive and metabolic disorder, but its pathogenesis is still unknown. Here, Mimouni, Paiva et al. report that in mice, transmission of PCOS-like traits to multiple generations occurs via an altered landscape of DNA methylation and transcriptome expression. These authors also identify methylome markers in women with PCOS as possible diagnostic landmarks and candidates for epigenetic-based therapies.

Mimouni et al., 2021, Cell Metabolism *33*, 513–530
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Clinical Research Article

Clinical Research Article

Women With Polycystic Ovary Syndrome Have an Increased Risk of Major Cardiovascular Events: a Population Study

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Abbreviations: BMI, body mass index; BP, blood pressure; CPHM, Cox proportional hazard model; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; HES, Hospital Episode Statistics; HR, hazard ratio; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems classification; IMD, Index of Multiple Deprivation; IQR, interquartile range; ONS, Office for National Statistics; OPCS-4, OPCS Classification of Interventions and Procedures version 4; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

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Abstract

Context: The effects of polycystic ovary syndrome (PCOS) on cardiovascular morbidity and mortality are unclear.

Objective: This work aims to establish the relative risk of myocardial infarction (MI), stroke, angina, revascularization, and cardiovascular mortality for women with PCOS.

Methods: Data were extracted from the Clinical Practice Research Datalink Aurum database. Patients with PCOS were matched to controls (1:1) by age, body mass index (BMI) category, and primary care practice. The primary outcome was the time to major adverse cardiovascular event (MACE); a composite end point incorporating MI, stroke, angina, revascularization and cardiovascular mortality. Secondary outcomes were the individual MACE end points.

Results: Of 219 034 individuals with a diagnosis of PCOS, 174 660 (79.7%) met the eligibility criteria and were matched. Crude rates of the composite end point, MI, stroke, angina, revascularization, and cardiovascular mortality were respectively 82.7, 22.7, 27.4, 32.8, 10.5, and 6.97 per 100 000 patient-years for cases, and 64.3, 15.9, 25.7, 19.8, 7.13, and 7.75 per 100 000 patient-years for controls. In adjusted Cox proportional hazard models (CPHMs), the hazard ratios (HRs) were 1.26 (95% CI, 1.13-1.41), 1.38 (95% CI, 1.11-1.72), 1.60 (95% CI, 1.32-1.94), and 1.50 (95% CI, 1.08-2.07) for the composite outcome, MI, angina, and revascularization, respectively. In a time-dependent CPHM, weight gain

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(HR 1.01; 1.00-1.01), prior type 2 diabetes mellitus (T2DM) (HR 2.40; 1.76-3.30), and social deprivation (HR 1.53; 1.11-2.11) increased risk of progression to the composite end point. **Conclusion:** The risk of incident MI, angina, and revascularization is increased in young women with PCOS. Weight and T2DM are potentially modifiable risk factors amenable to intervention.

Key Words: polycystic ovary syndrome, cardiovascular diseases, mortality, angina, myocardial infarction, stroke

Polycystic ovary syndrome (PCOS), the most common endocrine condition affecting young women, is characterized by hyperandrogenism, menstrual disturbance, and subfertility. In addition to its well-recognized reproductive sequelae, PCOS is now established as a metabolic disorder underpinned by defects in insulin secretion and action. We and others have confirmed that these lead to an increased risk of type 2 diabetes mellitus (T2DM) (1).

In addition to insulin resistance, women with PCOS display a range of metabolic and vascular risk factors, including central obesity (2), hypertension (3), and dyslipidemia (4), which are commonly present at a young age. Studies have shown that surrogate markers of cardiovascular risk are increased in patients with PCOS, including carotid intima media thickness (5), endothelial dysfunction (6), coronary artery calcification (7), and arterial stiffness (8). However, whether these disturbances lead to an increased risk of vascular events and mortality is still unknown. A substudy of the Women's Ischemia Evaluation Study demonstrated that women with PCOS had a higher prevalence of multivessel cardiovascular disease (CVD), and significantly lower cardiovascular event-free survival, than controls (9), results that were later retracted because of a failure to replicate these findings (10) but that have been included in previous meta-analyses (11, 12). Other population-based studies have been limited by comparatively small sample sizes and/or a failure to adjust for important confounders such as obesity (13-20). We (1) and others (21, 22) have previously failed to show an increased risk of cardiovascular events in women with PCOS, although these studies were likely underpowered because the crude incidence of cardiovascular and cerebrovascular events in this young female population is low. Longer-term population-based studies with a large sample size are therefore needed to clarify these risks further.

To address these uncertainties, we reexplored vascular outcomes in women with PCOS in a large primary care research database in the United Kingdom, with a view to exploiting the greater power offered by recent extension of this data set to provide coverage of the population on a much larger scale.

Materials and Methods

This was a retrospective cohort study using primary care data from the Clinical Practice Research Datalink (CPRD) Aurum database, a longitudinal, anonymized research database derived from 883 primary care practices in England. CPRD Aurum contains records for more than 28 million patients and is representative of the English population in terms of age, sex, and deprivation (23). Approximately 70% of practices participate in a linkage scheme, by which their patient records are linked to other data sources, including the Hospital Episode Statistics (HES) data set, which provides data on all inpatient and outpatient contacts occurring within National Health Service hospitals in the United Kingdom, and the Office for National Statistics (ONS) mortality data set. HES and ONS data are available for patients participating in the linkage scheme outside the period of primary care registration.

Diagnostic information in CPRD Aurum is recorded using a combination of SNOMED CT (UK Edition) and Read code classification, a UK primary-care practice standard. Diagnoses in HES and ONS data are recorded using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems classification (ICD-10). Surgical procedures in HES are recorded using the OPCS Classification of Interventions and Procedures version 4 (OPCS-4) classification.

Patient Selection and Matching of Controls

The study was undertaken using data from CPRD Aurum and linked HES and ONS mortality data sets. This study included patients identified by CPRD as being of an acceptable research quality (23), who were identified by diagnosis codes both from CPRD Aurum and HES, and who were eligible for linkage to the secondary care data. Patients with a diagnosis of PCOS, recorded in the primary-care data set using SNOMED codes and from HES by ICD-10 code E0.28.2, from 1998 to 2017 were selected. The earliest diagnosis date was selected as the index date and only women aged 18 years or older were included.

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Clinical Research Article

Clinical Research Article

Exenatide, Dapagliflozin, or Phentermine/Topiramate Differentially Affect Metabolic Profiles in Polycystic Ovary Syndrome

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Abbreviations: AE, adverse event; AGR, android-to-gynoid fat ratio; BMI, body mass index; BP, blood pressure; BW, body weight; CHOL, cholesterol; DAPA, dapagliflozin; DBP, diastolic blood pressure; DHEA-S, dehydroepiandrosterone sulfate; DXA, dual-energy x-ray absorptiometry; EQW, exenatide; FAI, free androgen index; GLP1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; IGI, insulinogenic index; IS-SI, insulin secretion–sensitivity index; LDL-C, low-density lipoprotein cholesterol; MBG, mean blood glucose; MET, extended-release metformin; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PG, plasma glucose; PHEN/TPM, phentermine topiramate extended release; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitors; SHBG, sex hormone–binding globulin; SI_{OGTT}, Matsuda's insulin sensitivity index; T2DM, type 2 diabetes mellitus; TBF, total body fat; TFM, total fat mass; TLR, trunk-to-leg fat ratio; TRG, triglycerides; TSH, thyrotropin; TT, total testosterone; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; XR, extended release.

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Abstract

Context: Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors reduce weight and improve insulin sensitivity via different mechanisms.
Objective: The efficacy of once-weekly exenatide (EQW) and dapagliflozin (DAPA) alone and coadministered (EQW/DAPA), DAPA/extended-release (ER) metformin (DAPA/MET), and phentermine topiramate extended release (PHEN/TPM) on metabolic parameters, body composition, and sex hormones were examined in obese women with PCOS.
Methods: Nondiabetic women (n = 119; aged 18-45 years) with a body mass index (BMI) greater than 30 and less than 45 and polycystic ovary syndrome (National Institutes of Health criteria) were randomly assigned in a single-blinded fashion to EQW (2 mg weekly); DAPA (10 mg daily), EQW/DAPA (2 mg weekly/10 mg daily), DAPA (10 mg)/MET (2000 mg XR daily), or PHEN (7.5 mg)/TPM (46 mg ER daily) treatment for 24 weeks. Study visits at baseline and 24 weeks included weight, blood pressure (BP), waist (WC) measures, and body composition evaluated by dual-energy x-ray absorptiometry (DXA).

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Oral glucose tolerance tests were conducted to assess glycemia and mean blood glucose (MBG), and compute insulin sensitivity (SI) and secretion (IS) measures. Sex steroids, free androgen index (FAI), and lipid profiles were measured in the fasting sample.
Results: EQW/DAPA and PHEN/TPM resulted in the most loss of weight and total body fat by DXA, and WC. Despite equivalent reductions in BMI and WC with PHEN/TPM, only EQW/DAPA and EQW resulted in significant improvements in MBG, SI, and IS. Reductions in fasting glucose, testosterone, FAI, and BP were seen with all drugs.
Conclusion: Dual therapy with EQW/DAPA was superior to either alone, DAPA/MET and PHEN/TPM in terms of clinical and metabolic benefits in this patient population.

Key Words: SGLT2 inhibitor, GLP1 agonist, obesity, weight loss, insulin resistance, PCOS

Polycystic ovary syndrome (PCOS) is one of the most common gynecological disorders, and it arises from multifactorial contributions including genetic, epigenetic, and environmental factors (1-3). The growing body of evidence linking PCOS to an inherited resistance to insulin action, aggravated by lifestyle problems such as obesity, poor diet, and physical inactivity has led to trials of diabetic therapies in patients with PCOS (4-6). Currently, a number of antidiabetes medications have been approved that facilitate weight loss and improve the underlying insulin resistance. Glucagon-like peptide-1 (GLP-1) agonists (GLP-1RAs) comprise a novel class of antidiabetic medications with multiple beneficial metabolic effects, including glucose-dependent stimulation of insulin secretion (IS), suppression of postprandial glucagon, inhibition of glucose production, enhanced glucose disposal, and slowing of gastric emptying in patients with type 2 diabetes mellitus (T2DM) (7). In addition to improving glucose tolerance, this class of drugs enhances satiety and weight loss. There are a limited number of studies that have evaluated the effect of GLP-1RAs in individuals without diabetes. In a 160-week study, 2254 prediabetic participants were randomly assigned to receive the GLP-1RA liraglutide vs placebo; liraglutide induced greater weight loss than placebo at week 160 (–6% vs –1.9%) in individuals with prediabetes (8). Clinical trials of GLP-1RA therapy in the treatment of excess body weight (BW) in women with PCOS showed that both liraglutide and exenatide were effective in weight reduction either as monotherapy or in combination with metformin (MET) (9, 10). Elkind-Hirsch et al further demonstrated that exenatide treatment significantly improved first-phase insulin responses to oral glucose administration in obese PCOS women (10). However, while GLP-1RAs have been associated with moderate weight loss, their use is limited by the need for administration by injection and gastrointestinal side effects.

Another newly approved class of glucose-lowering medications, sodium–glucose cotransporter 2 inhibitors (SGLT2i) afford modest weight loss. These agents can be administered orally and increase glycosuria, which also produces an osmotic diuresis that, in part, contributes to blood pressure (BP) reduction and calorie loss leading to weight loss. These drugs have been shown to be effective when used as monotherapy and as add-on therapy to other diabetes medications (12). Studies of these agents in the prediabetic population have been quite limited. A 12-week, randomized, controlled trial was performed with dapagliflozin (DAPA) at a dose of 10 mg daily in 24 individuals with metabolic syndrome that demonstrated significant decreases in BW, body mass index (BMI), waist circumference (WC), fasting glucose, and uric acid (13). In another study of obese adults without diabetes, DAPA plus once-weekly exenatide (EQW) dual therapy produced sustained reductions in BW, prediabetes, and systolic blood pressure (SBP) over 52 weeks (14). Studies of these drugs in PCOS patients are also limited. In a recent trial there was improvement in anthropometric parameters and body composition in overweight and obese women with PCOS after 12 weeks of treatment with the SGLT2i empagliflozin compared to MET, although no changes were seen in hormonal or metabolic parameters (15). An advantage of the SGLT2i over existing treatments is the weight loss seen with SGLT2i is similar to that seen with GLP-1RAs, and may be more acceptable because they are oral agents.

In the present study we measured the effects of 24 weeks of treatment with EQW once-weekly and DAPA (dual therapy or each alone), combination DAPA/MET extended release (XR) (DAPA/MET), and phentermine topiramate XR (PHEN/TPM) on metabolic profiles and body composition in obese, nondiabetic women with PCOS. The potential therapeutic effects of EQW/DAPA, EQW, DAPA, and DAPA/MET have never been evaluated in the subpopulation of obese nondiabetic women with PCOS. This is the first report comparing the efficacy of a GLP-1RA and SGLT2i, in combination and alone, SGLT2i plus MET vs a comparator weight loss medication in this patient population.

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Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke

Tiantian Zhu, Jinrui Cui, and Mark O. Goodarzi

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Polycystic ovary syndrome (PCOS) has been associated with diabetes and cardiovascular disease; however, whether the relationship is causal is uncertain. We conducted a two-sample Mendelian randomization study to investigate the associations of PCOS with type 2 diabetes, coronary heart disease (CHD), and stroke. Association between PCOS and diabetes risk was examined in European and Asian cohorts, both sex specific and sex combined. Causal effects of PCOS on risks of CHD and stroke were evaluated in European cohorts. Stroke was analyzed as any stroke as well as four subtypes of stroke (ischemic, large artery, cardioembolic, small vessel). We found no association of genetically predicted PCOS with risk of diabetes, CHD, or stroke. This suggests that PCOS in and of itself does not increase the risk of these outcomes. Other features of PCOS (obesity, elevated testosterone, low sex hormone binding globulin) may explain the association between PCOS and cardiometabolic diseases. In light of these results, efforts to prevent cardiometabolic complications in PCOS should focus on women with high-risk features rather than all women with PCOS.

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age. PCOS has been associated with significant adverse health conditions including obesity, diabetes, dyslipidemia, cardiovascular disease (CVD), sleep apnea, depression, and nonalcoholic fatty liver disease. A key question is whether these associations represent causal relationships. Such knowledge is critical to efforts to prevent morbidity in women with PCOS. The fact that PCOS is a syndrome with multiple features complicates efforts to establish causality between PCOS and adverse outcomes because individual features may contribute differentially to outcomes.

Observational epidemiologic studies do not establish causality because the relationship between two conditions may be driven by confounding factors or reverse causality. To avoid these pitfalls, investigators have used genetics to address questions of causality. In Mendelian randomization (MR), a risk factor or exposure is represented by genetic variants for that factor, which are then used in instrument variable analysis to yield unconfounded evidence to support causality of the exposure with an outcome of interest. Completion of genome-wide association studies (GWAS) of PCOS in Asian and European origin cohorts (1–5) has made MR possible for analysis of the relationship between PCOS and various traits and diseases. Recent MR studies suggested that obesity, age of menopause, insulin resistance/hyperinsulinemia, sex hormone binding globulin (SHBG) levels, and depression may be causal risk factors for PCOS (2,3).

A major focus in PCOS concerns its relationship with cardiometabolic diseases. Experts in the field generally agree that PCOS is a risk factor for type 2 diabetes, largely based on a substantial literature documenting that insulin resistance is frequent in women with PCOS. While obese women with PCOS consistently have greater insulin resistance than BMI-matched control subjects, some studies but not others find that this is also the case for nonobese PCOS (6,7). A meta-analysis of euglycemic-hyperinsulinemic clamp studies concluded that women with PCOS are nearly 30% less insulin sensitive than control subjects, independent of BMI but exacerbated by higher BMI and lower SHBG (8). Several observational studies have found higher rates of diabetes in women with PCOS versus unaffected control subjects. A meta-analysis of these studies found

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increased prevalent impaired glucose tolerance (odds ratio [OR] 3.26, 95% CI 2.17–4.90) and diabetes (OR 2.87, 95% CI 1.44–5.72) in women with PCOS (9). Whether PCOS also predisposes to coronary heart disease (CHD) and stroke is less certain, given the lack of large long-term studies following women with PCOS into older age, during which CVD events mainly occur. Meta-analyses of available case-control and cohort studies suggest that PCOS may increase the risk of CHD (OR 1.44, 95% CI 1.13–1.84) and stroke (OR 1.36, 95% CI 1.09–1.70), though risk estimates decrease with adjustment for BMI (10,11). Given the high clinical relevance of these questions, we carried out two-sample MR analyses to determine whether genetically increased risk of PCOS leads to an increased risk of type 2 diabetes, CHD, or stroke.

RESEARCH DESIGN AND METHODS

Instrumental Variables (Genetic Variants Associated With PCOS)

In a GWAS meta-analysis of PCOS consisting of 10,074 PCOS case and 103,164 control subjects of European ancestry, 14 independent single nucleotide polymorphisms (SNPs) were reported to be associated with PCOS risk at the genome-wide significance level ($P < 5 \times 10^{-8}$) (2). Of the 14 SNPs, all were included to construct the genetic instrument for PCOS except SNP rs853854, because it is a palindromic SNP (A/T) with an effect allele frequency close to 50% (12). We included another independent SNP (rs2349415), which was initially identified in Chinese PCOS GWAS (4) and was significantly associated with PCOS in the European PCOS meta-analysis (2). Therefore, 14 SNPs in total were included in our instrument for PCOS in Europeans (Table 1).

SNPs associated with PCOS in Asians were selected from two PCOS GWAS conducted in cohorts of Han Chinese ancestry (1,4). The GWAS by Chen et al. (1) consisted of 4,082 PCOS case and 6,687 control subjects and identified three independent SNPs strongly associated with PCOS. The GWAS of Shi et al. (4) including 10,480 case and 10,579 control subjects discovered 10 novel PCOS–associated SNPs. In total, 13 independent SNPs were used as instrumental variables for PCOS in Asians (Table 2).

We applied the *F* statistic to measure the strength of the instrument variables, with values >10 reflecting strong instruments (13). The 14-SNP instrument for PCOS in Europeans had an *F* statistic of 39.5, and the 13-SNP instrument for PCOS in Asians had an *F* statistic of 66.6.

Outcome Data Sources (GWAS of Diabetes, CHD, and Stroke)

Summary-level data, both sex combined and sex stratified, for type 2 diabetes GWAS in Europeans were obtained from the DIAbetes Meta-ANalysis of Trans-Ethnic association studies (DIAMANTE) consortium, which included 74,124 case and 824,006 control subjects of European ancestry (14). We obtained GWAS summary data on type 2 diabetes in Asians from the Asian Genetic Epidemiology Network (AGEN) consortium with 77,418 case and 356,122 control subjects of East Asian ancestry (15).

Genetic association data on CHD were acquired from the CHD GWAS meta-analysis of the UK Biobank (UKBB) with the Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) consortium, which encompassed 34,541 CHD case and 261,984 control subjects from UKBB and 88,192 case and 162,544 control subjects from CARDIoGRAMplusC4D, of whom ~90% were of European origin (16).

Summary statistics on stroke and stroke subtypes used in the current study were from the MEGASTROKE consortium including 40,585 case and 406,111 control subjects of European ancestry (17). We evaluated five sets of stroke subtypes, including any stroke, any ischemic stroke, large artery stroke, cardioembolic stroke, and small vessel stroke. Details of the studies included in our analysis are shown in Table 3.

Statistical Analysis

Associations of PCOS with risks of CHD and stroke were examined in European cohorts only. Association of PCOS with diabetes risk was evaluated in both European and Asian cohorts, both sex stratified and sex combined. MR analyses in Europeans were conducted with the 14-SNP instrument for PCOS in Europeans, while MR analyses in Asians were carried out with the 13-SNP instrument for PCOS in Asians.

Primary MR analyses were conducted with the inverse variance weighted (IVW) method with random effects (18). For each SNP, the ratio estimate of the causal effect of an exposure (herein, PCOS) on an outcome is the ratio of the effect of the SNP on the outcome over the effect of the SNP on the exposure. In IVW, the overall estimate is generated via IVW meta-analysis of the ratio estimates of all variants in the set of instrument variables. Given that the IVW method may be affected by directional pleiotropy (where a genetic variant affects the outcome through a pathway other than the exposure), we performed sensitivity analyses using MR-Egger (19) and weighted median methods (20) to check for robustness of the estimates from the IVW method. MR-Egger can detect and correct for the bias due to directional pleiotropy because it allows a nonzero intercept and provides a consistent estimate of the causal effect under the InSIDE (Instrument Strength Independent of Direct Effect) assumption (the genetic associations with the exposure are independent of the direct effects of the genetic variants on the outcome) (19). The weighted median approach can provide a consistent causal effect estimate as long as at least 50% of the information contributing to the analysis comes from valid instrumental variables (20). Furthermore, we tested the heterogeneity of the causal estimates using Cochran *Q* test

Trends in Endocrinology & Metabolism

CellPress REVIEWS

Review

Anti-Müllerian Hormone in PCOS: A Review Informing International Guidelines

Helena Teede,[1,*] Marie Misso,[1] Eliza C. Tassone,[1] Didier Dewailly,[2] Ernest Hy Ng,[3] Ricardo Azziz,[4] Robert J. Norman,[5] Marianne Andersen,[6] Stephen Franks,[7] Kathleen Hoeger,[8] Samantha Hutchison,[9] Sharon Oberfield,[10] Duru Shah,[11] Femke Hohmann,[12] Sasha Ottey,[13] Preeti Dabadghao,[14] and Joop S.E. Laven[15]

Polycystic ovary syndrome (PCOS) affects 8–13% of women. The Rotterdam diagnostic criteria include polycystic ovarian morphology (PCOM) on ultrasound, but given recognized challenges, serum anti-Müllerian hormone (AMH) is proposed as an alternative. To inform international PCOS guidelines, a systematic review was completed. Key identified gaps include large international studies in well-defined populations across the lifespan, clustering of AMH with PCOS features, relationships to long-term health outcomes, and improved quality, assay standardization, and sample handling, all needed to determine cut offs. Here we identify research priorities to address these gaps and enhance AMH utility in PCOS. Once issues are addressed, AMH levels could replace more costly and less accessible ultrasound in PCOS diagnosis.

Highlights

This systematic review investigates whether serum anti-Müllerian hormone (AMH) is an effective alternative for the detection of PCOM and/or diagnosis of PCOS.

There is significant heterogeneity in studies conducted in adolescents and adults, with a number of limitations identified.

Studies have lacked well-defined PCOS and control populations that varied across the lifespan, used inconsistent methods for defining cut offs, variably defined PCOM in comparator studies, and had methodological assay and sample handling challenges.

Challenges in Ultrasound PCOM Detection

PCOS is the most common endocrine disorder affecting women of reproductive age, with a reported prevalence of 8–13% [1–5]. The condition is heterogeneous [6] and women may present with reproductive, endocrine, metabolic, and psychosocial symptoms, which vary across their lifespan [7]. The Rotterdam criteria require that women fulfil two of the following three criteria to be diagnosed with PCOS: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound [8–10], with the exclusion of other relevant disorders.

Within the diagnostic criteria, PCOM on ultrasonography is defined by either total ovarian volume or follicle number per ovary (FNPO). Original cut offs for PCOM were based on limited evidence [11] and were recently revised in the new international PCOS guidelines, while also highlighting the controversy and challenges with this criterion [1–4]. Determining FNPO is operator and equipment dependent, limiting accuracy and reproducibility. Equipment advances increase sensitivity and in turn FNPO counts [1–4]. Ultrasound involves expensive equipment and trained personnel, leading to increasing costs and impacting accessibility. The ultrasound approach (transabdominal or transvaginal) impacts accuracy, and in some women transvaginal ultrasound is unacceptable or may be perceived as invasive. Multifollicular appearance on ultrasound overlaps with PCOM diagnostic cut offs especially in adolescents, while in older women with PCOS cut-off values might be considerably lower [11]. Recent international PCOS guidelines now recommend against using ultrasound in PCOS diagnosis within 8 years of menarche and call for greater accuracy in PCOS diagnostic criteria worldwide [1–4].

AMH as a Potential Alternative to Ultrasound PCOM Detection

AMH is a polypeptide of the *transforming growth factor beta* (TGFβ) family, solely secreted by granulosa cells of the pre-antral and small antral ovarian follicles [12]. AMH has been shown in

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MDPI

Article

SARS-CoV-2 Viral Entry Proteins in Hyperandrogenemic Female Mice: Implications for Women with PCOS and COVID-19

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Abstract: SARS-CoV-2, the causative agent of COVID-19, infects host cells using the angiotensin I converting enzyme 2 (ACE2) as its receptor after priming by host proteases, including TMPRSS2. COVID-19 affects multiple organ systems, and male patients suffer increased severity and mortality. Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in reproductive-age women and is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. PCOS is associated with obesity and cardiometabolic comorbidities, both being risk factors associated with severe COVID-19 pathology. We hypothesize that elevated androgens in PCOS regulate SARS-CoV-2 entry proteins in multiple tissues increasing the risk for this population. Female mice were treated with dihydrotestosterone (DHT) for 90 days. Body composition was measured by EchoMRI. Fasting glucose was determined by an enzymatic method. mRNA and protein levels of ACE2, Tmprss2, Cathepsin L, Furin, Tmprss4, and Adam17 were quantified by RT-qPCR, Western-blot, or ELISA in tissues, serum, and urine. DHT treatment increased body weight, fat and lean mass, and fasting glucose. Ace2 mRNA was upregulated in the lung, cecum, heart, and kidney, while downregulated in the brain by DHT. ACE2 protein was upregulated by DHT in the small intestine, heart, and kidney. The SARS-CoV-2 priming proteases Tmprss2, Cathepsin L, and Furin mRNA were upregulated by DHT in the kidney. ACE2 sheddase Adam17 mRNA was upregulated by DHT in the kidney, which corresponded with increased urinary ACE2 in DHT treated mice. Our results highlight the potential for increased cardiac, renal, and gastrointestinal dysfunction in PCOS women with COVID-19.

Keywords: SARS-CoV-2; COVID-19; Polycystic Ovary Syndrome; androgens; angiotensin I converting enzyme 2; androgen receptor

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1. Introduction

The continuing COVID-2019 pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was declared a public health emergency by the World Health Organization in January 2020. The SARS-CoV-2 virus has caused a global pandemic reaching over 215 countries and led to over 110 million cases. Until the most recent SARS-CoV-2 emergence, only two human coronaviruses had emerged in recent years. The 2002 SARS-CoV, which shares a 76% amino acid sequence homology to SARS-CoV-2, had a 10% case fatality rate and originated in China. Secondly, 2012 Middle East Respiratory Syndrome Coronavirus (MERS-CoV) had a case-fatality rate of 35% and originated from the Middle East [1]. Most known human betacoronaviruses primarily infect the nasopharynx,

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Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study

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Abstract

Objective: Several recent observational studies have linked metabolic comorbidities to an increased risk from COVID-19. Here we investigated whether women with PCOS are at an increased risk of COVID-19 infection.
Design: Population-based closed cohort study between 31 January 2020 and 22 July 2020 in the setting of a UK primary care database (The Health Improvement Network, THIN).
Methods: The main outcome was the incidence of COVID-19 coded as suspected or confirmed by the primary care provider. We used Cox proportional hazards regression model with stepwise inclusion of explanatory variables (age, BMI, impaired glucose regulation, androgen excess, anovulation, vitamin D deficiency, hypertension, and cardiovascular disease) to provide unadjusted and adjusted hazard risks (HR) of COVID-19 infection among women with PCOS compared to women without PCOS.
Results: We identified 21 292 women with a coded diagnosis of PCO/PCOS and randomly selected 78 310 aged and general practice matched control women. The crude COVID-19 incidence was 18.1 and 11.9 per 1000 person-years among women with and without PCOS, respectively. Age-adjusted Cox regression analysis suggested a 51% higher risk of COVID-19 among women with PCOS compared to women without PCOS (HR: 1.51 (95% CI: 1.27–1.80), $P < 0.001$). After adjusting for age and BMI, HR reduced to 1.36 (1.14–1.63)], $P = 0.001$. In the fully adjusted model, women with PCOS had a 28% increased risk of COVID-19 (aHR: 1.28 (1.05–1.56), $P = 0.015$).
Conclusion: Women with PCOS are at an increased risk of COVID-19 infection and should be specifically encouraged to adhere to infection control measures during the COVID-19 pandemic.
Significance statement: Women with polycystic ovary syndrome (PCOS) have an increased risk of cardio-metabolic disease, which have been identified as a risk factor for COVID-19. To investigate whether the increased metabolic risk in PCOS translates into an increased risk of COVID-19 infection, we carried out a population-based closed cohort study in the UK during its first wave of the SARS-CoV-2 pandemic (January to July 2020), including 21 292 women with PCOS and 78 310 controls matched for sex, age and general practice location. Results revealed a 52% increased risk of COVID-19 infection in women with PCOS, which remained increased at 28% above controls after adjustment for age, BMI, impaired glucose regulation and other explanatory variables.

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ORIGINAL ARTICLE *Reproductive epidemiology*

Association of maternal polycystic ovary syndrome or anovulatory infertility with obesity and diabetes in offspring: a population-based cohort study

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STUDY QUESTION: Are children of mothers with polycystic ovary syndrome (PCOS) or anovulatory infertility at increased risks of obesity or diabetes?

SUMMARY ANSWER: Maternal PCOS/anovulatory infertility is associated with an increased risk of offspring obesity from early age and diabetes in female offspring from late adolescence.

WHAT IS KNOWN ALREADY: Women with PCOS often have comorbid metabolic disorders such as obesity and diabetes, and children of mothers with PCOS have an increased risk of subtle signs of cardiometabolic alterations.

STUDY DESIGN, SIZE, DURATION: This was a nationwide cohort study of all live births (n = 1 105 997) during 1996–2014 in Finland, excluding those with maternal diagnoses sharing signs and symptoms with PCOS (n = 8244). A total of 1 097 753 births were included and followed up until 31 December 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS: National registries were linked to identify births with maternal PCOS or anovulatory infertility (n = 24 682). The primary outcomes were diagnoses of obesity (ICD-10: E65, E66) and diabetes (ICD-10: E10–E14) in offspring recorded in the Finnish Care Register for Health Care. Cox proportional hazards regression was modeled to analyze the risk of offspring obesity and diabetes in relation to prenatal exposure to maternal PCOS/anovulatory infertility. Differently adjusted models and stratified analyses were used to assess whether the risk was modified by maternal obesity or diabetes diagnoses, pre-pregnancy BMI, fertility treatment or perinatal problems.

MAIN RESULTS AND THE ROLE OF CHANCE: Exposure to maternal PCOS/anovulatory infertility was associated with a higher cumulative incidence of obesity in the children (exposed: 1.83%; 95% CI 1.66–2.00% vs unexposed: 1.24%; 95% CI 1.22–1.26%). Accounting for birth factors and maternal characteristics such as obesity and diabetes diagnoses, the hazard ratio (HR) for obesity was increased in offspring below 9 years of age (HR 1.58; 95% CI 1.30–1.81), and in those 10–16 years of age (HR 1.37; 95% CI 1.19–1.57), but not in those aged 17–22 years (HR 1.24; 95% CI 0.73–2.11). Sex-stratified analyses revealed similar risk estimates for boys (HR 1.48; 95% CI 1.31–1.68) and girls (HR 1.45; 95% CI 1.26–1.68). Notably, the joint effect of PCOS/anovulatory infertility and BMI-based pre-pregnancy obesity on offspring obesity (HR 8.89; 95% CI 7.06–11.20) was larger than that of either PCOS/anovulatory infertility or obesity alone. Furthermore, PCOS/anovulatory infertility was associated with offspring obesity in children without perinatal problems (HR 1.27; 95% CI 1.17–1.39), with larger effect size for maternal PCOS/anovulatory infertility and joint perinatal problems (HR 1.61; 95% CI 1.35–

1.91). However, the risk estimates were comparable between maternal PCOS/anovulatory infertility with (HR 1.54; 95% CI 1.17–2.03) and without fertility treatment (HR 1.46; 95% CI 1.32–1.61). For offspring diabetes, the HR was increased only between 17 and 22 years of age (HR 2.06; 95% CI 1.23–3.46), and specifically for Type 1 diabetes in females (HR 3.23; 95% CI 1.41–7.40).

LIMITATIONS, REASONS FOR CAUTION: The prevalence of PCOS/anovulatory infertility in this study was 2.2%, lower than that reported in previous studies. In addition, the incidence of obesity in offspring was lower than that reported in studies based on measured or self-reported weight and height and may include mainly moderate and severe obesity cases who needed and/or actively sought medical care. Moreover, mothers with PCOS/anovulatory infertility were identified based on ICD codes, with no information on PCOS phenotypes. Furthermore, maternal pre-pregnancy BMI was available only from 2004. The PCOS/anovulatory infertility association with female offspring diabetes was based on only a few cases. Mothers' weight gain during pregnancy, use of fertility treatment other than fresh or frozen IVF/ICSI, offspring lifestyle, as well as fathers' age, medical disorders or medication prescriptions were not available for this study.

WIDER IMPLICATIONS OF THE FINDINGS: These findings support that prenatal PCOS/anovulatory infertility exposure influences metabolic health in the offspring from early age.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by Shandong Provincial Natural Science Foundation, China [ZR2020MH064 to X.C.], Shandong Province Medical and Health Technology Development Plan [2018WS338 to X.C.], the joint research funding of Shandong University and Karolinska Institute [SDU-KI-2019-08 to X.C. and C.L.], the Finnish Institute for Health and Welfare: Drug and Pregnancy Project [M.G.], the Swedish Research Council [2014-10171 to C.L.], the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institute Stockholm County Council [SLL20170292 and SLL20190589 to C.L.], the Swedish Brain Foundation [FO2018-0141 and FO2019-0201 to C.L.]. X.C. received grants from the China Scholarship Council at the beginning of the study. The authors have no competing interests to disclose.

TRIAL REGISTRATION NUMBER: N/A.

Key words: polycystic ovary syndrome / anovulatory infertility / offspring / obesity / diabetes / perinatal outcomes / fertility treatment

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder in reproductive-aged women, characterized by oligoovulation/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries. Though women with PCOS have children as often as women without PCOS (Joham *et al.*, 2014), the affected women are more likely to face fertility problems and to seek help from ART. In addition, mothers with PCOS more often have pregnancy complications and less favorable pregnancy outcomes (Palomba *et al.*, 2015; Escobar-Morreale, 2018; Bahri Khomami *et al.*, 2019). Furthermore, PCOS is featured by a range of metabolic dysfunctions, such as obesity and Type 2 diabetes (Teede *et al.*, 2018).

PCOS status, associated comorbidities and pregnancy complications, provide a suboptimal intrauterine environment for the fetus. Together with genetic predisposition, and in consistence with the Barker hypothesis (Hales and Barker, 2001), PCOS may have implications for metabolic health in offspring. A meta-analysis observed subtle signs of altered cardiometabolic health such as increased insulin resistance and HDL-cholesterol concentrations in PCOS-exposed offspring aged 2–17 years old (Gunning *et al.*, 2020). In addition, cohort studies have revealed higher post-stimulated insulin levels or hyperinsulinism in PCOS-exposed daughters, present around puberty and persisting during postmenarchal period (Sir-Petermann *et al.*, 2007; Kent *et al.*, 2008; Sir-Petermann *et al.*, 2009; Crisosto *et al.*, 2019). In male children with PCOS exposure, heavier weight from infancy to adulthood, and altered lipid metabolism during puberty have been reported (Recabarren *et al.*, 2008; Crisosto *et al.*, 2017). Recently, a cohort study found increased risks of PCOS diagnosis in daughters with maternal PCOS (Risal *et al.*, 2019), but whether offspring with maternal PCOS are more likely to develop metabolic diseases such as obesity and diabetes remains unknown. In the general population, perinatal problems including preterm birth, large or small for gestational age (SGA) have been well established as risk factors for metabolic health (Mericq *et al.*, 2017). Also, it was recently reported that children born after fertility treatment were at increased risk of metabolic dysfunctions (Cui *et al.*, 2020). Whether a putative association of maternal PCOS with offspring obesity and/or diabetes would be modified by perinatal problems and fertility treatment, or not, is unknown.

Based on the nationwide birth cohort in Finland, this study aimed to examine the risks of offspring obesity and diabetes until 22 years of age in relation to maternal PCOS. The risks were assessed in both male and female children. Differently adjusted models and stratified analyses were performed to investigate the effects of maternal diagnosis of obesity and diabetes, pre-pregnancy BMI, fertility treatment, and perinatal problems.

Materials and methods

Ethical statement

Study approvals were obtained from the Finnish authorities providing the data, as well as the data protection authority (THL/1662/5.05.00/2015, THL/1853/5.05.00/2016 and THL/1496/5.05.00/2019). Based on regulations in Finland, informed consent was not required for analysis of anonymous data from registers.

Study population and data source

The index cases were all live births in Finland between 1996 and 2014, identified from the Drugs and Pregnancy Database (Artama *et al.*, 2011), originally registered in the Medical Birth Register (MBR). Clinical diagnoses were retrieved from the Finnish Care Registers for

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Mini-Review

Mini-Review

Update on PCOS: Consequences, Challenges, and Guiding Treatment

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Abbreviations: AMH, anti-Müllerian hormone; COC, combined oral contraceptive; CVD, cardiovascular disease; DM, diabetes mellitus; FNPO, follicle number per ovary; GnRH, gonadotropin-releasing hormone; mFG, modified Ferriman-Gallwey; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine disorders in women and despite this, diagnostic challenges, delayed diagnosis, and less-than-optimal treatment regimens plague the condition. The International PCOS network, consisting of geographically diverse international experts in PCOS as well as consumers, engaged in a multi-year international evidence-based guideline development process that was jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM). The guideline was published in 2018 and endorsed by more than 40 international societies involved in PCOS. Translation of this evidence-based guideline to medical practice and consumer groups remains a priority. However, there remain many challenges to both understanding the diagnosis and treatment of PCOS. Evidence suggests that both clinicians and consumers are not satisfied with the timeliness of diagnosis and treatment options. This review summarizes the important findings for diagnosis and treatment from the guidelines and expands on recent developments in the literature since its publication. Special attention to diagnosis at the ends of the reproductive spectrum are discussed and remaining areas of controversy are noted. Additionally, the review highlights some of the remaining challenges in the understanding and management of PCOS to help guide clinicians and investigators in this perplexing condition.

Key Words: PCOS, pathophysiology, diagnostic criteria, metabolic disease, lifestyle intervention

Polycystic ovary syndrome (PCOS) is the most common endocrinologic condition in women, affecting from 8% to 13% of reproductive-aged women (1, 2). It is an enigmatic condition that, while extremely common, creates challenges in its diagnosis and management, as leading symptoms may vary with age, and treatment may be tailored

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Trends in Endocrinology & Metabolism

Review

Anti-Müllerian Hormone in PCOS: A Review Informing International Guidelines

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Polycystic ovary syndrome (PCOS) affects 8–13% of women. The Rotterdam diagnostic criteria include polycystic ovarian morphology (PCOM) on ultrasound, but given recognized challenges, serum anti-Müllerian hormone (AMH) is proposed as an alternative. To inform international PCOS guidelines, a systematic review was completed. Key identified gaps include large international studies in well-defined populations across the lifespan, clustering of AMH with PCOS features, relationships to long-term health outcomes, and improved quality, assay standardization, and sample handling, all needed to determine cut offs. Here we identify research priorities to address these gaps and enhance AMH utility in PCOS. Once issues are addressed, AMH levels could replace more costly and less accessible ultrasound in PCOS diagnosis.

Highlights

This systematic review investigates whether serum anti-Müllerian hormone (AMH) is an effective alternative for the detection of PCOM and/or diagnosis of PCOS.

There is significant heterogeneity in studies conducted in adolescents and adults, with a number of limitations identified.

Studies have lacked well-defined PCOS and control populations that varied across the lifespan, used inconsistent methods for defining cut offs, variably defined PCOM in comparator studies, and had methodological assay and sample handling challenges.

Challenges in Ultrasound PCOM Detection

PCOS is the most common endocrine disorder affecting women of reproductive age, with a reported prevalence of 8–13% [1–5]. The condition is heterogeneous [6] and women may present with reproductive, endocrine, metabolic, and psychosocial symptoms, which vary across their lifespan [7]. The Rotterdam criteria require that women fulfil two of the following three criteria to be diagnosed with PCOS: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound [8–10], with the exclusion of other relevant disorders.

Within the diagnostic criteria, PCOM on ultrasonography is defined by either total ovarian volume or follicle number per ovary (FNPO). Original cut offs for PCOM were based on limited evidence [11] and were recently revised in the new international PCOS guidelines, while also highlighting the controversy and challenges with this criterion [1–4]. Determining FNPO is operator and equipment dependent, limiting accuracy and reproducibility. Equipment advances increase sensitivity and in turn FNPO counts [1–4]. Ultrasound involves expensive equipment and trained personnel, leading to increasing costs and impacting accessibility. The ultrasound approach (transabdominal or transvaginal) impacts accuracy, and in some women transvaginal ultrasound is unacceptable or may be perceived as invasive. Multifollicular appearance on ultrasound overlaps with PCOM diagnostic cut offs especially in adolescents, while in older women with PCOS cut-off values might be considerably lower [11]. Recent international PCOS guidelines now recommend against using ultrasound in PCOS diagnosis within 8 years of menarche and call for greater accuracy in PCOS diagnostic criteria worldwide [1–4].

AMH as a Potential Alternative to Ultrasound PCOM Detection

AMH is a polypeptide of the *transforming growth factor beta* (TGFβ) family, solely secreted by granulosa cells of the pre-antral and small antral ovarian follicles [12]. AMH has been shown in

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Research Article

Research Article

Neurokinin 3 Receptor Antagonism Ameliorates Key Metabolic Features in a Hyperandrogenic PCOS Mouse Model

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Abbreviations: AR, androgen receptor; ARC, arcuate nucleus; DHT, dihydrotestosterone; ER, estrogen receptor; GnRH, gonadotropin-releasing hormone; GTT, glucose tolerance test; LH, luteinizing hormone; KNDy, kisspeptin-/neurokinin B-/dynorphin; NK3R, neurokinin 3 receptor; NKB, neurokinin B; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome; RER, respiratory exchange ratio; RT-PCR, reverse transcription polymerase chain reaction; SEM, standard error of the mean; SNS, sympathetic nervous system

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Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine condition characterized by a range of endocrine, reproductive, and metabolic abnormalities. At present, management of women with PCOS is suboptimal as treatment is only symptomatic. Clinical and experimental advances in our understanding of PCOS etiology support a pivotal role for androgen neuroendocrine actions in PCOS pathogenesis. Hyperandrogenism is a key PCOS trait and androgen actions play a role in regulating the kisspeptin-/neurokinin B-/dynorphin (KNDy) system. This study aimed to investigate if targeted antagonism of neurokinin B signaling through the neurokinin 3 receptor (NK3R) would reverse PCOS traits in a dihydrotestosterone (DHT)-induced mouse model of PCOS. After 3 months, DHT exposure induced key reproductive PCOS traits of cycle irregularity and ovulatory dysfunction, and PCOS-like metabolic traits including increased body weight; white and brown fat pad weights; fasting serum triglyceride and glucose levels, and blood glucose incremental area under the curve. Treatment with a NK3R antagonist (MLE4901) did not impact the observed reproductive defects. In contrast, following NK3R antagonist treatment, PCOS-like females displayed decreased total body weight, adiposity, and adipocyte hypertrophy, but increased respiratory exchange ratio, suggesting NK3R antagonism altered the metabolic status of the PCOS-like females. NK3R antagonism did not improve circulating serum triglyceride or fasted glucose levels. Collectively, these findings demonstrate that NK3R antagonism may be beneficial in the treatment of adverse metabolic features associated with PCOS and support neuroendocrine targeting in the development of novel therapeutic strategies for PCOS.

Key Words: hyperandrogenism, polycystic ovary syndrome (PCOS), animal model, neuroendocrine

Polycystic ovary syndrome (PCOS) is a heterogenous endocrine condition that affects up to 20% of women of reproductive age (1-3). Women with PCOS can suffer from a wide range of ill-health traits as PCOS is associated with adverse reproductive, endocrine, metabolic, and psychological features (4, 5). Using the Rotterdam criteria, a woman is diagnosed with PCOS if she exhibits 2 of 3 features (clinical and/or biochemical hyperandrogenism, oligo-ovulation or anovulation, and polycystic ovary morphology [PCOM]) on ultrasound after exclusion of all other differential diagnoses (5). PCOS is associated with obesity, metabolic syndrome, hyperinsulinemia, insulin resistance, hepatic steatosis, and dyslipidemia, and heightens the risk of type 2 diabetes and cardiovascular disease (4, 6-8). Despite the high prevalence and significant health impact of PCOS, there is no specifically approved treatment for PCOS (9) and current treatment strategies for PCOS are suboptimal as they rely on treatment of symptoms (5). At present, mechanism-based treatments remain unavailable as the etiology of PCOS remains unclear. Hence, there is a real need for ongoing research to define the causative factors driving PCOS pathogenesis.

Hyperandrogenism represents a major feature of PCOS (5, 10). Numerous findings support a causative role for androgen excess acting via the androgen receptor (AR) in driving the pathogenesis of PCOS (11, 12). Exposure of nonhuman primates (13), sheep (14-16), and rodents (17) to androgen excess reliably induces the development of a range of key PCOS-like traits that closely resemble features of human PCOS. Blockade of androgen actions by the AR antagonist flutamide restores menstrual regularity and ovulation in some women with PCOS (18), and rectifies reproductive and/or metabolic traits in PCOS mouse and sheep models (19-22). Genetically modified mice that exhibit haplo- or complete AR insufficiency are protected against the development of PCOS traits (23, 24). Importantly, inactivation of AR solely in the brain protects female mice from developing the majority of reproductive and metabolic PCOS-like traits (24, 25). This highlights the brain as a key site at the core of PCOS pathogenesis and neuroendocrine AR-mediated pathways as potential targets for the development of novel therapeutic strategies.

The key neuroendocrine aberration in women with PCOS is increased luteinizing hormone (LH) pulse frequency driven by an increase in activity of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus (4). GnRH neuron activity and the pattern of pulsatile GnRH secretion are highly dependent upon homeostatic feedback from gonadal steroid hormone signaling in the brain. While GnRH neurons express estrogen receptor (ER) β, they do not express AR, ERα, or progesterone receptors (26). Hence, steroid-mediated negative feedback regulation is largely facilitated through the neuronal network that lies upstream to the GnRH neurons. The kisspeptin-/neurokinin B-/dynorphin-expressing "KNDy" neurons form a network that play a critical role in mediating gonadal steroid hormone feedback to GnRH neurons and control episodic GnRH/LH release (27-31). It is proposed that the colocalized KNDy peptides, in neurons of the arcuate nucleus (ARC), work in concert to regulate GnRH/LH pulse dynamics. Neurokinin B (NKB) activates local KNDy neurons through reciprocal connections within the ARC, promoting kisspeptin release and subsequent GnRH neuron activation and peptide secretion, while dynorphin plays a role in pulse termination (32). NKB can act through several tachykinin receptors (NK1R-NK3R); however, NK3R has the highest affinity for NKB (33). In humans, loss of function mutation in NK3R results in pubertal delay (34) and specific antagonism of NK3R decreases LH pulse frequency in women (35). KNDy neurons express AR (36) and AR-mediated actions have been shown to regulate the KNDy system (26). Moreover, KNDy neurons in ARC of rodents, sheep, and pigs appear to be targets for metabolic hormones such as leptin and insulin like growth factor 1

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Research Article

Research Article

Reproductive Deficits Induced by Prenatal Antimüllerian Hormone Exposure Require Androgen Receptor in Kisspeptin Cells

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Abbreviations: AF, antral follicle; AMH, antimüllerian hormone; AMHR2, AMH receptor 2; AR, androgen receptor; ARC, arcuate nucleus; AVPV, anteroventral periventricular nucleus; Ctrl, control; d, day; D, diestrus; DHT, dihydrotestosterone; e, embryonic day; E, estrus; E_2, estradiol; ER, estrogen receptor; F_1, first-generation; F_2, second-generation; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal axis; KARKO, kisspeptin-specific androgen receptor knockout; LH, luteinizing hormone; M, metestrus; mRNA, messenger RNA; P, proestrus; pAMH, prenatal antimüllerian hormone; PBS, phosphate-buffered saline; PCOS, polycystic ovary syndrome; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase–polymerase chain reaction; ST, seminiferous tubule; T, testosterone; VEH, vehicle

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Abstract

Polycystic ovary syndrome (PCOS) is a common reproductive disorder characterized by elevated androgens and antimüllerian hormone (AMH). These hormones remain elevated throughout pregnancy, and potential effects of hormone exposure on offspring from women with PCOS remain largely unexplored. Expanding on recent reports of prenatal AMH exposure in mice, we have fully characterized the reproductive consequences of prenatal AMH (pAMH) exposure throughout the lifespan of first- and second-generation offspring of both sexes. We also sought to elucidate mechanisms underlying pAMH-induced reproductive effects. There is a known reciprocal relationship between AMH and androgens, and in PCOS and PCOS-like animal models, androgen feedback is dysregulated at the level of the hypothalamus. Kisspeptin neurons express androgen receptors and play a critical role in sexual development and function. We therefore hypothesized that pAMH-induced reproductive phenotypes would be mediated by androgen signaling at the level of kisspeptin cells. We tested the pAMH model in kisspeptin-specific androgen receptor knockout (KARKO) mice and found that virtually all pAMH-induced phenotypes assayed are eliminated in KARKO offspring compared to littermate controls. By demonstrating the necessity of androgen receptor in kisspeptin cells to induce pAMH phenotypes, we have advanced understanding of the interactions between AMH and androgens in the context of prenatal exposure, which could have significant implications for children of women with PCOS.

Key Words: antimüllerian hormone, androgen receptor, kisspeptin, PCOS, prenatal hormone exposure

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Polycystic ovary syndrome (PCOS) affects 1 in 10 reproductive-age women and is the most common cause of anovulatory infertility (1). PCOS classically presents with disrupted ovulation, polycystic ovaries, and androgen excess. Hyperandrogenism persists throughout any pregnancies (2-5), with potential consequences for offspring. Daughters from women with PCOS have a 5-fold increased risk for developing PCOS themselves (6), and sons have been shown to have altered hormones during puberty (7, 8). Since loci identified by PCOS genome-wide association studies account for less than 10% of disease heritability (9) and more than 20% of the variation observed in PCOS can be explained by environmental factors (10), nongenetic influences such as altered gestational hormones could confer risk to offspring.

In addition to the characteristic increase in androgens, antimüllerian hormone (AMH) levels have been found to correlate with the severity of clinical manifestations of PCOS, including signs of hyperandrogenism (11-14), and genetic studies in PCOS women have identified associations between androgen levels and polymorphisms in the genes encoding AMH and its ligand-binding receptor, AMHR2 (15-17). In PCOS patients, ovarian follicles are arrested at a stage in follicular development when AMH production is highest (18), and each individual follicle produces more AMH than follicles from healthy controls (19). AMH levels in follicular fluid and serum are at least 5- and 3-fold higher, respectively, in PCOS women (20-22). These increased AMH levels remain elevated into the second trimester of pregnancy and at term (23, 24). The effects of prenatal AMH exposure on offspring have yet to be fully examined.

Although AMH is clearly dysregulated in PCOS, only one group has explored the effects of prenatal AMH (pAMH) exposure thus far (23, 25). In mice, peripheral administration of AMH late in gestation resulted in marked reproductive disruptions in female offspring (23). pAMH females showed delayed puberty and disrupted early estrous cycling, as well as alteration at all levels of the hypothalamic-pituitary-gonadal (HPG) axis. pAMH-induced reproductive phenotypes are transgenerational, with second- and third-generation females also affected (25). However, initial investigations did not examine time points beyond puberty and early adulthood. Assessments of late adulthood are especially relevant because in utero androgen exposure results in altered reproductive senescence in mice (26). Further, possible consequences to pAMH male offspring have not been explored, and underlying pathophysiological mechanisms have yet to be fully elucidated.

One proposed pathway for pAMH-induced reproductive effects is AMH action at the level of the hypothalamus to activate the HPG axis and favor excess androgen production (23). Although peripherally administered AMH does not cross the placenta, it does alter maternal serum hormones and placental gene expression to create an androgenic environment in utero (23). Prenatal androgen excess in mice contributes to the development of PCOS-like reproductive features (26-29). pAMH phenotypes can be reversed and prevented with a gonadotropin-releasing hormone (GnRH) antagonist (23), further suggesting a central, androgen-mediated mechanism. However, the contribution of androgens to pAMH-induced phenotypes has not been directly tested.

Because GnRH neurons do not express androgen receptors (ARs), androgens would act upstream, possibly on hypothalamic kisspeptin neurons. Kisspeptin neurons in the arcuate nucleus (ARC) of the hypothalamus are considered the pacemakers of pulsatile GnRH release (30) and are critical for normal sexual maturation and function (31). Normally, androgens negatively feed back to the hypothalamus by binding to AR in ARC kisspeptin neurons, decreasing kisspeptin expression and suppressing luteinizing hormone (LH) pulses (32). In PCOS and PCOS-like mouse models, sex steroid feedback to the HPG axis is altered, as LH pulsatility remains high despite the presence of elevated androgens (23, 33, 34). Together, this evidence led us to hypothesize that the pAMH-induced reproductive phenotype would be mediated by androgen signaling at the level of kisspeptin cells.

Here, we characterize a full profile throughout the lifespan of first- and second-generation pAMH offspring of both sexes. Using Cre-LoxP technology, we generated a kisspeptin-specific AR knockout (KARKO) mouse line and assessed the reproductive consequences of pAMH in KARKO offspring to determine whether androgens were mediating this phenotype and where they might be acting. We found that nearly every pAMH-induced deficit present in controls was eliminated in their KARKO littermates. By determining the necessity of AR in kisspeptin cells to induce pAMH phenotypes, we have advanced understanding of the interactions between AMH and androgens in the context of prenatal exposure.

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Full length article

Circulating kisspeptin and anti-müllerian hormone levels, and insulin resistance in women with polycystic ovary syndrome: A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Objective: This systematic review and meta-analysis aimed to summarize the available evidence regarding circulating kisspeptin and anti-müllerian hormone (AMH) and the homeostasis model assessment of insulin resistance (HOMA-IR) index in adolescents and women with and without polycystic ovary syndrome (PCOS).

Method: We performed a comprehensive literature search in Medline, Embase, Cochrane, Scopus, and Web of Science for studies evaluating circulating kisspeptin levels in women with and without PCOS published until September 24th, 2020. Co-primary outcomes were the HOMA-IR index and AMH. The quality of included studies was assessed using the Newcastle-Ottawa Scale. Random-effects models were used to estimate outcomes, and effects reported as mean difference (MD) or standardized MD (SMD) and their 95 % confidence interval (CI). The systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as number CRD42020205030.

Results: We evaluated 18 studies including, 1282 PCOS cases and 977 controls. Participants with PCOS were younger (MD = −2.38 years, 95 %CI -4.32 to -0.44), with higher BMI (MD = 1.16, 95 % CI 0.54–1.78), waist-to-hip ratio (MD = 0.04, 95 %CI 0.02 to 0.05), circulating kisspeptin (SMD = 1.15, 95 %CI 0.68–1.62), luteinizing hormone (SMD = 1.29, 95 %CI 0.76–1.83), AMH (SMD = 0.97, 95 %CI 0.60–1,34), total testosterone (SMD = 2.48, 95 %CI 1.73–3.23), free testosterone (SMD = 1.37, 95 %CI 0.56–2.17), and dehydroepiandrosterone sulphate (SMD = 0.72, 95 %CI 0.32–1.13) levels, and Ferriman-Gallwey score (SMD = 5.08, 95 %CI 2.76–7.39), and lower sex hormone-binding globulin level (SMD = −1.34, 95 %CI −2.15 to −0.52). Besides, participants with PCOS had higher HOMA-IR index (SMD = 0.76, 95 %CI 0.35–1.17), and circulating insulin (SMD = 0.75, 95 %CI 0.30–1.19), leptin (SMD = 2.82, 95 %CI 1.35–4.29), and triglycerides (SMD = 2.15, 95 %CI 1.08–3.23) levels than participants without the syndrome. The meta-regression did not identify significant factors influencing circulating kisspeptin.

Conclusion: Patients with PCOS showed higher kisspeptin, LH, insulin, AMH, and androgen levels and HOMA-IR index, and lower sex hormone-binding globulin levels than those without the syndrome.

Introduction

Kisspeptins are a group of brain neuropeptides initially described as metastasis suppressors [1]. The kisspeptin precursor has 145 amino acids that, by proteolysis, produce kisspeptin-54 (also know as metastin) that is considered the active product. Kisspeptin 13 and kisspeptin-14 are products from the degradation of kisspeptin-54 [2,3]. Kisspeptin (encoded by KISS1) influences gonadotrophin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion and might contribute to the development of

Abbreviations: AMH, Anti-müllerian hormone; BMI, Body mass index; CI, Confidence interval; DHEA-S, dehydroepiandrosterone sulphate; FSH, Follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; HDL, High density lipoprotein; HOMA-IR, Homeostatic model assessment of insulin resistance; IQR, Interquartile range; LDL, Low density lipoprotein; LH, Luteinizing hormone; MD, Mean difference; NOS, Newcastle–Ottawa Scale; PCOS, polycystic ovary syndrome (PCOS); SD, Standard deviation; SHBG, Sex hormone-binding globulin; SMD, Standardized mean difference; VLDL, Very low density lipoprotein cholesterol.

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RESEARCH ARTICLE

Maternal PCOS status and metformin in pregnancy: Steroid hormones in 5–10 years old children from the PregMet randomized controlled study

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Abstract

Objective

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, with potential effects on offspring both genetically and through altered intrauterine environment. Metformin, which ameliorate hormonal disturbances in non-pregnant women with PCOS is increasingly used in pregnancy. It passes the placenta, and the evidence on potential consequences for offspring endocrine development is scarce. We explore the potential effects of maternal PCOS status and intrauterine metformin exposure on offspring steroid hormone levels.

Design

This is a follow-up study of 5–10 years old children from the PregMet-study–a randomized controlled trial comparing metformin (2000 mg/day) to placebo during PCOS pregnancies. Of the 255 children invited, 117 (46%) were included.

Methods

There was no intervention in this follow-up study. Outcomes were serum levels of androstenedione, testosterone, SHBG, cortisol, 17-hydroxyprogesterone, 11-deoxycortisol and calculated free testosterone converted to gender-and age adjusted z-scores from a Norwegian reference population. These were compared in i) placebo-exposed children versus

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human reproduction

ORIGINAL ARTICLE ***Reproductive epidemiology***

Early initiation of anti-androgen treatment is associated with increased probability of spontaneous conception leading to childbirth in women with polycystic ovary syndrome: a population-based multiregistry cohort study in Sweden

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STUDY QUESTION: Is anti-androgen treatment during adolescence associated with an improved probability of spontaneous conception leading to childbirth in women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Early initiation of anti-androgen treatment is associated with an increased probability of childbirth after spontaneous conception among women with PCOS.

WHAT IS KNOWN ALREADY: PCOS is the most common endocrinopathy affecting women of reproductive age. Hyperandrogenism and menstrual irregularities associated with PCOS typically emerge in early adolescence. Previous work indicates that diagnosis at an earlier age (<25 years) is associated with higher fecundity compared to a later diagnosis.

STUDY DESIGN, SIZE, DURATION: This population-based study utilized five linked Swedish national registries. A total of 15 106 women with PCOS and 73 786 control women were included. Women were followed from when they turned 18 years of age until the end of 2015, leading to a maximum follow-up of 10 years. First childbirth after spontaneous conception was the main outcome, as identified from the Medical Birth Registry.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants included all women born between 1987 and 1996 with a diagnosis of PCOS in the Swedish Patient Registry and randomly selected non-PCOS controls (ratio 1:5). Information on anti-androgenic treatment was retrieved from the Swedish Prescribed Drug Registry with the use of Anatomic Therapeutic Chemical (ATC) codes. Women with PCOS who were not treated with any anti-androgenic medication were regarded as normo-androgenic, while those treated were regarded as hyperandrogenic. Women were further classified as being mildly hyperandrogenic if they received anti-androgenic combined oral contraceptive (aaCOC) monotherapy, or severely hyperandrogenic if they received other anti-androgens with or without aaCOCs. Early and late users comprised women with PCOS who started anti-androgenic treatment initiated either during adolescence ($\leq$ 18 years of age) or after adolescence (>18 years), respectively. The probability of first childbirth after spontaneous conception was analyzed with the use of Kaplan–Meier hazard curve. The fecundity rate (FR) and 95% confidence interval for the time to first childbirth that were conceived spontaneously were calculated using Cox proportional hazards regression models, with adjustment for obesity, birth year, country of birth and education level.

MAIN RESULTS AND THE ROLE OF CHANCE: The probability of childbirth after spontaneous conception in the PCOS group compared to non-PCOS controls was 11% lower among normo-androgenic (adjusted FR 0.68 (95% CI 0.64–0.72)), and 40% lower among hyperandrogenic women with PCOS (adjusted FR 0.53 (95% CI 0.50–0.57)). FR was lowest among severely hyperandrogenic women with PCOS compared to normo-androgenic women with PCOS (adjusted FR 0.60 (95% CI 0.52–0.69)), followed by mildly hyperandrogenic women with PCOS (adjusted FR 0.84 (95% CI 0.77–0.93)). Compared to early anti-androgenic treatment users, late users exhibited a lower probability of childbirth after spontaneous conception (adjusted FR 0.79 (95% CI 0.68–0.92)).

LIMITATIONS, REASONS FOR CAUTION: We lacked direct information on the intention to conceive and the androgenic biochemical status of the PCOS participants, applying instead the use of anti-androgenic medications as a proxy of hyperandrogenism. The duration of anti-androgenic treatment utilized is not known, only the age at prescription. Results are not adjusted for BMI, but for obesity diagnosis. The period of follow-up (10 years) was restricted by the need to include only those women for whom data were available on the dispensing of medications during adolescence (born between 1987 and 1996). Women with PCOS who did not seek medical assistance might have been incorrectly classified as not having the disease. Such misclassification would lead to an underestimation of the true association between PCOS and outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: Early initiation of anti-androgen treatment is associated with better spontaneous fertility rate. These findings support the need for future interventional randomized prospective studies investigating critical windows of anti-androgen treatment.

STUDY FUNDING/COMPETING INTEREST(S): This study was funded by the Health Research Council of New Zealand (18-671), the Swedish Society of Medicine and the Uppsala University Hospital. Evangelia Elenis has, over the past year, received lecture fee from Gedeon Richter outside the submitted work. Inger Sundström Poromaa has, over the past 3 years, received compensation as a consultant and lecturer for Bayer Schering Pharma, MSD, Gedeon Richter, Peptonics and Lundbeck A/S. The other authors declare no competing interests.

TRIAL REGISTRATION NUMBER: N/A

Key words: PCOS / fertility / childbirth / anti-androgen / adolescence

Introduction

Polycystic ovary syndrome (PCOS) is an endocrinopathy affecting women of reproductive age with a reported prevalence ranging from 5 to 25% (March *et al.*, 2010; Rosenfield and Ehrmann, 2016; Wolf *et al.*, 2018). PCOS is characterized by clinical or biochemical hyperandrogenism, menstrual irregularities and ultrasonographic polycystic ovarian morphology (Rosenfield and Ehrmann, 2016). Symptoms typically emerge during early adolescence (Driscoll, 2003; Ryan *et al.*, 2018) and may persist into adulthood. The common denominator for PCOS development appears to be ovarian and/or adrenal hyperandrogenism in synergy with tissue-selective insulin-resistant hyperinsulinism (Ibáñez *et al.*, 2017; Witchel *et al.*, 2019). The disorder is multifactorial and heterogeneous, implicating both intrauterine and postnatal environmental factors, as well as endocrinological, genetic and epigenetic factors (Rosenfield and Ehrmann, 2016). PCOS pathogenesis likely results from the combination of a prenatal predisposing factor (referred to as a 'first hit') with an activating postnatal factor (referred to as the 'second hit') (Rosenfield, 2020). For example, genetically susceptible girls or those exposed to androgen excess *in utero* develop hyperandrogenism prepubertally through hyperactivation of their hypothalamic–pituitary–ovarian (HPO) axis; that, in addition to the normal physiological or obesity-related hyperinsulinism during adolescence, potentiates the hyperandrogenic state and accelerates the syndrome's clinical manifestations and/or aggravates the syndrome's clinical course (Bremer, 2010). A more recent evolution of this idea suggests that a mismatch between prenatal and postnatal weight gain, resulting in greater hepatovisceral fat, drives accelerated body growth and maturation, which in turn establishes persistent PCOS features (de Zegher *et al.*, 2018).

In population-based studies (Koivunen *et al.*, 2008; West *et al.*, 2014; Persson *et al.*, 2019), we and others have previously demonstrated that women with PCOS, especially those with obesity, need a longer time to achieve childbirth and give birth to a lower number of children compared to non-PCOS counterparts. A novel finding was the fact that PCOS diagnosis at an earlier age (<25 years) was associated with higher fecundity rate (FR) compared to a later diagnosis (Persson *et al.*, 2019). Since symptoms appear to be progressive in women with PCOS, timely interventions that improve hyperandrogenism, either directly or indirectly through lowering insulin levels, have been recommended (Bremer, 2010). Therefore, whether specific interventions, such as pharmacological treatment during a specific therapeutic window, i.e. during adolescence, can decrease androgen actions and mitigate the future adverse effects of PCOS remains unknown.

Clinical and animal-based evidence indicates that long-term anti-androgen therapy can restore impaired reproductive function. Long-term AR blockade is associated with improved testosterone levels and ovulatory function in adult women with PCOS (De Leo *et al.*, 1998; Paradisi *et al.*, 2013), and a restoration of normal steroid hormone feedback to the reproductive axis (Eagleson *et al.*, 2000). In addition, in prenatally androgenized mice that model PCOS in adulthood (Sullivan and Moenter, 2004; Moore *et al.*, 2013; Moore *et al.*, 2015; Silva *et al.*, 2018), anti-androgen therapy restores estrous cyclicity (Sullivan and Moenter, 2004; Silva *et al.*, 2018). In addition, continuous androgen blockade from an 'adolescent' period following puberty is associated with improved ovarian morphology and a reversal of brain wiring changes induced by prenatal androgen exposure (Silva *et al.*, 2018).

Therefore, our study hypothesizes that the probability of childbirth after spontaneous conception among PCOS women improves if preceded by anti-androgen therapy during adolescence. The aim of the current study was therefore to explore whether treatment with anti-androgen medications initiated during adolescence is associated with a higher probability of childbirth after spontaneous conception in women with PCOS.

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ORIGINAL ARTICLE ***Reproductive endocrinology***

Individual and combined effects of 5-year exposure to hyperandrogenemia and Western-style diet on metabolism and reproduction in female rhesus macaques

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STUDY QUESTION: What is the impact of prolonged exposure to hyperandrogenemia (T), Western-style diet (WSD) and the combination on metabolic and reproductive function in female rhesus macaques, particularly in the post-partum period?

SUMMARY ANSWER: Combined T + WSD worsened measures of insulin sensitivity and parameters of cyclicity following prolonged (5 years) exposure, but there was no effect on post-partum metabolic function.

WHAT IS KNOWN ALREADY: Women with hyperandrogenemia due to polycystic ovary syndrome are at higher risk for gestational diabetes and Type 2 diabetes post-partum, but it is unknown if this is related to hyperandrogenemia. Hyperandrogenemia in the presence of a WSD worsens metabolic function in female nonhuman primates.

STUDY DESIGN, SIZE, DURATION: Female rhesus macaques began treatment near menarche (roughly 2.5 years of age) consisting of either cholesterol (control; C) or testosterone (T) implants (average serum levels 1.4 ng/ml) and exposure to standard monkey chow or a WSD (15 vs 36% of calories from fat, respectively). The four groups were maintained on treatment for 3 years, underwent a fertility trial in Year 4 and continued with treatments through Year 5.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Metabolic measurements (glucose tolerance tests and double X-ray absorptiometry scans) were performed yearly, and results from 5 years of treatment are reported for all animals. Animals were bled daily for 30 days at 5 years to capture changes in ovarian cycle hormones, and ultrasound measurements were performed during the early follicular and luteal phase.

MAIN RESULTS AND THE ROLE OF CHANCE: After 5 years of treatment, WSD exposure moderately increased body weight and body fat, although control animals also had a high body mass index due to *ad libitum* feeding. Animals in the T + WSD group had increased fasting insulin and insulin secretion during an intravenous glucose tolerance test. WSD exposure also altered ovarian cycles, delaying the time to the E2 surge, decreasing progesterone and anti-Müllerian hormone levels and increasing the number of antral follicles present by ultrasound. Longitudinal assessment of metabolic function for only those animals that became pregnant in Year 4 of treatment revealed no differences in post-partum metabolism between groups, although WSD resulted in overall elevated weights, body fat and measures of insulin resistance.

LARGE SCALE DATA: None.

LIMITATIONS, REASONS FOR CAUTION: The small sample size and heterogeneity in metabolic effects observed in the T + WSD group are limitations of the current study, with only a subset of animals in this group showing impaired insulin resistance relative to controls. In addition, obesity in the C group prevented comparisons to lean animals.

WIDER IMPLICATIONS OF THE FINDINGS: Hyperandrogenemia combined with WSD had a greater impact on insulin sensitivity and ovarian function than either treatment alone.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by NIH grant P50 HD071836 to C.T.R., J.H. and C.T. and P51 OD011092 for support of the Oregon National Primate Research Center. All authors declare no competing interests.

Key words: hyperandrogenemia/ polycystic ovary syndrome/ obesity/ high-fat diet/ post-partum

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent cause of subfertility, affecting an estimated 5–10% of reproductive-age women in the USA (Azziz *et al.*, 2016). The most commonly used diagnostic criteria require that women have at least two of the following symptoms: oligo- or anovulation, polycystic ovaries upon ultrasound and hyperandrogenemia. In addition, patients with PCOS have higher rates of both obesity and insulin resistance, which also have a negative impact on fertility (Clark *et al.*, 1995, 1998; Pasquali *et al.*, 2003; Brewer and Balen, 2010; Rubin *et al.*, 2017; Yao et al., 2017). Consistent with worsened measures of insulin sensitivity, PCOS women are at increased risk of developing gestational diabetes during pregnancy (Pan *et al.*, 2015; Rubin *et al.*, 2017; Yao *et al.*, 2017). Gestational diabetes further increases the risk for the development of Type 2 diabetes post-partum (Kim *et al.*, 2002; Bellamy *et al.*, 2009). It is unclear from clinical data whether the risk for gestational diabetes and post-partum Type 2 diabetes in PCOS patients is secondary to PCOS-associated obesity, or if it may be inherent to the disease and elevated levels of androgens.

Our group has developed a nonhuman primate model to explore the independent and combined impact of elevated androgens and an obesogenic Western-style diet (WSD) on metabolic and reproductive health. Female macaques were exposed to elevated testosterone (T), WSD or the combination (T + WSD) beginning at puberty. The timing of treatment initiation was chosen to mimic the emergence of hyperandrogenemia in obese adolescent females at this developmental period (McCartney *et al.*, 2006, 2007). Previous data have shown the most significant metabolic and reproductive impairments were present in the combination T + WSD group, consistent with the hypothesis that both factors may contribute to adverse health outcomes in PCOS patients (True *et al.*, 2017; Bishop *et al.*, 2018*a*, *b*). The T + WSD group had the greatest insulin resistance and lowest fertility rate, although significant heterogeneity in response to treatment was present in this group as well. Animals that failed to achieve pregnancy after three timed matings during the window of fertility, or that had unviable pregnancies, had higher levels of fasting insulin compared to those that conceived, suggesting that hyperinsulinemia and insulin resistance are associated with infertility. Because animals that became pregnant tended to have better indices of insulin sensitivity, only modest group differences during gestation were observed, including elevated fasting glucose levels and reduced glucose clearance during a second-trimester intravenous glucose tolerance test (ivGTT) in the T + WSD group compared to controls (Bishop *et al.*, 2018*a*). It is unknown whether androgens, in isolation or combination with a WSD, can contribute to a further metabolic decline in the post-partum period, which is often observed in women who experience gestational diabetes (Kim *et al.*, 2002; Bellamy *et al.*, 2009). The current study sought to expand upon our previous reporting in this model into 5 years of continuous T, WSD and T + WSD treatment on overall metabolic and reproductive health. In addition, we examined whether those animals that experienced a pregnancy in Year 4 of treatment showed differential metabolic responses in the acute and long-term post-partum period.

Materials and methods

Animals

All animal procedures were approved by the Oregon National Primate Research Center (ONPRC) Institutional Animal Care and Use Committee and comply with the Animal Welfare Act and the APA Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research. The model and treatments have been described previously (True *et al.*, 2017). Female rhesus macaques, aged roughly 2.5 years at the time of treatment initiation, were in one of four treatment groups: control animals receiving cholesterol implants and a control diet (C), animals receiving T implants and a control diet (T), animals receiving cholesterol implants and a WSD and animals receiving T implants and a WSD (T + WSD). Average serum T levels in the T-treated group were 1.35 ng/ml compared to an average value of 0.27 ng/ml in cholesterol-treated animals (True *et al.*, 2017). The WSD (Purina 5LOP) has roughly 36% of calories from fat compared to the 15% of calories from fat in standard monkey chow (Purina 5000/5052). Animals were typically pair-housed in the same treatment group and maintained on a 0700–1900 light cycle with *ad libitum* access to water. All animals underwent 3 years of treatment, and in the fourth year, underwent a fertility trial where they were mated with a proven male breeder over a maximum of three menstrual cycles during the window of fertility. A large subset of the animals became pregnant and had pregnancies terminated by C-section in the third trimester, as reported previously (Bishop *et al.*, 2018*a*). T and/or WSD treatments were continued throughout and after the fertility trial up to 5 years of treatment.

Metabolic measurements

Body composition and ivGTTs were not performed at a specific menstrual cycle stage and have been described previously (True *et al.*, 2017).

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ARTICLE

Identification of epigenetic interactions between microRNA and DNA methylation associated with polycystic ovarian syndrome

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Abstract

Aberration in microRNA expression or DNA methylation is a causal factor for polycystic ovarian syndrome. However, the epigenetic interactions between miRNA and DNA methylation remain unexplored in PCOS. We conducted a novel integrated analysis of RNA-seq, miRNA-seq, and methylated DNA-binding domain sequencing on ovarian granulosa cells to reveal the epigenetic interactions involved in the pathogenesis of PCOS. We identified 830 genes and 30 miRNAs that were expressed differently in PCOS, and seven miRNAs negatively regulated target mRNA expression. 130 miRNAs' promoters were significantly differently methylated, while 13 were associated with miRNA expression. Furthermore, the hypermethylation of miR-429, miR-141-3p, and miR-126-3p′ promoter was found related to miRNA expression suppression and therefore their corresponding genes upregulation, including *XIAP*, *BRD3*, *MAPK14,* and *SLC7A5*. Our findings provide a novel insight in PCOS. The consequential reversal of genes silencing may participate in PCOS pathogenesis and served as potential molecular targets for PCOS.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent endocrine disorders with the symptoms of hyperandrogenism, chronic anovulation, and polycystic ovaries [1]. It is also considered to be a common cause of body malfunction in women, with symptoms including hirsutism, acne, obesity, menstrual dysfunction, and infertility. It also appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinism, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial carcinoma [2, 3].

Ovarian granulosa cells (GCs) have been demonstrated to play a major role in deciding the fate of follicles. In the early stage of follicle development, oocyte apoptosis results in follicular atresia-induced ambient GC death, which results in molecules that are essential for oocyte development and maintenance as well as self-renewal by apoptotic processes [4, 5]. Therefore, it is important to investigate the role of GCs in the pathogenesis of PCOS.

Current research has shown that the influence of multiple factors, including age, the environment/lifestyle, and the disease state environment, can modify the clinical presentation of PCOS via epigenetic modifications [6]. DNA methylation and microRNAs (miRNAs) are two main epigenetic modifications in the regulation of gene expression. MiRNAs are small noncoding RNAs acting as post-transcriptional negative regulators of gene expression, which are involved in the regulation of various diseases such as diabetes, insulin resistance, inflammatory disease, and cancer. Meanwhile, aberrant DNA methylation manifests in both global genome stability preservation and in localized gene promoter changes, which influences the transcription of disease-causing genes [7].

Recently, compelling evidence has indicated the roles of DNA methylation and miRNAs in PCOS, respectively. Previous studies detected significant alteration in genome-wide DNA methylation and transcriptional patterns in human ovaries, GCs, and the adipose tissue of PCOS involved in metabolic disturbances [8–10]. These studies

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REVIEW

WILEY

The role of androgen and its related signals in PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women at reproductive age. However, the underlying pathogenic mechanisms have not been completely understood. Hyperandrogenism is an important clinic feature in patients with PCOS, suggesting its pathologic role in the development and progression of PCOS. However, the actual role of androgen and the related signals in PCOS and PCOS-related complications have not yet been clarified. In this review, we surveyed the origin and effects of androgen on PCOS and the related complications, highlighted the cellular signals affecting androgen synthesis and summarized the pathological processes caused by hyperandrogenism. Our review well reveals the important mechanisms referring the pathogenesis of PCOS and provides important clues to the clinic strategies in patients with PCOS.

KEYWORDS
androgen, cell signal, complication, hyperandrogenism, PCOS

1 | INTRODUCTION

Nowadays, that 5%-20% of reproductive-age women are suffering from PCOS. However, PCOS is still an intractable problem in medical society.

Hyperandrogenism is an important criterion for diagnosis to PCOS. In patients with PCOS, incidence rate of hyperandrogenism is as high as 60%-80%. Androgen hyperactivation leads to ovulation disorder, menstrual disorder, hairy and acne, suggesting that hyperandrogenism is not only a clinical characteristic of PCOS, but also an

Wenting Ye and Tingting Xie contributed equally to this work.

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Clinical Research Article

Clinical Research Article

Insulin-Mediated Substrate Use in Women With Different Phenotypes of PCOS: the Role of Androgens

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Abbreviations: BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FFA, free fatty acid; FSH, follicle-stimulating hormone; Gnonox, nonoxidative glucose metabolism; Gox, glucose oxidation; HDL, high-density lipoprotein; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LH, luteinizing hormone; Lox, lipid oxidation; PCOm, polycystic ovarian morphology; PCOS, polycystic ovary syndrome; PKA-HSL, protein kinase A–hormone-sensitive lipase complex; SHBG, sex hormone–binding globulin; WHR, waist to hip ratio.

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Abstract

Context: Few studies have explored in vivo insulin action on substrate use in women with PCOS. In particular, no data are available in women with different PCOS phenotypes.
Objective: The aim of the study was to evaluate insulin action on glucose (Gox) and lipid (Lox) oxidation, nonoxidative glucose metabolism (Gnonox), and serum free fatty acids (FFAs) in different PCOS phenotypes.
Methods: Participants included 187 nondiabetic women with PCOS diagnosed according to the Rotterdam criteria. Data from a historical sample of 20 healthy women were used as reference values. Whole-body substrate use data were obtained by the hyperinsulinemic euglycemic clamp associated with indirect calorimetry. Serum androgens were assessed by liquid chromatography–mass spectrometry and equilibrium dialysis.
Results: During hyperinsulinemia, the increase of Gox (ΔGox), Gnonox, as well as the suppression of Lox (ΔLox) and serum FFA (Δ% FFA) were altered in each PCOS phenotype. Moreover, Gnonox and Δ% FFA were lower in women with the classic phenotype than in those with the ovulatory or the normoandrogenic phenotypes, and ΔGox was lower in women with the classic than in those with the ovulatory phenotype. In multivariable analysis fat mass and free testosterone were independent predictors of ΔGox, Gnonox, and Δ% FFA, whereas only fat mass predicted ΔLox.
Conclusion: In women with PCOS, regardless of phenotype, insulin-mediated substrate use is impaired. This phenomenon is greater in individuals with the classic phenotype. Free testosterone plays an independent role in insulin action abnormalities in glucose and lipid metabolism.

Key Words: glucose oxidation, lipid oxidation, lipolysis, insulin sensitivity, PCOS phenotypes, androgens

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Insulin resistance is a common finding in women with polycystic ovary syndrome (PCOS). When evaluated by gold-standard methodologies, this metabolic abnormality affects about 70% to 75% of patients, involving the large majority of overweight-obese women and more than half of normal-weight women (1, 2).

By using the hyperinsulinemic euglycemic clamp, insulin action on glucose metabolism is directly measured as the amount of glucose metabolized by the whole body, with skeletal muscle being the predominant tissue in hyperinsulinemic conditions (3). Interestingly, when the clamp is combined with calorimetry, it is possible to estimate separately in vivo insulin action both on the oxidative (Gox) and nonoxidative (Gnonox) glucose metabolism, as well as on lipid oxidation (Lox) (4). Moreover, the assessment of serum free fatty acid (FFA), at baseline and during hyperinsulinemia, gives information on insulin inhibition of lipolysis, that is, on adipose tissue insulin resistance.

Available data on substrate use in women with PCOS are limited, and they mainly refer to obese individuals with both hyperandrogenism and oligoanovulation (ie, the classic phenotype of PCOS) (5, 6). A reduced insulin action in Gox, Lox, and Gnonox was found in some studies that included obese women with PCOS, compared with obese controls. However, conflicting results have been reported when both obese and lean participants were investigated (7-9). In these studies, the impairment of insulin action has been attributed either to obesity (8) or to PCOS status (9). It is noteworthy that other major clinical characteristics of these women, such as hyperandrogenemia, were generally not taken into account when analyzing these parameters.

Interestingly, divergence in whole-body glucose metabolism between the different phenotypes of PCOS has been documented and suggests that not all women with PCOS are exposed to the same metabolic risk (10). In particular, women with both hyperandrogenism and oligoanovulation (ie, with the classic phenotype of PCOS) showed a more severe insulin resistance on whole-body glucose use than women without oligoanovulation (the ovulatory phenotype) or without hyperandrogenism (the normoandrogenic phenotype).

To better define the metabolic risk of women with PCOS, it would be useful to assess insulin action on substrate use in women with different PCOS phenotypes. To the best of our knowledge, no data on this issue are available yet.

The aim of this study was to evaluate insulin action on Gox, Gnonox, Lox, as well as on serum FFA concentration in a well-characterized cohort of women with PCOS, including individuals with different phenotypes of the syndrome, and to establish the potential role of excess body fat and excess androgen in these alterations.

Materials and Methods

Participants

A total of 187 White women with PCOS with normal glucose tolerance were included in the present retrospective study. All were individuals who had undergone a hyperinsulinemic euglycemic clamp procedure associated with indirect calorimetry, and all were among the women recruited to the Verona PCOS Pathophysiology and Phenotype (Verona 3P) Study (10). All these women were referred to the outpatient clinic of the Division of Endocrinology, Diabetes and Metabolism of the Verona Hospital (Italy), for hirsutism and/or menstrual abnormalities. PCOS was diagnosed according to the Rotterdam workshop criteria, that is, the presence of at least 2 of the 3 following features: clinical and/or biochemical hyperandrogenism, chronic oligoanovulation, and polycystic ovarian morphology (PCOm), after exclusion of secondary causes (11). Clinical hyperandrogenism was defined by the presence of hirsutism (modified Ferriman-Gallwey score ≥ 8), and biochemical hyperandrogenism by increased free testosterone levels, according to the Androgen Excess and PCOS Society consensus statement on PCOS (12). Chronic oligoanovulation was diagnosed by the presence of either oligomenorrhea (≤ 8 cycles/year) or, in women with regular menses, by luteal-phase serum progesterone of less than 12 nmol/L during 2 consecutive menstrual cycles. PCOm was diagnosed according to the Rotterdam workshop recommendations (11), whenever possible by a transvaginal approach. To rule

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A high-androgen microenvironment inhibits granulosa cell proliferation and alters cell identity

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ABSTRACT

A naturally occurring bovine model with excess follicular fluid androstenedione (High A4), reduced fertility, and polycystic ovary syndrome (PCOS)-like characteristics has been identified. We hypothesized High A4 granulosa cells (GCs) would exhibit altered cell proliferation and/or steroidogenesis. Microarrays of Control and High A4 GCs combined with Ingenuity Pathway Analysis indicated that High A4 GCs had cell cycle inhibition and increased expression of microRNAs that inhibit cell cycle genes. Granulosa cell culture confirmed that A4 treatment decreased GC proliferation, increased anti-Müllerian hormone, and increased mRNA for *CTNNBIP1*. Increased *CTNNBIP1* prevents CTNNB1 from interacting with members of the WNT signaling pathway thereby inhibiting the cell cycle. Expression of CYP17A1 was upregulated in High A4 GCs presumably due to reduced FOS mRNA expression compared to Control granulosa cells. Furthermore, comparisons of High A4 GC with thecal and luteal cell transcriptomes indicated an altered cellular identity and function contributing to a PCOS-like phenotype.

1. Introduction

It is well established that high androgen concentrations, both circulating and within the ovary, are associated with ovarian dysfunction and systemic metabolic issues. Ovarian hyperandrogenism as seen with polycystic ovary syndrome (PCOS) causes symptoms such as hirsutism, anovulation, and metabolic dysfunction (which also compounds fertility problems) (Azziz et al., 2009; Hayek et al., 2016; Padwal, 2020; Rosenfield and Ehrmann, 2016). Other causes of hyperandrogenism such as congenital adrenal hyperplasia also result in reproductive disruptions (e.g. precocious puberty), virilization, and metabolic syndromes (Azziz et al., 2004; Hayek et al., 2016; Merke and Bornstein, 2005; Rosenfield and Ehrmann, 2016). Androgens affect many systems, including the hypothalamic-pituitary-gonadal axis. Disrupted regulation of gonadotropin releasing hormone and gonadotropins are sufficient to substantially impact fertility (Bateman and Patisaul, 2008; Dierich et al., 1998; Viau, 2002). There are also local effects of androgens on the follicular cells within the ovary. The theca cells of the follicle are

Abbreviations: A4, androstenedione; GCs, granulosa cells; IPA, Ingenuity Pathway Analysis; LLCs, large luteal cells; PCA, Principal Component Analysis; PCOS, Polycystic Ovary Syndrome; SLCs, small luteal cells; TCs, theca cells; AMH, Anti-Mullerian Hormone; CTNNB1, beta-catenin; CTNNBIP1, catenin beta interacting protein 1; WNT, wingless-type mouse mammary tumor virus integration site.

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Testosterone Enanthate/Norma®

Testosterone Enantate inj.sol. 250mg/ml

NORMA

Υψηλή Ποιότητα Ελέγχου

Testosterone Enanthate/Norma®

ΠΕΡΙΛΗΨΗ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ (SmPC)

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ

Testosterone Enanthate/Norma® ενέσιμο διάλυμα 250 mg/ml

2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ

Κάθε ml **Testosterone Enanthate/Norma®** (μία φύσιγγα) περιέχει 250 mg Ενανθικής Τεστοστερόνης (αντιστοιχεί περίπου σε 180 mg Τεστοστερόνης) σε ελαιώδες διάλυμα.
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.
– Ιστορικό 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 [δακτυλική διορθική 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 θρομβοφιλία, 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 ευγοναδικών επιπέδων τεστοστερόνης. Σε ασθενείς που λαμβάνουν μακροχρόνια θεραπεία με ανδρογόνα, οι ακόλουθες εργαστηριακές παράμετροι θα πρέπει επίσης να παρακολουθούνται τακτικά: αιμοσφαιρίνη και αιματοκρίτης, 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 ομοφωνία 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, δασυτριχισμός, 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 αυστηρώς 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 αναστρέψιμες. 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 χοληφόρων	Παθολογικός έλεγχος ηπατικής λειτουργίας, Ίκτερος
Διαταραχές του δέρματος και του υποδόριου 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 λίμπιντο, Μείωση της λίμπιντο, 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 σπερματογένεση αναστέλλεται 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 ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω του εθνικού συστήματος αναφοράς

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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®, κατατάσσεται στις 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 ATC: 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 ηπατικό 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 ένεση 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 εστερασών σε ελεύθερη τεστοστερόνη, η αξιολόγηση 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 μεταλλαξιογένεσης 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 ενδομυική 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 αντιτίθενται 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 25^{0} C. Να προφυλάσσεται από το φως.
Κάθε αχρησιμοποίητο 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»

Υψηλή Ποιότητα Ελέγχου

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ΑΝΔΡΙΚΗ ΑΝΑΠΑΡΑΓΩΓΗ

ΜΠΙΛΛΑ Θ. ΕΥΑΓΓΕΛΙΑ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ - ΚΛΙΝΙΚΟΣ ΑΝΔΡΟΛΟΓΟΣ (EAA cert)

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ORIGINAL ARTICLE

ANDROLOGY WILEY

The European Academy of Andrology (EAA) ultrasound study on healthy, fertile men: Scrotal ultrasound reference ranges and associations with clinical, seminal, and biochemical characteristics

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Abstract

Background: Scrotal color Doppler ultrasound (CDUS) still suffers from lack of standardization. Hence, the European Academy of Andrology (EAA) has promoted a multicenter study to assess the CDUS characteristics of healthy fertile men (HFM) to obtain normative parameters.

Objectives: To report and discuss the scrotal organs CDUS reference ranges and characteristics in HFM and their associations with clinical, seminal, and biochemical parameters.

Methods: A cohort of 248 HFM (35.3 ± 5.9years) was studied, evaluating, on the same day, clinical, biochemical, seminal, and scrotal CDUS following Standard Operating Procedures.

Results: The CDUS reference range and characteristics of the scrotal organs of HFM are reported here. CDUS showed a higher accuracy than physical examination in detecting scrotal abnormalities. Prader orchidometer (PO)- and US-measured testicular volume (TV) were closely related. The US-assessed TV with the ellipsoid formula showed the best correlation with the PO-TV. The mean TV of HFM was ~ 17 ml. The lowest reference limit for right and left testis was 12 and 11 ml, thresholds defining testicular hypotrophy. The highest reference limit for epididymal head, tail, and vas deferens was 12, 6, and 4.5 mm, respectively. Mean TV was associated positively with sperm concentration and total count and negatively with gonadotropins levels and pulse pressure. Subjects with testicular inhomogeneity or calcifications showed lower sperm vitality and concentration, respectively, than the rest of the sample. Sperm normal morphology and progressive motility were positively associated with epididymal head size/vascularization and vas deferens size, respectively. Increased epididymis and vas deferens sizes were associated with MAR test positivity. Decreased epididymal tail homogeneity/vascularization were positively associated with waistline, which was negatively associated with intratesticular vascularization. CDUS varicocele was detected in 37.2% of men and was not associated with seminal or hormonal parameters. Scrotal CDUS parameters were not associated with time to pregnancy, number of children, history of miscarriage.

Conclusions: The present findings will help in better understanding male infertility pathophysiology, improving its management.

KEYWORDS

healthy fertile men, scrotal ultrasound, scrotal organs reference ranges, scrotal organs normative parameters, clinical seminal hormonal and metabolic parameters

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1 | INTRODUCTION

One out of ten men of reproductive age suffers from fertility problems.[1-3] Despite many technical advances that have improved diagnostic skills, the causes of male infertility are still obscure in half of cases.[1,3,4] To fill this gap, in infertility clinics the imaging of the male genital tract (MGT) has been used more and more to detect MGT abnormalities.[4] Among imaging techniques, color Doppler ultrasound (CDUS) is the easiest to perform, less expensive, and time consuming, and is essentially free of side effects. CDUS is the gold standard for scrotal investigation, assessing reproductive-, inflammatory-, and oncological-related features.[4,5] In fact, scrotal CDUS can detect alterations in size, echotexture, and vascularization of the testis and epididymis that could eventually be associated with sperm abnormalities or inflammation (orchitis, epididymitis).[4,5] In particular, various testicular US parameters can be combined to predict sperm and testosterone levels impairment.[6] In addition, scrotal CDUS can detect lesions within the testis and epididymis suggesting benign or malignant findings.[4,5,7-11] Furthermore, scrotal CDUS provides information on epididymal and deferential abnormalities or agenesis, often correlated with obstructive infertility.[4,5] Finally, scrotal CDUS is able to detect and stage varicocele, which can exert a negative impact on sperm parameters.[4,5,7] Hence, scrotal CDUS has a relevant impact not only on reproductive but also on general male health, detecting abnormalities with a higher accuracy than physical examination[4] and, often, than other imaging techniques.[5]

Although CDUS is widely used to explore the MGT, there is still no consensus on the method to assess several qualitative and quantitative CDUS parameters.[4] In addition, in clinical practice, there are often operator-dependent differences among sonographers in assessing and interpreting CDUS parameters. Furthermore, MGT normative parameters and the cutoff for distinguishing normal and pathologic features are still lacking.[4] Finally, the possible correlation/impact of several CDUS findings on semen parameters and male fertility is still unclear.[4] The aforementioned critical issues exert either a scientific or a clinical practice negative impact, including low comparability and reproducibility of data among operators, and no evidence-based CDUS reports for patients, respectively. Due to the lack of MGT-CDUS standardization, the European Academy of Andrology (EAA) has promoted an international multicenter study entitled "Standardization of the MGT-CDUS parameters in healthy, fertile men" (shortened to "EAA ultrasound study"; see http://www.andrologyacademy.net/studies) [12] aimed at establishing a cohort of healthy, fertile men of reference to define MGT-CDUS normative parameters. In a previous study[13] on this cohort of 248 healthy, fertile men, we described: (a) the development and methodology of the "EAA ultrasound study," (ii) the clinical, seminal, and biochemical parameters of the cohort, and (iii) the correlations of both fertility history and seminal features with the aforementioned parameters. In particular, we reported that the seminal characteristics of the population studied were consistent with those reported by the WHO[14] for the 50th and 5th centile for fertile men. This finding identifies the EAA cohort as a reference population to assess MGT-CDUS normative parameters.[13]

In the present study, we report and discuss the scrotal organs reference ranges and characteristics in healthy, fertile men, and

Articles

Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial

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See Comment page 5

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Summary

Background Men who are overweight or obese frequently have low serum testosterone concentrations, which are associated with increased risk of type 2 diabetes. We aimed to determine whether testosterone treatment prevents progression to or reverses early type 2 diabetes, beyond the effects of a community-based lifestyle programme.

Methods T4DM was a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial done at six Australian tertiary care centres. Men aged 50–74 years, with a waist circumference of 95 cm or higher, a serum testosterone concentration of 14·0 nmol/L or lower but without pathological hypogonadism, and impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose 7·8–11·0 mmol/L) or newly diagnosed type 2 diabetes (provided OGTT 2-h glucose ≤15·0 mmol/L) were enrolled in a lifestyle programme and randomly assigned (1:1) to receive an intramuscular injection of testosterone undecanoate (1000 mg) or placebo at baseline, 6 weeks, and then every 3 months for 2 years. Randomisation was done centrally, including stratification by centre, age group, waist circumference, 2-h OGTT glucose, smoking, and first-degree family history of type 2 diabetes. The primary outcomes at 2 years were type 2 diabetes (2-h OGTT glucose ≥11·1 mmol/L) and mean change from baseline in 2-h OGTT glucose, assessed by intention to treat. For safety assessment, we did a masked monitoring of haematocrit and prostate-specific antigen, and analysed prespecified serious adverse events. This study is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12612000287831.

Findings Between Feb 5, 2013, and Feb 27, 2017, of 19 022 men who were pre-screened, 1007 (5%) were randomly assigned to the placebo (n=503) and testosterone (n=504) groups. At 2 years, 2-h glucose of 11·1 mmol/L or higher on OGTT was reported in 87 (21%) of 413 participants with available data in the placebo group and 55 (12%) of 443 participants in the testosterone group (relative risk 0·59, 95% CI 0·43 to 0·80; p=0·0007). The mean change from baseline 2-h glucose was –0·95 mmol/L (SD 2·78) in the placebo group and –1·70 mmol/L (SD 2·47) in the testosterone group (mean difference –0·75 mmol/L, –1·10 to –0·40; p<0·0001). The treatment effect was independent of baseline serum testosterone. A safety trigger for haematocrit greater than 54% occurred in six (1%) of 484 participants in the placebo group and 106 (22%) of 491 participants in the testosterone group, and a trigger for an increase of 0·75 µg/mL or more in prostate-specific antigen occurred in 87 (19%) of 468 participants in the placebo group and 109 (23%) of 480 participants in the testosterone group. Prespecified serious adverse events occurred in 37 (7·4%, 95% CI 5·4 to 10·0) of 503 patients in the placebo group and 55 (10·9%, 8·5 to 13·9) of 504 patients in the testosterone group. There were two deaths in each group.

Interpretation Testosterone treatment for 2 years reduced the proportion of participants with type 2 diabetes beyond the effects of a lifestyle programme. Increases in haematocrit might be treatment limiting. Longer-term durability, safety, and cardiovascular effects of the intervention remain to be further investigated.

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Introduction

Low serum testosterone concentrations, which are common in men who are overweight or obese, are associated with an increased risk of incident type 2 diabetes.[1] In an analysis of longitudinal data from the Florey Adelaide Male Ageing Study, incident diabetes was increased in men with a serum testosterone concentration of less than 16 nmol/L (461 ng/dL).[2] In a systematic review and meta-analysis,[3] men with a serum testosterone concentration greater than 15·5 nmol/L (447 ng/dL) had a

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Clinical Research Article

Clinical Research Article

Effect of Testosterone Treatment on Bone Microarchitecture and Bone Mineral Density in Men: A 2-Year RCT

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Abbreviations: aBMD, areal bone mineral density; BMD, bone mineral density;BV/TV, bone volume/tissue volume; CT, computed tomography; CTX, C-terminal type I collagen telopeptide; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; HA, hydroxyapatite; HR-pQCT, high resolution–peripheral quantitative computed tomography; LCMS/MS, liquid chromatography–tandem mass spectrometry; MAD, mean adjusted difference; P1NP, procollagen type 1 N-terminal propeptide; QCT, quantitative computed tomography; RCT, randomized controlled trial; T4Bone, a planned substudy of the T4DM trial; T4DM, Testosterone for Diabetes Mellitus trial; vBMD, volumetric bone mineral density.

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Abstract

Context: Testosterone treatment increases bone mineral density (BMD) in hypogonadal men. Effects on bone microarchitecture, a determinant of fracture risk, are unknown.

Objective: We aimed to determine the effect of testosterone treatment on bone microarchitecture using high resolution–peripheral quantitative computed tomography (HR-pQCT).

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Methods: Men ≥ 50 years of age were recruited from 6 Australian centers and were randomized to receive injectable testosterone undecanoate or placebo over 2 years on the background of a community-based lifestyle program. The primary endpoint was cortical volumetric BMD (vBMD) at the distal tibia, measured using HR-pQCT in 177 men (1 center). Secondary endpoints included other HR-pQCT parameters and bone remodeling markers. Areal BMD (aBMD) was measured by dual-energy x-ray absorptiometry (DXA) in 601 men (5 centers). Using a linear mixed model for repeated measures, the mean adjusted differences (95% CI) at 12 and 24 months between groups are reported as treatment effect.

Results: Over 24 months, testosterone treatment, versus placebo, increased tibial cortical vBMD, 9.33 mg hydroxyapatite (HA)/cm^3) (3.96, 14.71), $P < 0.001$ or 3.1% (1.2, 5.0); radial cortical vBMD, 8.96 mg HA/cm^3 (3.30, 14.62), $P = 0.005$ or 2.9% (1.0, 4.9); total tibial vBMD, 4.16 mg HA/cm^3 (2.14, 6.19), $P < 0.001$ or 1.3% (0.6, 1.9); and total radial vBMD, 4.42 mg HA/cm^3 (1.67, 7.16), $P = 0.002$ or 1.8% (0.4, 2.0). Testosterone also significantly increased cortical area and thickness at both sites. Effects on trabecular architecture were minor. Testosterone reduced bone remodeling markers CTX, −48.1 ng/L [−81.1, −15.1], $P < 0.001$ and P1NP, −6.8 μg/L[−10.9, −2.7], $P < 0.001$. Testosterone significantly increased aBMD at the lumbar spine, 0.04 g/cm^2 (0.03, 0.05), $P < 0.001$ and the total hip, 0.01 g/cm^2 (0.01, 0.02), $P < 0.001$.

Conclusion: In men ≥ 50 years of age, testosterone treatment for 2 years increased volumetric bone density, predominantly via effects on cortical bone. Implications for fracture risk reduction require further study.

Key Words: testosterone, bone, microarchitecture, T4DM

Pathological hypogonadism due to pituitary or testicular disease is a risk factor for osteoporosis in men (1) and testosterone replacement increases bone mineral density (BMD) (2). Observational studies in community dwelling men suggest that age-related reductions in circulating sex steroids are associated with loss of BMD (3) and increased fracture risk (4), effects which are reversed by testosterone treatment in randomized controlled clinical trials (RCT) (5-7). Such RCTs have utilized dual-energy x-ray absorptiometry (DXA) (5, 6), measuring areal BMD (aBMD), or more recently quantitative computed tomography (QCT) (7) measuring volumetric BMD (vBMD). Previous findings suggest that testosterone treatment increases BMD predominantly at the lumbar spine, inferring a predominant effect on trabecular bone (5-7).

Although QCT measures cortical and trabecular bone at central sites, it lacks sufficient resolution to provide information about microstructure. By contrast, high resolution–peripheral QCT (HR-pQCT) can distinguish cortical from trabecular bone with sufficiently high precision to accurately elucidate microarchitecture of cortical and trabecular structures (8) and predict fracture risk independent of aBMD and Fracture Risk Assessment Tool (FRAX) score (9). RCTs assessing the effects of testosterone treatment on bone microarchitecture defined by HR-pQCT in men are lacking. Therefore we conducted Testosterone for Bone (T4Bone), a planned substudy of Testosterone for Diabetes Mellitus (T4DM), a 2-year placebo-controlled RCT testing whether testosterone treatment reduces the incidence of type 2 diabetes mellitus (10, 11). In T4Bone we investigated the effects of testosterone treatment on vBMD and bone microarchitecture as well as on aBMD at the lumbar spine and proximal femur. As longitudinal studies report an association between lowered sex steroids and bone loss at cortical sites (12-14) and changes in cortical bone may be more closely associated with fracture risk (15-18), cortical vBMD at the tibia, a weight-bearing site, was chosen as the primary prespecified endpoint. Areal bone mineral density at lumbar spine was the main outcome of the second aim, the DXA study.

Methods

Study Design

T4DM was a randomized, placebo-controlled, double-blind, 2-year trial conducted in 6 Australian academic centers testing whether testosterone treatment prevents or reverses type 2 diabetes in high-risk men beyond the effects of a lifestyle program (10, 11). The T4Bone substudy assessed the effects of testosterone treatment on skeletal outcomes. Bone

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

Maternal occupational exposure to endocrine-disrupting chemicals during pregnancy and semen parameters in adulthood: results of a nationwide cross-sectional study among Swiss conscripts

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STUDY QUESTION: Is there a relationship between maternal occupational exposure to endocrine-disrupting chemicals (EDCs) during pregnancy and the semen quality of their sons?

SUMMARY ANSWER: Our results suggest an association between maternal occupational exposure to potential EDCs, especially to pesticides, phthalates and heavy metals, and a decrease in several semen parameters.

WHAT IS KNOWN ALREADY: Sexual differentiation, development and proper functioning of the reproductive system are largely dependent on steroid hormones. Although there is some animal evidence, studies on maternal exposure to EDCs during pregnancy and its effect on the semen quality of sons are scarce and none have focused on maternal occupational exposure.

STUDY DESIGN, SIZE, DURATION: A cross-sectional study aiming to evaluate semen quality was carried out among Swiss conscripts aged 18 to 22 years between 2005 and 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Conscript and parent questionnaires were completed prior to the collection of a semen sample. Semen parameters were categorised according to the guidelines of the World Health Organization (WHO). Data on maternal employment during pregnancy were provided by the parent questionnaire. Maternal occupational exposure to potential EDC categories was defined using a job-exposure matrix (JEM). Logistic regressions were used to analyse the relationship between maternal occupational exposure to EDCs and each semen parameter adjusted for potential confounding factors. Results are presented using odds ratios and 95% confidence intervals.

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 1,737 conscripts provided a conscript and parent questionnaire, as well as a semen sample; among these 1,045 of their mothers worked during pregnancy. Our study suggests an association between occupational exposure of mothers during pregnancy to potential EDCs and low semen volume and total sperm count, particularly for exposure to pesticides (OR 2.07, 95% CI 1.11–3.86 and OR 2.14, 95% CI 1.05–4.35), phthalates (OR 1.92, 95% CI 1.10–3.37 and OR 1.89, 95% CI 1.01–3.55), and heavy metals (OR 2.02, 95% CI 1.14–3.60 and OR 2.29, 95% CI 1.21–4.35). Maternal occupational exposure to heavy metals was additionally associated with a low sperm concentration (OR 1.89, 95% CI 1.06–3.37).

LIMITATIONS, REASONS FOR CAUTION: Several limitations should be noted, such as the indirect method for maternal occupational exposure assessment during the pregnancy (JEM) and the cross-sectional design of the study.

WIDER IMPLICATIONS OF THE FINDINGS: Our observations reinforce the need to inform pregnant women of potential hazards during pregnancy that could impair their child's fertility. Additional studies are needed to confirm the involvement of EDCs.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the Swiss Centre for Applied Human Toxicology: SCAHT and the 'Fondation privée des Hôpitaux Universitaires de Genève'. The collection of human biological material used for this study was supported by the FABER Foundation, the Swiss National Science Foundation (SNSF): NFP 50 'Endocrine Disruptors: Relevance to Humans, Animals and Ecosystems', the Medical Services of the Swiss Army (DDPS) and Medisupport. The authors declare they have no competing financial interests.

TRIAL REGISTRATION NUMBER: N/A

Key words: maternal exposure / endocrine disrupting / occupational exposure / semen parameters / male infertility

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Clinical Research Article

Clinical Research Article

Serum Testosterone is Inversely and Sex Hormone-binding Globulin is Directly Associated with All-cause Mortality in Men

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Abstract

Context: Serum testosterone concentrations decline with age, while serum sex hormone-binding globulin (SHBG) concentrations increase.

Objective: To analyze associations of baseline serum testosterone and SHBG concentrations, and calculated free testosterone (cFT) values, with all-cause and cause-specific mortality in men.

Design, Setting, and Participants: The UK Biobank prospective cohort study of community-dwelling men aged 40–69 years old, followed for 11 years.

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Main Outcome Measures: All-cause, atherosclerotic cardiovascular disease (CVD) and cancer-related mortality. Cox proportional hazards regression was performed, adjusting for age, waist circumference, medical conditions, and other covariates. Models for testosterone included SHBG and vice versa.

Results: In a complete case analysis of 149 436 men with 10 053 deaths (1925 CVD and 4927 cancer-related), men with lower testosterone had a higher mortality rate from any cause (lowest vs highest quintile, Q1 vs Q5, fully-adjusted hazard ratio [HR] = 1.14, 95% confidence interval [CI] = 1.06–1.22, overall trend $P < 0.001$), and cancer (HR = 1.20, CI = 1.09–1.33, $P < 0.001$), with no association for CVD deaths. Similar results were seen for cFT. Men with lower SHBG had a lower mortality rate from any cause (Q1 vs Q5, HR = 0.68, CI = 0.63–0.73, $P < 0.001$), CVD (HR = 0.70, CI = 0.59–0.83, $P < 0.001$), and cancer (HR = 0.80, CI = 0.72–0.89, $P < 0.001$). A multiply imputed dataset (N = 208 425, 15 914 deaths, 3128 CVD-related and 7468 cancer-related) and analysis excluding deaths within the first 2 years (9261, 1734, and 4534 events) yielded similar results.

Conclusions: Lower serum testosterone is independently associated with higher all-cause and cancer-related, but not CVD-related, mortality in middle-aged to older men. Lower SHBG is independently associated with lower all-cause, CVD-related, and cancer-related mortality. Confirmation and determination of causality requires mechanistic studies and prospective trials.

Freeform/Key Words: testosterone, sex hormone-binding globulin, mortality, cardiovascular disease, cancer

As men grow older, serum testosterone concentrations decline, while concentrations of its main binding protein, sex hormone-binding globulin (SHBG), increase (1). Obesity and medical comorbidities contribute to the decline in circulating testosterone (2, 3). Obesity, particularly central adiposity and insulin resistance, is associated with lower SHBG concentrations, and liver or thyroid disease are associated with higher SHBG concentrations (4, 5).

Previous studies have reported no associations of testosterone concentrations with mortality (6–10), or associated lower testosterone with higher all-cause mortality (11–17). Similarly, associations of testosterone concentrations with cardiovascular disease (CVD)-related deaths are inconsistent: some studies reported no associations (6, 8, 10, 13, 17, 18), while others reported inverse associations (11, 12, 14, 15, 19). Cancer is another major cause of death. Testosterone concentrations have been inversely associated with cancer mortality in some studies (11, 16), positively associated in one study (20), and not associated in other studies (12, 19). Several cohort studies have reported no association of SHBG concentrations with mortality, nor with deaths from CVD (6, 8, 17–19, 21). Other studies in middle-aged and older men (20, 22), and men with diabetes (23–25), associated higher SHBG concentrations with mortality. In addition to inconsistent results, the heterogeneity of these studies with respect to geography, participant selection, and covariates included in different analytical models adds further uncertainty to the findings.

To accommodate the relationship between serum testosterone and SHBG, free testosterone is commonly calculated from (total) testosterone and SHBG using formulae based on mass action equations (calculated free testosterone [cFT]) (26, 27). Some studies reported similar findings for cFT and (total) testosterone concentrations with respect to mortality in men (10, 16, 19), whereas some reported associations of low cFT but not (total) testosterone with all-cause (7, 9) or CVD-related mortality (20). Thus, studies of cFT and mortality risk in men have reported inconsistent results, and it remains unclear whether cFT offers additional information over testosterone alone for mortality-related outcomes.

A sufficiently large dataset with a correspondingly large number of outcome events would clarify the associations of serum testosterone and SHBG with mortality, enabling more precise estimates of effect sizes. Analysis of deaths from any cause, CVD, and those that are cancer-related could be performed. Associations of serum testosterone and SHBG with mortality outcomes could also be compared with associations of cFT. The UK Biobank, with a large number of men from a broadly based community-dwelling population who were prospectively followed for outcome events, is ideally suited to this purpose (28).

We aimed to elucidate the associations of circulating testosterone, SHBG, and cFT with overall mortality and CVD and cancer-related deaths in a large cohort of community-dwelling men aged 40–69 years from the UK

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GUIDELINES

WILEY

Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism

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Abstract

Male hypogonadism (MH) is a common endocrine disorder. However, uncertainties and variations in its diagnosis and management exist. There are several current guidelines on testosterone replacement therapy that have been driven predominantly by single disciplines. The Society for Endocrinology commissioned this new guideline to provide all care providers with a multidisciplinary approach to treating patients with MH. This guideline has been compiled using expertise from endocrine (medical and nursing), primary care, clinical biochemistry, urology and reproductive medicine practices. These guidelines also provide a patient perspective to help clinicians best manage MH.

KEYWORDS

diagnosis treatment and monitoring, guidance, male hypogonadism, sexual dysfunction, testis, testosterone

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ANDROLOGY WILEY

ORIGINAL ARTICLE

Risk of health status worsening in primary infertile men: A prospective 10-year follow-up study

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Abstract

Background: A severe male infertility factor has been associated with both lower health status and increased mortality in infertile men.

Objectives: To investigate reproductive factors associated with health status impairment in infertile men over a 10-year time frame since the first clinical evaluation.

Materials and methods: Data from 899 infertile men were analysed at baseline between 2003 and 2010. Health-significant comorbidities were scored with the Charlson Comorbidity Index. Patients were followed up yearly recording any worsening in their health status until 2019. Cox regression models were used to estimate hazard ratios and 95% confidence intervals of Charlson Comorbidity Index score increase.

Results: At a median follow-up of 136 months (Interquartile range: 121, 156), 85 men (9.5%) depicted an increase of their baseline Charlson Comorbidity Index score of at least one point. The most frequent reason for Charlson Comorbidity Index upgrade was cancer (34%), cardiovascular diseases (29%) and diabetes mellitus (22%). Compared to patients without a Charlson Comorbidity Index increase, patients with a Charlson Comorbidity Index increase presented with higher body mass index and follicle-stimulating hormone values, a higher rate of baseline Charlson Comorbidity Index ≥ 1 (all $p < 0.01$) and a greater proportion of non-obstructive azoospermia ($p < 0.001$). In the Cox regression model, the patient's BMI ($p < 0.001$), baseline Charlson Comorbidity Index ≥ 1 ($p < 0.01$) and azoospermia status ($p = 0.001$) were found to be independently associated with Charlson Comorbidity Index increases.

Conclusions: Almost 10% of men presenting for primary infertility had a decrease of the overall health status already in the relatively short 10-year time frame after the first presentation. Non-obstructive azoospermic men showed the worst health status impairment and should be strictly followed-up regardless of their fertility status.

KEYWORDS
comorbidities, follow-up, health, infertility, male, risk factor, spermatozoa

ASRM PAGES

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Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I

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Purpose: The summary presented herein represents Part I of the two-part series dedicated to the Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline. Part I outlines the appropriate evaluation of the male in an infertile couple. Recommendations proceed from obtaining an appropriate history and physical exam (Appendix I), as well as diagnostic testing, where indicated.

Materials/Methods: The Emergency Care Research Institute Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January, 2000 through May, 2019. When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions. (Table 1) This summary is being simultaneously published in Fertility and Sterility and The Journal of Urology.

Results: This Guideline provides updated, evidence-based recommendations regarding evaluation of male infertility as well as the association of male infertility with other important health conditions. The detection of male infertility increases the risk of subsequent development of health problems for men. In addition, specific medical conditions are associated with some causes for male infertility. Evaluation and treatment recommendations are summarized in the associated algorithm. (Figure 1)

Conclusion: The presence of male infertility is crucial to the health of patients and its effects must be considered for the welfare of society. This document will undergo updating as the knowledge regarding current treatments and future treatment options continues to expand. (Fertil Steril® 2021;115:54–61. ©2020 by American Urological Association Education and Research, Inc. and American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Keywords: Male infertility, evaluation, chemotherapy, surgery, health

BACKGROUND

The overall goal of the male evaluation is to identify conditions that may affect management or health of the patient or their offspring. The specific goals of the evaluation of the infertile male are to identify the following:

- potentially correctable conditions;
- irreversible conditions that are amenable to assisted reproductive technologies (ART)using the sperm of the male partner;
- irreversible conditions that are not amenable to the above, and for which donor insemination or adoption are possible options;
- life- or health-threatening conditions that may underlie the infertility or associated medical comorbidities that require medical attention; and
- genetic abnormalities or lifestyle and age factors that may affect the health of the male patient or of offspring particularly if ART are to be employed.

In this guideline, the term "male" or "men" is used to refer to biological or genetic men.

The complete unabridged version of the guideline is available at https://www.asrm.org/news-and-publications/practice-committee-documents/.

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GUIDELINE STATEMENTS

Assessment

1. For initial infertility evaluation, both male and female partners should undergo concurrent assessment. (Expert Opinion)
2. Initial evaluation of the male for fertility should include a reproductive history. (Clinical Principle) Initial evaluation of the male should also include one or more semen analyses (SAs). (Strong Recommendation; Evidence Level: Grade B)
3. Men with one or more abnormal semen parameters or presumed male infertility should be evaluated by a male reproductive expert for complete history and physical examination as well as other directed tests when indicated. (Expert Opinion)

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Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II

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Purpose: The summary presented herein represents Part II of the two-part series dedicated to the Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline. Part II outlines the appropriate management of the male in an infertile couple. Medical therapies, surgical techniques, as well as use of intrauterine insemination (IUI)/in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) are covered to allow for optimal patient management. Please refer to Part I for discussion on evaluation of the infertile male and discussion of relevant health conditions that are associated with male infertility.

Materials/Methods: The Emergency Care Research Institute Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January 2000 through May 2019. When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions. (Table 1) This summary is being simultaneously published in Fertility and Sterility and The Journal of Urology.

Results: This Guideline provides updated, evidence-based recommendations regarding management of male infertility. Such recommendations are summarized in the associated algorithm. (Figure 1)

Conclusion: Male contributions to infertility are prevalent, and specific treatment as well as assisted reproductive techniques are effective at managing male infertility. This document will undergo additional literature reviews and updating as the knowledge regarding current treatments and future treatment options continues to expand. (Fertil Steril® 2021;115:62–9. ©2020 by American Urological Association Education and Research, Inc. and American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Keywords: Male infertility, evaluation, chemotherapy, surgery, health

BACKGROUND

Failure to conceive within 12 months of attempted conception is due in whole or in part to the male in approximately one-half of all infertile couples. Although many couples can achieve a pregnancy with assisted reproductive technologies (ART), evaluation of the male is important to identify conditions that may be medically important, counsel men regarding future health considerations and to most appropriately direct therapy. Most male factor conditions are specifically treatable with medical or surgical therapy, while others may only be managed with donor sperm or adoption.

In this guideline, the term "male" or "men" is used to refer to biological or genetic men.

Treatment

Varicocele Repair/Varicocelectomy.

25. Surgical varicocelectomy should be considered in men attempting to conceive, who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level: Grade B)
26. Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level: Grade C)
27. For men with clinical varicocele and non-obstructive azoospermia (NOA), couples should be informed of the absence of definitive evidence supporting varicocele repair prior to ART. (Expert Opinion)

Varicoceles have long been recognized as a condition that can affect male fertility, where correction of a clinical varicocele can result in substantial improvements in semen parameters and the chance of achieving a pregnancy. The largest most recent meta-analysis by Wang et al. reported significantly higher pregnancy rates

The complete unabridged version of the guideline is available at https://www.asrm.org/news-and-publications/practice-committee-documents/.

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European Association of Urology

Review – Andrology

European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update: Male Sexual Dysfunction

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Abstract

Context: The present summary of the European Association of Urology (EAU) guidelines is based on the latest guidelines on male sexual health published in March 2021, with a last comprehensive update in January 2021.
Objective: To present a summary of the 2021 version of the EAU guidelines on sexual and reproductive health.
Evidence acquisition: A literature review was performed up to January 2021. The guidelines were updated, and a strength rating for each recommendation was included based on either a systematic review of the evidence or a consensus opinion from the expert panel.
Evidence synthesis: Late-onset hypogonadism is a clinical condition in the ageing male combining low levels of circulating testosterone and specific symptoms associated with impaired hormone production and/or action. A comprehensive diagnostic and therapeutic work-up, along with screening recommendations and contraindications, is provided. Erectile dysfunction (ED) is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Along with a detailed basic and advanced diagnostic approach, a novel decision-making algorithm for treating ED in order to better tailor therapy to individual patients is provided. The EAU guidelines have adopted the definition of premature ejaculation (PE), which has been developed by the International Society for Sexual Medicine. After the subtype of PE has been defined, patient's expectations should be discussed thoroughly and pharmacotherapy must be considered as the first-line treatment for patients with lifelong PE, whereas treating the underlying cause must be the initial goal for patients with acquired PE. Haemospermia is defined as the appearance of blood in the ejaculate. Several reasons of haemospermia have been acknowledged; the primary goal over the management work-up is to exclude malignant conditions and treat any other underlying cause.
Conclusions: The 2021 guidelines on sexual and reproductive health summarise the most recent findings, and advise in terms of diagnosis and treatment of male hypogonadism and sexual dysfunction for their use in clinical practice. These guidelines reflect the multidisciplinary nature of their management.
Patient summary: Updated European Association of Urology guidelines on sexual and reproductive health are presented, addressing the diagnosis and treatment of the most prevalent conditions in men. Patients must be fully informed of all relevant diagnostic and therapeutic options and, together with their treating physicians, decide on optimal personalised management strategies.

1. Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on male sexual health were published in 2010 [1] and 2012 [2]. The present summary is based on the latest guidelines published in March 2021 [3], with the last comprehensive update in January 2021. The 2021 version of the EAU guideline document is a further comprehensive update of the 2020 guidelines, which already includes an update of the 2018 versions of male sexual dysfunction, Male infertility, and male hypogonadism, along with several new topics. It must be emphasised that guidelines present the best evidence available to the experts, who have participated fully in the evaluation of all the material revised systematically for individual chapters.

This article summarises the EAU guideline recommendations on male sexual health management (namely, late-onset hypogonadism [LOH], erectile dysfunction [ED], premature ejaculation [PE], and recurrent haemospermia). The panel presents a summary of these latter conditions because of their epidemiological importance, and a number of innovative updates in terms of their management and their relevance to men's health. Moreover, the full text on male sexual health management can be found in the EAU guideline textbook and at uroweb.org [3].

2. Evidence acquisition

The panel performed a broad and comprehensive literature search, covering all sections of the guidelines. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2013 and 2020 and restricted to English-language publications.

A strength rating has been provided for each recommendation according to the EAU Guideline Office methodology (modified from the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology) [4].

3. Evidence synthesis

3.1. *Male hypogonadism*

3.1.1. *Definition and epidemiology*

Male hypogonadism is a disorder associated with decreased functional activity of the testes, with decreased production and/or action of androgens and/or impaired sperm production [5]. This is caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary-gonadal (HPG) axis. Likewise, several congenital or acquired disorders causing impaired action of androgens have also been described [5].

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Clinical Research Article

Clinical Research Article

Aging Men With Insufficient Vitamin D Have a Higher Mortality Risk: No Added Value of its Free Fractions or Active Form

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Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, total 25-hydroxyvitamin D; BMI, body mass index; DBP, vitamin D binding protein; ELISA, enzyme-linked immunosorbent assay; EMAS, European Male Ageing Study; HR, hazard ratio; NIST, National Institute of Standards and Technology; PASE, Physical Activity Scale for the Elderly; PTH, parathyroid hormone; VDSP, Vitamin D Standardization Program.

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Abstract

Context: Low total 25-hydroxyvitamin D (25(OH)D) has been associated with mortality. Whether vitamin D in its free form or 1,25-dihydroxyvitamin D (1,25(OH)$_2$D), provide any additional information is unclear.

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Review

Review

Androgen Misuse and Abuse

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Abstract

Androgens are potent drugs requiring prescription for valid medical indications but are misused for invalid, unproven, or off-label reasons as well as being abused without prescription for illicit nonmedical application for performance or image enhancement. Following discovery and first clinical application of testosterone in the 1930s, commercialization of testosterone and synthetic androgens proliferated in the decades after World War II. It remains among the oldest marketed drugs in therapeutic use, yet after 8 decades of clinical use, the sole unequivocal indication for testosterone remains in replacement therapy for pathological hypogonadism, organic disorders of the male reproductive system. Nevertheless, wider claims assert unproven, unsafe, or implausible benefits for testosterone, mostly representing wishful thinking about rejuvenation. Over recent decades, this created an epidemic of testosterone misuse involving prescription as a revitalizing tonic for anti-aging, sexual dysfunction and/or obesity, where efficacy and safety remains unproven and doubtful. Androgen abuse originated during the Cold War as an epidemic of androgen doping among elite athletes for performance enhancement before the 1980s when it crossed over into the general community to become an endemic variant of drug abuse in sufficiently affluent communities that support an illicit drug industry geared to bodybuilding and aiming to create a hypermasculine body physique and image. This review focuses on the misuse of testosterone, defined as prescribing without valid clinical indications, and abuse of testosterone or synthetic androgens (androgen abuse), defined as the illicit use of androgens without prescription or valid indications, typically by athletes, bodybuilders and others for image-oriented, cosmetic, or occupational reasons.

Key Words: androgen, aging, testosterone, synthetic androgens, SARMs, anabolic steroid, drug abuse

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ORIGINAL ARTICLE

ANDROLOGY WILEY

Distribution of semen examination results 2020 – A follow up of data collated for the WHO semen analysis manual 2010

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Abstract

Background: It is now 11 years since publication of the WHO 2010 guidelines for semen assessment values, and it is critical to determine whether they are still valid and/or whether they should be modified.

Objectives: To utilise data published since 2010 and combine these with data used in the 2010 assessment to provide an updated and more comprehensive representation of the fertile man. This may be utilised to present an updated distribution of values for use by WHO in 2021.

Materials and Methods: Two specific analyses were performed namely, (1) Analysis 1: Examination of published data following publication of WHO 2010 [termed 2010–2020 data]. (2) Analysis 2: Examination of the data used to help formulate the 2010 distribution of values combined with the data from Analysis (1) [termed WHO 2020].

Results: In total, data from more than 3500 subjects, from twelve countries and five continents were analysed. The 5th centile values for concentration, motility and morphology are: 16 × 10^6/ml, 30% progressive motility [42% total motility] and 4% normal forms.

Discussion: This study presents substantial additional information to establish more comprehensive and globally applicable lower reference values for semen parameters for fertile men although they do not represent distinct limits between fertile and subfertile men. There are still data missing from many countries and, some geographical regions are not represented. Moreover, the number of subjects although significant is still relatively low (<4000).

Conclusion: These distributions of values now include semen analysis providing a more global representation of the fertile man. Increasing the number of subjects provides robust information that is also more geographically representative.

KEYWORDS
semen analysis, WHO, reference values, fertile man

[Correction added on XX April 2021, after first online publication: the funding information has been updated in this version].

ORIGINAL ARTICLES: ANDROLOGY

Check for updates

Effect of varicocelectomy on sperm deoxyribonucleic acid fragmentation rates in infertile men with clinical varicocele: a systematic review and meta-analysis

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Objective: To evaluate the effect of varicocelectomy on sperm deoxyribonucleic acid fragmentation (SDF) rates in infertile men with clinical varicocele.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Infertile men with clinical varicocele subjected to varicocelectomy.
Intervention(s): Systematic search using PubMed/Medline, EMBASE, Cochrane's central database, Scielo, and Google Scholar to identify relevant studies published from inception until January 2021. We included studies comparing SDF rates before and after varicocelectomy in infertile men with clinical varicocele.
Main Outcome Measure(s): The primary outcome was the difference between the SDF rates before and after varicocelectomy. A meta-analysis of weighted data using random-effects models was performed. Results were reported as weighted mean differences (WMD) with 95% confidence intervals (CIs). Subgroup analyses were performed on the basis of the SDF assay, varicocelectomy technique, preoperative SDF levels, varicocele grade, follow-up time, and study design.
Result(s): Nineteen studies involving 1,070 patients provided SDF data. Varicocelectomy was associated with reduced postoperative SDF rates (WMD −7.23%; 95% CI: −8.86 to −5.59; $I^2 = 91\%$). The treatment effect size was moderate (Cohen's d = 0.68; 95% CI: 0.77 to 0.60). The pooled results were consistent for studies using sperm chromatin structure assay, terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling, sperm chromatin dispersion test, and microsurgical varicocele repair. Subgroup analyses showed that the treatment effect was more pronounced in men with elevated vs. normal preoperative SDF levels, but the impact of varicocele grade remained equivocal. Meta-regression analysis demonstrated that SDF decreased after varicocelectomy as a function of preoperative SDF levels (coefficient: 0.23; 95% CI: 0.07 to 0.39).
Conclusion(s): We concluded that pooled results from studies including infertile men with clinical varicocele indicated that varicocelectomy reduced the SDF rates. The treatment effect was greater in men with elevated (vs. normal) preoperative SDF levels. Further research is required to determine the full clinical implications of SDF reduction for these men. (Fertil Steril® 2021;116:696-712. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Male infertility, oxidative stress, semen, sperm DNA fragmentation, varicocele

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RANKL regulates male reproductive function

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Infertile men have few treatment options. Here, we demonstrate that the transmembrane receptor activator of NF-kB ligand (RANKL) signaling system is active in mouse and human testis. RANKL is highly expressed in Sertoli cells and signals through RANK, expressed in most germ cells, whereas the RANKL-inhibitor osteoprotegerin (OPG) is expressed in germ and peritubular cells. OPG treatment increases wild-type mouse sperm counts, and mice with global or Sertoli-specific genetic suppression of Rankl have increased male fertility and sperm counts. Moreover, RANKL levels in seminal fluid are high and distinguishes normal from infertile men with higher specificity than total sperm count. In infertile men, one dose of Denosumab decreases RANKL seminal fluid concentration and increases serum Inhibin-B and anti-Müllerian-hormone levels, but semen quality only in a subgroup. This translational study suggests that RANKL is a regulator of male reproductive function, however, predictive biomarkers for treatment-outcome requires further investigation in placebo-controlled studies.

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ΕΝΔΟΚΡΙΝΟΛΟΓΙΑ - ΔΙΑΒΗΤΟΛΟΓΙΑ - ΜΕΤΑΒΟΛΙΣΜΟΣ ενδοραμα'21

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Clinical Research Article

Clinical Research Article

Serum Insulin-like Factor 3 Levels Are Reduced in Former Androgen Users, Suggesting Impaired Leydig Cell Capacity

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Abbreviations: AAS, anabolic androgenic steroids; hCG, human chorionic gonadotropin; INSL3, insulin-like factor 3; LH, luteinizing hormone; RXFP2, relaxin family peptide receptor 2; SHBG, sex hormone–binding globulin; TT, total testosterone.

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Abstract

Context: Illicit use of anabolic androgenic steroids (AAS) is frequently observed in men and is associated with subsequent testosterone deficiency although the long-term effect on gonadal function is still unclear. Serum insulin-like factor 3 (INSL3) has been suggested to be a superior biomarker of Leydig cell secretory capacity compared to testosterone.

Objective: This study aimed to investigate serum INSL3 concentrations in AAS users.

Methods: This community-based, cross-sectional study included men aged 18 to 50 years, involved in recreational strength training and allocated to 1 of 3 groups: never-AAS users as controls (n = 44), current (n = 46), or former AAS users (n = 42) with an average duration since AAS cessation of 32 (23 ; 45) months.

Results: Serum INSL3 was lower in current AAS users and former AAS users than in controls, median (interquartile range), 0.04 μg/L (nondetectable [ND]-0.07 μg/L) and 0.39 μg/L (0.24-0.62 μg/L) vs 0.59 μg/L (0.45-0.72 μg/L), *P* less than .001. Former AAS users exhibited lower serum INSL3 levels than controls in a multivariable linear regression even after adjusting for serum total testosterone (TT) and other relevant confounders, (B) (95% CI), –0.16 μg/L (95% CI, –0.29 to –0.04 μg/L), *P* equal to .011. INSL3 and TT were not associated in the model, *P* equal to .821. Longer accumulated AAS duration (log2)

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Review

Review

Androgen Misuse and Abuse

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Abstract

Androgens are potent drugs requiring prescription for valid medical indications but are misused for invalid, unproven, or off-label reasons as well as being abused without prescription for illicit nonmedical application for performance or image enhancement. Following discovery and first clinical application of testosterone in the 1930s, commercialization of testosterone and synthetic androgens proliferated in the decades after World War II. It remains among the oldest marketed drugs in therapeutic use, yet after 8 decades of clinical use, the sole unequivocal indication for testosterone remains in replacement therapy for pathological hypogonadism, organic disorders of the male reproductive system. Nevertheless, wider claims assert unproven, unsafe, or implausible benefits for testosterone, mostly representing wishful thinking about rejuvenation. Over recent decades, this created an epidemic of testosterone misuse involving prescription as a revitalizing tonic for anti-aging, sexual dysfunction and/or obesity, where efficacy and safety remains unproven and doubtful. Androgen abuse originated during the Cold War as an epidemic of androgen doping among elite athletes for performance enhancement before the 1980s when it crossed over into the general community to become an endemic variant of drug abuse in sufficiently affluent communities that support an illicit drug industry geared to bodybuilding and aiming to create a hypermasculine body physique and image. This review focuses on the misuse of testosterone, defined as prescribing without valid clinical indications, and abuse of testosterone or synthetic androgens (androgen abuse), defined as the illicit use of androgens without prescription or valid indications, typically by athletes, bodybuilders and others for image-oriented, cosmetic, or occupational reasons.

Key Words: androgen, aging, testosterone, synthetic androgens, SARMs, anabolic steroid, drug abuse

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

Maternal occupational exposure to endocrine-disrupting chemicals during pregnancy and semen parameters in adulthood: results of a nationwide cross-sectional study among Swiss conscripts

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STUDY QUESTION: Is there a relationship between maternal occupational exposure to endocrine-disrupting chemicals (EDCs) during pregnancy and the semen quality of their sons?

SUMMARY ANSWER: Our results suggest an association between maternal occupational exposure to potential EDCs, especially to pesticides, phthalates and heavy metals, and a decrease in several semen parameters.

WHAT IS KNOWN ALREADY: Sexual differentiation, development and proper functioning of the reproductive system are largely dependent on steroid hormones. Although there is some animal evidence, studies on maternal exposure to EDCs during pregnancy and its effect on the semen quality of sons are scarce and none have focused on maternal occupational exposure.

STUDY DESIGN, SIZE, DURATION: A cross-sectional study aiming to evaluate semen quality was carried out among Swiss conscripts aged 18 to 22 years between 2005 and 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Conscript and parent questionnaires were completed prior to the collection of a semen sample. Semen parameters were categorised according to the guidelines of the World Health Organization (WHO). Data on maternal employment during pregnancy were provided by the parent questionnaire. Maternal occupational exposure to potential EDC categories was defined using a job-exposure matrix (JEM). Logistic regressions were used to analyse the relationship between maternal occupational exposure to EDCs and each semen parameter adjusted for potential confounding factors. Results are presented using odds ratios and 95% confidence intervals.

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 1,737 conscripts provided a conscript and parent questionnaire, as well as a semen sample; among these 1,045 of their mothers worked during pregnancy. Our study suggests an association between occupational exposure of mothers during pregnancy to potential EDCs and low semen volume and total sperm count, particularly for exposure to pesticides (OR 2.07, 95% CI 1.11–3.86 and OR 2.14, 95% CI 1.05–4.35), phthalates (OR 1.92, 95% CI 1.10–3.37 and OR 1.89, 95% CI 1.01–3.55), and heavy metals (OR 2.02, 95% CI 1.14–3.60 and OR 2.29, 95% CI 1.21–4.35). Maternal occupational exposure to heavy metals was additionally associated with a low sperm concentration (OR 1.89, 95% CI 1.06–3.37).

LIMITATIONS, REASONS FOR CAUTION: Several limitations should be noted, such as the indirect method for maternal occupational exposure assessment during the pregnancy (JEM) and the cross-sectional design of the study.

WIDER IMPLICATIONS OF THE FINDINGS: Our observations reinforce the need to inform pregnant women of potential hazards during pregnancy that could impair their child's fertility. Additional studies are needed to confirm the involvement of EDCs.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the Swiss Centre for Applied Human Toxicology: SCAHT and the 'Fondation privée des Hôpitaux Universitaires de Genève'. The collection of human biological material used for this study was supported by the FABER Foundation, the Swiss National Science Foundation (SNSF): NFP 50 'Endocrine Disruptors: Relevance to Humans, Animals and Ecosystems', the Medical Services of the Swiss Army (DDPS) and Medisupport. The authors declare they have no competing financial interests.

TRIAL REGISTRATION NUMBER: N/A

Key words: maternal exposure / endocrine disrupting / occupational exposure / semen parameters / male infertility

Introduction

Humans are exposed to numerous environmental agents that can be harmful for their reproductive capacity. In particular, male reproductive function is known to be highly sensitive to a number of chemical compounds generated by industrial and agricultural activities (Bonde *et al.*, 1996; Spira and Multigner, 1998). There is convincing evidence that exposure to chemical agents present in certain occupational activities and environments during adulthood can affect testicular function and male fertility (De Fleurian *et al.*, 2009; Wang *et al.*, 2016; Sifakis *et al.*, 2017; Radke *et al.*, 2018). Furthermore, exposure during antenatal development is suspected to influence male reproductive health later in life, including fertility (Guo *et al.*, 2000; Charlier and Foidart, 2005; Mocarelli *et al.*, 2011; Axelsson *et al.*, 2015; Ho *et al.*, 2017; Hart *et al.*, 2018a).

Sexual development and proper functioning of the reproductive system are largely dependent on steroid hormones. It has been suggested that developmental exposure to chemicals with hormonal properties, also called endocrine-disrupting chemicals (EDCs), particularly those that mimic steroid sex hormones, alter the endocrine system and can lead to reproductive dysfunction in adulthood (Sharpe and Skakkebaek, 1993).

Numerous animal studies have shown that gestational exposure to selected EDCs may influence male reproductive-tract development, including that of the testis as well as sperm production and quality in adulthood (Sharpe, 2001; Ho *et al.*, 2017). However, human studies are scarce (Bonde *et al.*, 2016). Most available studies in humans have focused on individual chemical agents, based on samples of limited size, and have reported inconsistent results. Although several studies have reported reduced sperm parameters (number, motility and morphology) or reduced fecundity in men born to mothers who took diethylstilbestrol during pregnancy, others have not (Giusti *et al.*, 1995; Ho *et al.*, 2017). Maternal exposure to the industrial by-products polychlorinated bipehnyls (PCBs) during pregnancy was shown to be associated with impaired sperm motility and morphology in the context of the ingestion of contaminated oil in food (Guo *et al.*, 2000) but this association was not observed in young Danish men prenatally exposed to background levels (Vested *et al.*, 2014). Charlier and Foidart (Charlier and Foidart, 2005) reported higher maternal levels of p, p'-dichlorodiphenyldichloroethylene (DDE, the main persistent metabolite of the insecticide dichlorodiphenyltrichloroethane, DDT) in 19 subfertile men relative to 23 fertile men at the time of semen analysis in a small case-control study. However, in a Danish population-based pregnancy cohort, maternal levels of p'p'-DDE and PCBs during pregnancy were not associated with later semen quality in 166 sons in early adult life (Vested *et al.*, 2014). Exposure to heptachlor epoxide during pregnancy following milk contamination in Hawaii was also not associated with semen parameters of 216 young men (Luderer *et al.*, 2013). Two mother–child cohorts have studied maternal exposure to phthalates during pregnancy and semen parameters in adulthood. One was conducted in Sweden on 112 conscripts and showed an association between maternal concentrations of two phthalate metabolites, mono-carboxy-iso-octyl phthalate (MCiOP) and mono-(2-ethyl-5-hydroxylhexyl) phthalateand low semen volume (Axelsson *et al.*, 2015). The second focused on 111 men from the Raine Australian pregnancy cohort and found an association between mono-ethyl phthalateand low semen volume and between MCiOP and lowsperm motility (Hart *et al.*, 2018b). Finally, maternal exposure to bisphenol A (BPA) during pregnancy has been shown to positively but marginally correlate with sperm concentration and sperm motility in young men (Hart *et al.*, 2018a). The overall inconsistency of these results may be explained by different levels of exposure between studies and potential residual confounding and exposure measurement error, particularly for non-persistent chemicals, such as phthalates and BPA, for which exposure was determined using only one or two measurements.

None of the above studies have examined occupational exposure to EDCs during pregnancy, a situation in which exposure is likely greater than that for the general population. Here, we sought to assess whether occupational exposure during pregnancy to potential EDCs, according to the classification and job-exposure matrix (JEM) developed by Van Tongeren *et al.* (2002) and expanded by Brouwers *et al.* (2009), could be associated with semen quality in young adult men.

Materials and methods

Study population

This cross-sectional study took place in Switzerland, where the military draft system requires that more than 97% of all young men aged between 18 and 22 years attend a 2- to 3-day military camp to undergo a medical examination for determination of their fitness for military service. Young men with a serious chronic disease or physical or mental disability were excluded from the study. Between 2005 and 2017, conscripts of all recruitment centres, covering all 26 cantons (member states of the Swiss confederation) located in Lausanne (Vaud), Rüti (Zürich), Windisch (Aargau), Monteceneri (Ticino), Sumiswald (Bern) and Mels (St-Gallen), were sequentially invited to participate in this

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ARTICLE

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RANKL regulates male reproductive function

Martin Blomberg Jensen[1,2✉], Christine Hjorth Andreassen[1,7], Anne Jørgensen[3,7], John Erik Nielsen[3], Li Juel Mortensen[1,2], Ida Marie Boisen[1,2], Peter Schwarz[4,5], Jorma Toppari[6], Roland Baron[2], Beate Lanske[2] & Anders Juul[3,5]

Infertile men have few treatment options. Here, we demonstrate that the transmembrane receptor activator of NF-kB ligand (RANKL) signaling system is active in mouse and human testis. RANKL is highly expressed in Sertoli cells and signals through RANK, expressed in most germ cells, whereas the RANKL-inhibitor osteoprotegerin (OPG) is expressed in germ and peritubular cells. OPG treatment increases wild-type mouse sperm counts, and mice with global or Sertoli-specific genetic suppression of Rankl have increased male fertility and sperm counts. Moreover, RANKL levels in seminal fluid are high and distinguishes normal from infertile men with higher specificity than total sperm count. In infertile men, one dose of Denosumab decreases RANKL seminal fluid concentration and increases serum Inhibin-B and anti-Müllerian-hormone levels, but semen quality only in a subgroup. This translational study suggests that RANKL is a regulator of male reproductive function, however, predictive biomarkers for treatment-outcome requires further investigation in placebo-controlled studies.

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ΥΠΟΦΥΣΗ

ΓΕΩΡΓΙΑ ΝΤΑΛΗ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ ΕΠΙΜΕΛΗΤΡΙΑ Α,
ΕΝΔΟΚΡΙΝΟΛΟΓΙΚΟ ΤΜΗΜΑ, ΔΙΑΒΗΤΟΛΟΓΙΚΟ ΚΕΝΤΡΟ,
ΚΕΝΤΡΟ ΕΜΠΕΙΡΟΓΝΩΜΟΣΥΝΗΣ ΣΠΑΝΙΩΝ ΕΝΔΟΚΡΙΝΟΛΟΓΙΚΩΝ ΝΟΣΗΜΑΤΩΝ ΓΝΑ
«Ο ΕΥΑΓΓΕΛΙΣΜΟΣ ΟΦΘΑΛΜΙΑΤΡΕΙΟ-ΠΟΛΥΚΛΙΝΙΚΗ»

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Reports and Recommendations

Reports and Recommendations

Pituitary Neoplasm Nomenclature Workshop: Does Adenoma Stand the Test of Time?

Ken Ho,[1] Maria Fleseriu,[2] Ursula Kaiser,[3] Roberto Salvatori,[4] Thierry Brue,[5] M. Beatriz Lopes,[6] Pamela Kunz,[7] Mark Molitch,[8] Sally A. Camper,[9] Mônica Gadelha,[10] Luis V. Syro,[11] Edward Laws,[3] Martin Reincke,[12] Hiroshi Nishioka,[13] Ashley Grossman,[14] Ariel Barkan,[9] Felipe Casanueva,[15] John Wass,[16] Adam Mamelak,[17] Laurence Katznelson,[18] Aart J. van der Lely,[19] Sally Radovick,[20] Martin Bidlingmaier,[12] Margaret Boguszewski,[21] Jens Bollerslev,[22] Andrew R. Hoffman,[18] Nelson Oyesiku,[23] Gerald Raverot,[24] Anat Ben-Shlomo,[17] Rob Fowkes,[25] Ilan Shimon,[26] Hidenori Fukuoka,[27] Alberto M. Pereira,[28] Yona Greenman,[29] Anthony P. Heaney,[30] Mark Gurnell,[31] Gudmundur Johannsson,[32] Robert Y. Osamura,[33] Michael Buchfelder,[34] Maria Chiara Zatelli,[35] Marta Korbonits,[36] Philippe Chanson,[37] Nienke Biermasz,[28] David R. Clemmons,[38] Niki Karavitaki,[39] Marcello D. Bronstein,[40] Peter Trainer,[41] and Shlomo Melmed[17]

Abstract

The *WHO Classification of Endocrine Tumours* designates pituitary neoplasms as adenomas. A proposed nomenclature change to pituitary neuroendocrine tumors (PitNETs) has been met with concern by some stakeholder groups. The Pituitary Society coordinated the Pituitary Neoplasm Nomenclature (PANOMEN) workshop to address the topic. Experts in pituitary developmental biology, pathology, neurosurgery, endocrinology, and oncology, including representatives nominated by the Endocrine Society, European Society of Endocrinology, European Neuroendocrine Association, Growth Hormone Research Society, and International Society of Pituitary Surgeons. Clinical epidemiology, disease phenotype, management, and prognosis of pituitary adenomas differ from that of most NETs. The vast majority of pituitary adenomas are benign and do not adversely impact life expectancy. A nomenclature change to PitNET does not address the main challenge of prognostic prediction, assigns an uncertain malignancy designation to benign pituitary adenomas, and may adversely affect patients. Due to pandemic restrictions, the workshop was conducted virtually, with audiovisual lectures and written précis on each topic provided to all participants. Feedback was collated and summarized by Content Chairs and discussed during a virtual writing meeting moderated by Session Chairs, which yielded an evidence-based draft document sent to all participants for review and approval. There is not yet a case for adopting the PitNET nomenclature. The PANOMEN Workshop recommends that the term adenoma be retained and that the topic be revisited as new evidence on pituitary neoplasm biology emerges.

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A Pituitary Society update to acromegaly management guidelines

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Abstract

Guidelines and consensus statements ensure that physicians managing acromegaly patients have access to current information on evidence-based treatments to optimize outcomes. Given significant novel recent advances in understanding acromegaly natural history and individualized therapies, the Pituitary Society invited acromegaly experts to critically review the current literature in the context of Endocrine Society guidelines and Acromegaly Consensus Group statements. This update focuses on how recent key advances affect treatment decision-making and outcomes, and also highlights the likely role of recently FDA-approved therapies as well as novel combination therapies within the treatment armamentarium.

Table 1 Presentation, monitoring, and outcomes: summary points

Presentation, comorbidities, and mortality

Although men present at a younger age than do women, women may show both increased incidence and mortality risk. (MQ, DR)
Biochemical control remains the strongest predictor of patient outcomes, reflecting improvements in glucose metabolism, OSA, cardiovascular disease, and VFs. However, structural heart and joint changes are unlikely to resolve. (MQ, DR)
The observed decline in reported mortality among acromegaly patients is likely due to more effective therapies, which, in turn, yield higher biochemical control rates and reduce the likelihood of developing respiratory and cardiovascular comorbidities that increase mortality. Rate of thyroid malignancies is not greater among acromegaly patients than among those without the condition. After screening colonoscopy at diagnosis, further testing should be performed similar to the general population, as per previous recommendations. (LQ, DR)

Assays

Reference GH nadir levels after OGTT using the IDS-iSYS assay accounting for BMI, sex, and ethinylestradiol-containing oral contraceptive use confirm the importance of these factors as confounders in GH measurements. (MQ, SR)
IGF-I levels measured 6 weeks postoperatively can be used in most patients to assess remission, although patients with mildly elevated IGF-I may yet normalize by 3–6 months. (MQ, SR)

Sex, age, and surgical outcomes

Women, especially when postmenopausal, may exhibit lower surgical remission rates from TSS, as they tend to have larger and more invasive tumors that are less amenable to total resection. (LQ, DR)
Patient age is likely not a predictor of surgical outcomes, nor does it impact the favorable effects of postsurgical remission on alleviating disease comorbidities. (LQ, DR)

Radiotherapy outcomes

Long-term follow-up of patients treated with SRS and FRT show that approximately half achieve and maintain biochemical control. However, up to one-third of patients with normal pituitary function develop hypopituitarism, confirming the need for ongoing monitoring. (LQ, SR)

Table 2 Medical therapy: summary points

Injectable SRL

Older age, female sex, lower IGF-I levels, and tumor T2 MRI hypointensity at baseline predict more favorable long-term biochemical responses to primary lanreotide 120 mg therapy every 4 weeks. (MQ, SR)
Recent studies confirm that extended-dosing intervals (> 4 weeks) for 120 mg lanreotide may be effective among selected patients previously controlled with long-acting SRLs. (LQ, DR)
Several studies confirm efficacy of pasireotide LAR for some patients uncontrolled on lanreotide or octreotide LAR. However, rates of treatment-induced hyperglycemia and DM are high, requiring careful monitoring for glycemic side effects. (HQ, SR)

Pegvisomant

Ten-year follow-up from ACROSTUDY shows a 73% biochemical control rate with very low rates of transient elevated transaminases and 6.8% exhibiting tumor growth visible on MRI. (HQ, SR)
Pegvisomant use in patients with DM improves glucose metabolism independent of IGF-I control, but does not affect glycemic endpoints in patients without DM. (MQ, SR)
Patients with DM and those with a higher BMI require higher doses of pegvisomant and more rapid up-titration to achieve IGF-I normalization. (MQ, SR)

Combination therapy with SRL + pegvisomant

Low-dose octreotide LAR or lanreotide plus weekly pegvisomant is a cost-effective and efficacious option for patients requiring combination therapy. (HQ, SR)
Combination of pasireotide plus pegvisomant can yield biochemical control rates exceeding 70% even when pegvisomant doses are kept low. However, the addition of pegvisomant does not ameliorate the high rates of pasireotide-induced hyperglycemia. (MQ, SR)
Patient selection for combination pasireotide plus pegvisomant should be carefully considered. (LQ, DR)

Table 3 Oral octreotide capsules: recommendations

How should OOC be integrated into the current treatment algorithm for medical management of acromegaly?

OOC are suitable for patients who have demonstrated complete or partial biochemical response on injectable octreotide or lanreotide. (HQ, SR) *Rationale:* As octreotide and lanreotide have similar efficacy, patients who have responded to these injectable agents are candidates for OOC therapy, and results of the OPTIMAL study demonstrate that biochemically controlled patients (IGF-I ≤ 1.0 × ULN) on stable doses of injectable octreotide or lanreotide maintain response to OOC [4]. There are no data regarding efficacy of switching patients from pasireotide LAR to OOC.There are no data on the use of OOC as primary medical therapy in SRL-naïve patients. However, it is reasonable to expect that patients who respond to injectable octreotide LAR or lanreotide in this setting would also respond to OOC

Due to a lack of available data, OOC is not currently recommended for patients who have tumor characteristics predictive of octreotide resistance. (MQ, SR) *Rationale:* Tumor characteristics associated with octreotide and lanreotide resistance (e.g., MRI T2 hyperintensity, sparsely granulated tumors) [5, 6] are presumed to also predict resistance to OOC

How should OOC be initiated?

OOC is initiated at a dose of 40 mg/day, given as 20 mg capsules twice per day taken 1 h before a meal or 2 h after a meal to maximize bioavailability. (MQ, SR) However, clinical study data suggest a starting dose of 60 mg/d may be optimal for most patients. *Rationale:* The 40 mg/day dose is the approved initiation dose [7]. Most responders in the OPTIMAL study up-titrated to 60 mg/d or 80 mg/d by study end, and all patients enrolling in the open label extension study were reinitiated at the 60 mg/d dose [4, 8]

OOC should be initiated at the time of the previously scheduled SRL injection. (HQ, SR) *Rationale:* In clinical trials, OOC was initiated at the time of the next SRL injection, i.e., at the end of the once-monthly injection period [4, 9]. IGF-I levels may increase toward the end of the injection period with waning of injectable drug levels [10], and likely account for reported exacerbation of acromegaly symptoms [11–13]

How should OOC dose be escalated?

OOC can be up-titrated by an increment of 20 mg every 2–4 weeks based on IGF-I and clinical symptoms. (MQ, SR) *Rationale:* The pharmacokinetics of OOC [14] enable a dose titration every 2–4 weeks. This is a more rapid escalation compared with injectable SRLs, which often are up-titrated every 3 months. Slower titration may risk re-emergence of disease signs and symptoms and loss of biochemical control

Clinical Study | M Fleseriu and others | Long-term data of pegvisomant | 185:4 | 525–538

More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY

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Abstract

Objective: To report the final long-term safety and efficacy analyses of patients with acromegaly treated with pegvisomant from the ACROSTUDY.

Design: Global (15 countries), multicentre, non-interventional study (2004–2017).

Methods: The complete ACROSTUDY cohort comprised patients with acromegaly, who were being treated with pegvisomant (PEGV) prior to the study or at enrolment. The main endpoints were long-term safety (comorbidities, adverse events (AEs), pituitary tumour volumes, liver tests) and efficacy (IGF1 changes).

Results: Patients (n = 2221) were treated with PEGV for a median of 9.3 years (range, 0–20.8 years) and followed up for a median of 7.4 years (range, 0–13.9 years). Before PEGV, 96.3% had received other acromegaly treatments (surgery/radiotherapy/medications). Before PEGV treatment, 87.2% of patients reported comorbidities. During ACROSTUDY, 5567 AEs were reported in 56.5% of patients and of these 613 were considered treatment-related (in 16.5% of patients) and led to drug withdrawal in 1.3%. Pituitary imaging showed a tumour size increase in 7.1% of patients; the majority (71.1%) reported no changes. Abnormal AST or ALT liver tests occurred in 3.2% of patients. IGF1 normalization rate improved over time, increasing from 11.4% at PEGV start to 53.7% at year 1, and reaching 75.4% at year 10 with the use of ≥30 mg PEGV/day in an increasing proportion of patients.

Conclusion: This comprehensive review of the complete cohort in ACROSTUDY confirmed the overall favourable benefit-to-risk profile and high efficacy of PEGV as mono- and combination therapy in patients with an aggressive course/uncontrolled/active acromegaly requiring long-term medical therapy for control.

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Clinical Research Article

Clinical Research Article

Incidence of Benign and Malignant Tumors in Patients With Acromegaly Is Increased: A Nationwide Population-based Study

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Abbreviations: GH, growth hormone; ICD, International Classification of Diseases; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor 1-binding protein 3; NC, not calculated; SD, standard deviation; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

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Abstract

Context: Whether cancer risk in acromegaly is increased remains controversial, and the risk of benign tumors has been little studied.

Objective: To investigate the incidence of benign and malignant tumors in acromegaly in a nationwide population-based study.

Methods: Adult patients diagnosed with acromegaly between 1987 and 2017 were identified in the Swedish National Patient Registry. The diagnoses of benign and malignant tumors were recorded. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) for neoplasms with 95% CIs were calculated using the Swedish general population as reference.

Results: The study included 1296 patients (52% women). Mean (SD) age at diagnosis was 51.6 (14.7) years. Median (range) follow-up time was 11.7 (0-31) years. Overall, 186 malignancies were identified in acromegalic patients compared with 144 expected in the general population (SIR 1.3; 95% CI 1.1-1.5). The incidence of colorectal and anal cancer (SIR 1.5; 95% CI 1.0-2.2), and renal and ureteral cancer (SIR 4.0; 95% CI 2.3-6.5) was increased, whereas the incidence of malignancies of the respiratory system, brain, prostate, and breast was not. Only 3 cases of thyroid cancer were recorded. Mortality due to malignancies was not increased (SMR 1.1; 95% CI 0.9-1.4). Incidence of benign tumors was increased more than 2-fold (SIR 2.4; 95% CI 2.1-2.7).

Conclusion: Patients with acromegaly had an increased risk of both benign and malignant tumors, including colorectal and anal cancer, and renal and ureteral cancer. Whether this is associated with acromegaly itself or due to more intensive medical surveillance remains to be shown.

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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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Abstract

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.

Consensus on diagnosis and management of Cushing's disease: a guideline update

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Cushing's disease requires accurate diagnosis, careful treatment selection, and long-term management to optimise patient outcomes. The Pituitary Society convened a consensus workshop comprising more than 50 academic researchers and clinical experts to discuss the application of recent evidence to clinical practice. In advance of the virtual meeting, data from 2015 to present about screening and diagnosis; surgery, medical, and radiation therapy; and disease-related and treatment-related complications of Cushing's disease summarised in recorded lectures were reviewed by all participants. During the meeting, concise summaries of the recorded lectures were presented, followed by small group breakout discussions. Consensus opinions from each group were collated into a draft document, which was reviewed and approved by all participants. Recommendations regarding use of laboratory tests, imaging, and treatment options are presented, along with algorithms for diagnosis of Cushing's syndrome and management of Cushing's disease. Topics considered most important to address in future research are also identified.

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Introduction

Cushing's disease, the most common cause of endogenous Cushing's syndrome, is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumour.[1] Optimal patient outcomes require accurate diagnosis, careful treatment selection, and management of the disease and its associated comorbidities to optimise patient outcomes.[2] Notably, compared with patients with adrenal causes of Cushing's syndrome, long-term quality of life is worse for patients with Cushing's disease.[3] Since the publication of clinical guidelines in 2003,[4] 2008,[5,6] and 2015,[7] novel screening and diagnostic modalities have been identified and new treatments approved for use. These new developments highlight the need for updates to clinical guidelines on this challenging disorder.

The Pituitary Society convened a 2-day virtual consensus workshop in October, 2020, to discuss management of Cushing's disease, critically review current literature, and provide recommendations for screening and diagnosis; optimal use of and monitoring outcomes from surgery, medical therapy, and radiation therapy; and identification and management of disease-related and treatment-related complications. The focus was on pituitary, rather than adrenal or ectopic Cushing's syndrome, and overlapping topics that had been recently covered in other consensus statements or reviews were not included.

This guideline update reviews recent evidence and recommendations for clinical practice, grading the quality of the evidence and the strength of the consensus recommendations. Key considerations for use of different laboratory tests and medical therapies are presented in the tables. Consensus recommendations for the diagnosis and monitoring of Cushing's syndrome, management of Cushing's disease complications, and use of medical therapy for Cushing's disease are presented in the panels. Grading schema[8,9] for quality of evidence and strong or discretionary recommendations are presented in the appendix (p 3). Algorithms for diagnosis of Cushing's syndrome (figure 1) and management of Cushing's disease are also presented.

Recommendations for adults with Cushing's disease are presented for use in clinical practice but should be considered alongside patient-specific and disease-specific factors for personalised care. A brief section regarding unique considerations in paediatric Cushing's disease is also included.

Methods

Workshop co-chairs and steering committee members identified 28 discrete topics related to Cushing's disease diagnosis, complications, and treatment to be addressed. Methods for critical review of the literature, pre-workshop lectures, and workshop discussions are described in the appendix.

Diagnosis of Cushing's syndrome: screening, confirmatory, and localisation modalities

Laboratory tests

Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious, progressive disease process and testing complexity.[10] Screening and diagnostic tests for Cushing's syndrome assess cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-h urinary free cortisol (UFC; panel 1).[5,6,11,12] In this setting, sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific.[12,13]

LNSC

The diagnostic utility of LNSC is based on the assumption that patients with Cushing's syndrome lose the normal circadian nadir of cortisol secretion;[14,15] at least two or three LNSC tests are recommended.[5,16] Patients with mild Cushing's syndrome may have LNSC just above the upper limit of normal (ULN). Sampling saliva at usual bedtime rather than at midnight could decrease false-positive results.[17] as cortisol nadir is tightly entrained to sleep onset. Liquid chromatography tandem mass spectrometry can detect both cortisol and cortisone, thereby identifying contamination from topical hydrocortisone preparations, which typically do not contain cortisone. Thus, specificity is higher when using mass spectrometry while immunoassay has higher sensitivity for Cushing's syndrome.[18] Multiple, periodic, sequential LNSC tests are particularly useful for the longitudinal surveillance needed in distinguishing patients with cyclic Cushing's syndrome who exhibit weeks to months of normal cortisol secretion interspersed with episodes of cortisol excess.[19] By contrast, LNSC should not be done in patients with disruption of the normal day and night cycle, such as night-shift workers.[14,15]

Overnight 1-mg DST

In healthy individuals, a supraphysiological dexamethasone dose inhibits vasopressin and ACTH secretion, thereby decreasing cortisol concentrations. Thus, a serum cortisol concentration of less than 1·8 µg/dL (50 nmol/L) at 0800 h in the morning after 1 mg dexamethasone given between 2300 h and midnight is considered to be a normal response.[5] A negative result strongly predicts absence of Cushing's syndrome. At higher cutoff points (eg, 5 µg/dL [138 nmol/L]), DST sensitivity is reduced.[12] Cortisol concentrations of less than 1·8 µg/dL excludes dysregulated cortisol production from an adrenal incidentaloma;[20] in this setting, values higher than 5 µg/dL generally identify patients with dysregulated cortisol secretion from an incidentaloma with overt Cushing's syndrome. False positive results might be seen with rapid absorption or malabsorption of dexamethasone due to increased gut transit time, chronic diarrhoea, or coeliac disease; from concomitant treatment with CYP3A4-inducers (eg, phenobarbital, carbamazepine, St John's wort); and from increased corticosteroid-binding globulin (CBG) concentrations caused by oral oestrogens, pregnancy, or chronic active hepatitis, which can increase total cortisol concentrations.[21–23] Measuring dexamethasone concomitantly with cortisol, using laboratory-specific ranges of expected values, can reduce the risk for false-positive results.[24,25] False-negative results are less common, typically resulting from inhibition of dexamethasone metabolism by concomitant medications such as fluoxetine, cimetidine, or diltiazem, leading to a higher biologically available dose. Decreased CBG and albumin concentrations, which can be noted in patients with concurrent nephrotic syndrome, also might produce a falsely low value.[26]

UFC

At least two or three 24-h urine collections are advised to measure UFC to account for intra-patient variability.[5,27] One advantage with UFC over DST is that overall cortisol production is independent of CBG changes and dexamethasone metabolism or compliance. However, although calculating the mean of several collections aids

Panel 1: Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence

If Cushing's syndrome is suspected:
- Start with urinary-free cortisol (UFC), late-night salivary cortisol (LNSC), or both; dexamethasone suppression test (DST) could also be an option if LNSC not feasible
- Multiple LNSC might be easier for patient collection

If confirming Cushing's syndrome:
- Can use any test
- UFC average two-to-three collections
- LNSC (two or more tests)
- DST useful in shift workers, not in women on oestrogen-containing oral contraceptives
- Measuring dexamethasone concentration, with cortisol concentration, the morning after 1 mg dexamethasone ingestion improves test interpretability

If Cushing's syndrome due to adrenal tumour is suspected:
- Start with DST
- LNSC has lower specificity in these patients

Monitoring for recurrence:
- Consider which tests were abnormal at initial diagnosis
- LNSC most sensitive, should be done annually
- DST and UFC usually become abnormal after LNSC
- UFC is usually the last to become abnormal

Figure 1: Algorithm for diagnosis of Cushing's syndrome
ACTH=adrenocorticotropic hormone. CBG=corticosteroid-binding globulin; CRH=corticotropin-releasing hormone. DST=dexamethasone suppression test. IPSS=inferior petrosal sinus sampling. UFC=urinary free cortisol. *There is consensus that all patients with lesions smaller than 6 mm in diameter should have IPSS and those with lesions of ≥10 mm do not need IPSS, but expert opinions differed for lesions 6–9 mm in diameter. †This alternative option does not have clear consensus and needs further research, and this is indicated by darker boxes. Green boxes indiate points to consider; darker colours indicate less validated testing pathways.

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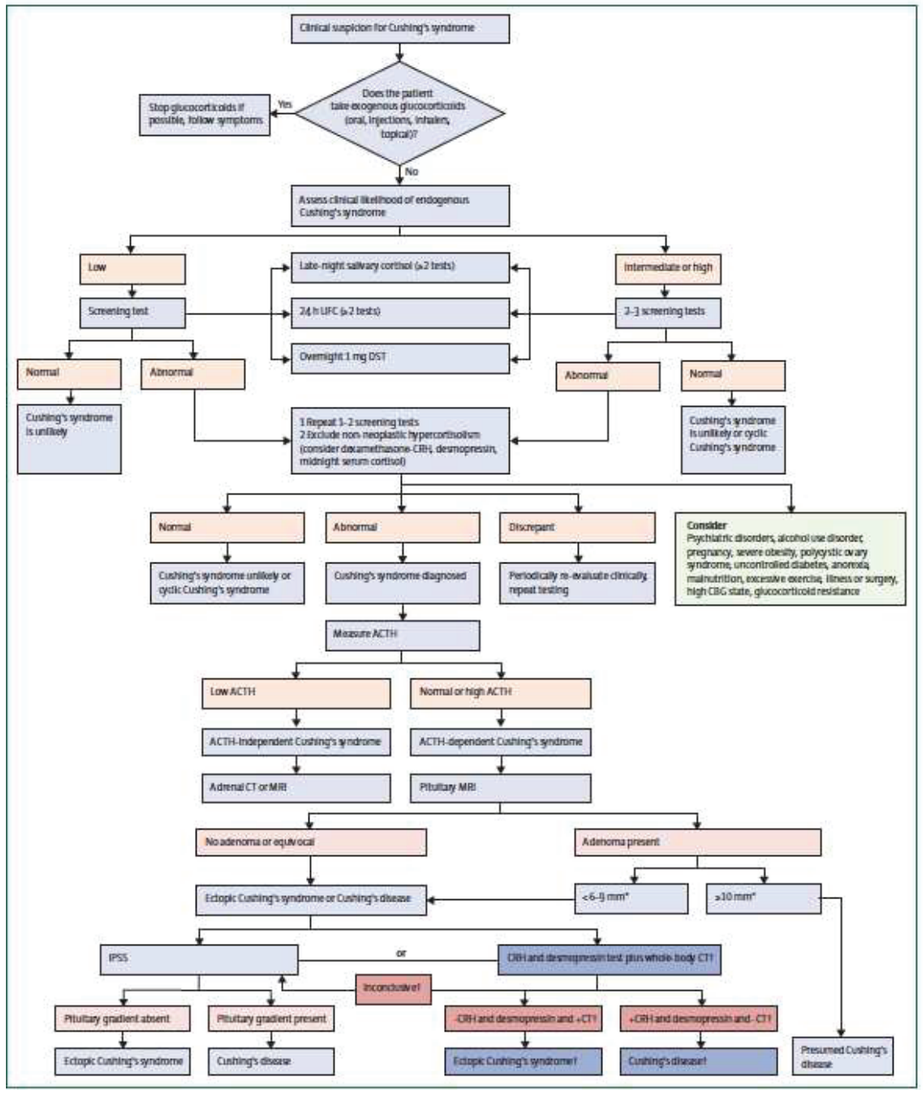

***Panel 2:* Recommendations regarding complications of Cushing's disease**

Hypercoagulability

- There is currently no standard practice for preoperative or postoperative thromboprophylaxis in patients with Cushing's disease. Some experts pause oestrogen therapy in women who are awaiting surgery, but care should be taken if it was being used as contraception, because pregnancy also is associated with increased risk of thrombosis (low quality, discretionary recommendation)
- Prophylactic anticoagulation should be considered for patients at risk for venous thromboembolic events, including history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism; current use of oestrogen or oral contraceptives; poor mobility; extended preoperative or postoperative hospital stay; and high postoperative cortisol concentrations or cortisol over-replacement in patients with adrenal insufficiency (moderate quality, strong recommendation)
- Early postoperative ambulation and use of compression stockings should be encouraged for all patients (high quality, strong recommendation)
- If thromboprophylaxis is administered, there was strong consensus for preference of low molecular weight heparin over oral anticoagulants given the long half-life of the latter and the absence of therapy to reverse their effect, which could be especially concerning in the preoperative setting (low quality, discretionary recommendation)
- Anticoagulants could be discontinued before surgery to minimise intraoperative bleeding risk, although the timing of when to stop and when to reinitiate after surgery is unclear (low quality, discretionary recommendation)
- Among meeting participants, recommended anticoagulation duration in the preoperative setting ranged from 2–4 days to 1–2 weeks, and in the postoperative setting from 1–2 days of the hospital stay up to 2–4 weeks, or even longer, to 2–3 months (low quality, discretionary recommendation)
- Thromboprophylaxis should not be routinely used in paediatric patients because of bleeding risk but is reserved for selected patients

Cardiovascular disease

- Evaluate, monitor, and treat according to current guidelines for patients at high risk of cardiovascular disease (high quality, strong recommendation)
- Management approach should be individualised (high quality, strong recommendation) on the basis of the complications present (eg, hypertension or hyperlipidaemia) and care should be coordinated with primary care and cardiology physicians as needed (very low quality, discretionary recommendation)

Bone disease

- Risk assessment for bone loss and fracture recommended in all patients (high quality, strong recommendation)
- Given the risk for fracture even in patients without osteoporosis, standard dual X-ray absorptiometry alone may not be sufficiently informative; bone quality (microscanner or trabecular bone score) or morphometric vertebral assessment is recommended where available (high quality, strong recommendation) and can be useful in detecting subclinical fractures (high quality, strong recommendation), but might not be practical for all patients. The FRAX tool to assess fracture risk is not validated for Cushing's disease
- Monitor and follow-up as for all adult high-risk populations (high quality, strong recommendation)
- Consider conventional osteoporosis treatments (eg, bisphosphonates) for patients with persistent Cushing's disease, even if bone mineral density is normal, because of increased fracture risk due to cortisol excess (high quality, strong recommendation)

Growth hormone deficiency

- There is currently no standard practice for whether, when, and how to test for growth hormone deficiency in adults with Cushing's disease. As postoperative hypothalamic–pituitary–adrenal (HPA) axis recovery is often delayed, we recommend waiting at least 6–12 months after surgery before considering growth hormone deficiency assessment (moderate quality, strong recommendation)
- Patients with macroadenomas and more aggressive surgical resection are at increased risk of hypopituitarism; patients with three or more pituitary hormone deficiencies are more likely to have growth hormone deficiency and do not need dynamic testing (high quality, strong recommendation)
- Serum insulin-like growth factor I concentration alone is not likely to be a reliable indicator of growth hormone deficiency, because concentrations can be in the lower half of the normal range.
- Accessibility of growth hormone replacement can be an important factor in determining testing and treatment considerations. If growth hormone replacement is implemented earlier than 2 years after pituitary surgery, we recommend retesting periodically to determine whether growth hormone secretion has normalised upon HPA axis recovery (moderate quality, strong recommendation)
- As Cushing's syndrome-associated myopathy does not always spontaneously resolve during remission, physical rehabilitation is recommended for all patients (low quality, discretionary recommendation).
- In children, evaluate for growth hormone deficiency 3–6 months after surgery and immediately initiate growth hormone replacement if needed to ensure proper growth

Clinical considerations and recommendations for repeat pituitary surgery

If there are no contraindications for surgery, we suggest repeat transsphenoidal surgery in patients with biochemical evidence of recurrent Cushing's disease if tumour is evident on MRI, especially if the first surgery was not done in a pituitary tumour centre of excellence (low quality, discretionary recommendation). If MRI

	Commonly used doses	Efficacy	Adverse effects	Key considerations
Adrenal steroidogenesis inhibitor				
Ketoconazole	400–1600 mg total per day, orally, given twice or three times a day	Retrospective studies: approximately 65% of patients had UFC normalisation initially, but 15–25% escape	Gastrointestinal disturbances, increased liver enzymes, gynecomastia, skin rash, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; increasing doses may be needed to counter escape; needs gastric acid for absorption (avoid proton-pump inhibitors); decrease in testosterone would be preferred in women, men need follow-up for hypogonadism; risk of serious hepatotoxicity, mostly transient but regular liver function test monitoring required; risk of QTc prolongation; careful review of other medications for potential drug-drug interactions is essential
Osilodrostat	4–14 mg total per day, orally, given twice a day as maintenance dose; some patients require lower starting doses at 2 mg per day; 30 mg, twice a day maximum	Phase 3 randomised withdrawal study showed 86% UFC normalisation	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, asthenia, adrenal insufficiency	FDA-approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; EMA and Japan have approved for treatment of endogenous Cushing's syndrome; not yet widely available; rapid decrease in UFC; risk of hypocortisolism, hypokalaemia, and QTc prolongation; 11-deoxycortisol can cross-react in cortisol immunoassays; careful monitoring for hyperandrogenism in women
Metyrapone	500 mg to 6 g total per day, orally, given three or four times a day	UFC normalisation in retrospective studies approximately 70%; in a prospective study, 47% at week 12	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; rapid decrease in UFC, typically in first month; 11-deoxycortisol can cross-react in cortisol immunoassays; hyperandrogenism needs to be monitored with long-term use in women
Mitotane	500 mg to 4 g total per day, orally, up to 5 g in Cushing's disease per day given three times a day	Retrospective studies show approximately 80% UFC normalisation	Gastrointestinal disturbances, dizziness, cognitive alterations, adrenal insufficiency; increased liver enzymes; treatment should be stopped if elevations are >5 × ULN	Approved by the FDA and EMA for treatment of adrenal cancer with endogenous Cushing's syndrome; slow onset of action, highly variable bioavailability; narrow therapeutic window (dose titration based on mitotane plasma concentrations); 11-deoxycortisol can cross-react in cortisol immunoassays; neurological toxicity could be a limiting factor; teratogenicity and abortifacient activity, coupled with a long half-life, could limit use in women who desire future pregnancy
Etomidate	0·04–0·1 mg/kg/h intravenously for patients in the intensive care unit; 0·025 mg/kg/h for patients not in the intensive care unit	Retrospective studies show approximately 100% serum cortisol control (10–20 μg/dL)	Sedation or anaesthesia; adrenal insufficiency, myoclonus, nausea, vomiting, and dystonic reactions at higher anaesthetic doses	Off-label use only; very rapid onset of action, appropriate for acute treatment of severe hypercortisolism; intravenous hydrocortisone required at high doses to avoid adrenal insufficiency
Levoketoconazole*	300–1200 mg total per day, orally, given twice a day	Phase 3 open label study showed 31% UFC normalisation (primary endpoint), 42% normalisation when using imputed data (comparable with other studies); phase 3 randomised withdrawal study showed that 41% lost response with drug *vs* 96% with placebo; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, oedema, increased liver enzymes, adrenal insufficiency	Investigational; FDA and EMA orphan drug status for treatment of endogenous Cushing's syndrome; possible lower risk for hepatotoxicity than with ketoconazole based on animal models, although no head-to-head studies in humans available; needs gastric acid for absorption (avoid proton-pump inhibitors); risk of QTc prolongation; careful review of other medications for potential drug-drug interactions is essential
Somatostatin receptor ligands				
Pasireotide	0·6–1·8 mg/mL subcutaneously total per day, given twice a day	Phase 3 study showed 15–26% UFC normalisation	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; may decrease tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Pasireotide long-acting release	10–30 mg per month, intramuscularly	Phase 3 study showed 40% UFC normalisation; clinical signs and symptoms of hypercortisolism improved	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; decreases tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Dopamine receptor agonists				
Cabergoline	0·5–7 mg total per week, orally	Retrospective studies showed approximately 40% UFC normalisation initially, but roughly 25–40% escape; clinical signs and symptoms of hypercortisolism improved	Headache, nasal congestion, hypotension, depression, dizziness	Off-label use only for Cushing's disease; decreases tumour volume in up to 50% of the patients evaluated; poor response could be due to under-titration; risk of treatment-induced impulse-control disorder; unclear risk for cardiac valvulopathy
Glucocorticoid receptor blocker				
Mifepristone	300–1200 mg total per day orally, given once a day	Open-label phase 3 study showed significant improvement in glycaemia (approximately 60% of patients) and blood pressure; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, hypokalaemia, arthralgia, peripheral oedema, hypertension, vaginal bleeding, adrenal insufficiency	FDA-approved for hyperglycaemia associated with Cushing's syndrome; no cortisol markers of efficacy; challenging to use outside specialised clinical practice; risk of hypokalaemia and adrenal insufficiency, needs close monitoring; careful review of other medications for potential drug-drug interactions is essential

(Table 2 continues on next page)

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EMA=European Medicines Agency. FDA=US Food and Drug Administration. ULN=upper limit of normal. UFC=urinary-free cortisol. *Investigational drug with completed phase 3 clinical trials.

Table 2: **Summary of medical therapies for Cushing's disease**

ΥΠΟΦΥΣΗ | ΓΕΩΡΓΙΑ ΝΤΑΛΗ

Panel 3: Medical therapy for Cushing's disease

Which factors are helpful in selection of a medical therapy?

- If there is a need for rapid normalisation of cortisol, we recommend an adrenal steroidogenesis inhibitor; osilodrostat and metyrapone have the fastest action and are orally available, while etomidate can be used intravenously in very severe cases (high quality, strong recommendation)
- In mild disease, if residual tumour is present and there is a potential for tumour shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation)
- If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation)
- If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation); we recommend counselling patients that cortisol cannot be used to monitor treatment response or adrenal insufficiency (high quality, strong recommendation). Drug–drug interactions must be considered when this medication is used
- In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, discretionary recommendation), although no Cushing's disease medications are approved for use in pregnancy
- Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension, should further guide type of medication used (moderate quality, strong recommendation)
- Consider cost and estimated therapy duration, especially if definitive treatment (ie, pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation)

Which factors are used in selecting an adrenal steroidogenesis inhibitor?

- Rapidity of action, tolerability, ease-of-use, degree of probable biochemical normalisation, and specific clinical improvement, as well as local availability and cost of each drug, should be considered at therapy start (moderate quality, strong recommendation)
- Ketoconazole might be favoured for ease of dose titration; concern about inducing hepatotoxicity and the need to monitor liver enzymes can lead to under-dosing (moderate quality, strong recommendation). Drug–drug interactions must be considered and hypogonadism may occur in men
- Osilodrostat achieves high rates of cortisol normalisation. Dosing schedule might be more convenient for patients than with metyrapone, but neither metyrapone nor osilodrostat is limited by hypogonadism in men (high quality, strong recommendation)
- Mitotane is rarely used as monotherapy in Cushing's disease in most centres (low quality, discretionary recommendation)

How is tumour growth monitored when using an adrenal steroidogenesis inhibitor or glucocorticoid receptor blocker?

- MRI is typically obtained 6–12 months after initiating treatment and repeated every few years depending on the clinical scenario (moderate quality, strong recommendation)
- It can be difficult to determine whether tumour progression is due to loss of cortisol feedback or reflects the underlying behaviour of aggressive, recurrent disease (low quality, discretionary recommendation)
- We suggest monitoring ACTH concentrations, because progressive elevations in ACTH could be a sign of tumour growth and a need for MRI; although the half-life of ACTH is short, concentrations fluctuate, and they do not necessarily reflect tumour growth (low quality, discretionary recommendation)
- If progressive tumour growth is seen, medical treatment should be suspended and the management plan reassessed (moderate quality, strong recommendation)

When is preoperative medical therapy used?

- There are no rigorous data supporting use of preoperative medical therapy (moderate quality, strong recommendation)
- Most experts would consider use of adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or because of external factors (low quality, discretionary recommendation)
- Patients with severe Cushing's disease who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular or thromboembolic complications might benefit from preoperative medical therapy in select cases (low quality, discretionary recommendation)

How is treatment response monitored? Which factors are considered in deciding whether to use combination therapy or to switch to another therapy?

- Response should be defined on the basis of a combination of clinical endpoints (eg, improved phenotype, weight, hypertension, glucose metabolism, quality of life) and biochemical endpoints, or only clinical endpoints when glucocorticoid receptor blockers are used (moderate quality, strong recommendation)
- Cortisol concentrations are often measured by urinary free cortisol (except when using mifepristone); urinary free cortisol is not useful if adrenal insufficiency is a concern and morning serum cortisol is preferred (high quality, strong recommendation)
- Because of the loss of biological circadian rhythm, it is unclear whether targeting diurnal secretion alone with morning cortisol or with late-night salivary cortisol is meaningful (low quality, discretionary recommendation)

(Panel 3 continues on next page)

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- Change in treatment should be considered if cortisol levels are persistently elevated after 2–3 months on maximum tolerated doses (moderate quality, strong recommendation)
- If cortisol does not normalise but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation)
- If there is clear resistance to treatment despite dose escalation, we suggest switching to a different therapy (low quality, discretionary recommendation)

Which drugs are used for optimal combination therapy?

- There are few rigorous data supporting specific regimens for combination therapy (high quality, strong recommendation)
- Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximise adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation)
- Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumour present (low quality, discretionary recommendation)
- Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation)

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Clinical Research Article

Clinical Research Article

Diagnostic Pitfalls in Cushing Disease: Surgical Remission Rates, Test Thresholds, and Lessons Learned in 105 Patients

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Abbreviations: AUC, area under the curve; CD, Cushing disease; CS, Cushing syndrome; DST, dexamethasone stimulation test; IA, immunoassay; IPSS, inferior petrosal sinus sampling; LC-MS/MS, liquid chromatography tandem mass spectometry; LNSC, late night salivary cortisol; ROC, receiver operating characteristic; UFC, 24-h urinary free cortisol.

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Abstract

Context: Confirming a diagnosis of Cushing disease (CD) remains challenging, yet is critically important before recommending transsphenoidal surgery for adenoma resection.

Objective: To describe predictive performance of preoperative biochemical and imaging data relative to post-operative remission and clinical characteristics in patients with presumed CD.

Design, Setting, Patients, Interventions: Patients (n = 105; 86% female) who underwent surgery from 2007 through 2020 were classified into 3 groups: group A (n = 84) pathology-proven ACTH adenoma; group B (n = 6) pathology-unproven but with postoperative hypocortisolemia consistent with CD; and group C (n = 15) pathology-unproven, without postoperative hypocortisolemia. Group A + B were combined as confirmed CD and group C as unconfirmed CD.

Main outcomes: Group A + B was compared with group C regarding predictive performance of preoperative 24-hour urinary free cortisol (UFC), late night salivary cortisol (LNSC), 1-mg dexamethasone suppression test (DST), plasma ACTH, and pituitary magnetic resonance imaging (MRI).

Results: All groups had a similar clinical phenotype. Compared with group C, group A + B had higher mean UFC ($P < 0.001$), LNSC ($P = 0.003$), DST ($P = 0.06$), and ACTH ($P = 0.03$) and larger MRI-defined lesions ($P < 0.001$). The highest accuracy thresholds were: UFC 72 μg/24 hours; LNSC 0.122 μg/dL, DST 2.70 μg/dL, and ACTH 39.1 pg/mL. Early (3-month) biochemical remission was achieved in 76/105 (72%) patients: 76/90(84%) and 0/15(0%) of group A + B vs group C, respectively, $P < 0.0001$. In group A + B, nonremission was strongly associated with adenoma cavernous sinus invasion.

Conclusions: Use of strict biochemical thresholds may help avoid offering transsphenoidal surgery to presumed CD patients with equivocal data and improve surgical remission rates. Patients with Cushingoid phenotype but equivocal biochemical data warrant additional rigorous testing.

ΥΠΟΦΥΣΗ | ΓΕΩΡΓΙΑ ΝΤΑΛΗ

Consensus Statement | M Reincke, A Albani and others | Consensus on diagnosis and treatment of corticotroph tumor progression | 184:2 | P1–P16

Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations

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Abstract

Background: Corticotroph tumor progression (CTP) leading to Nelson's syndrome (NS) is a severe and difficult-to-treat complication subsequent to bilateral adrenalectomy (BADX) for Cushing's disease. Its characteristics are not well described, and consensus recommendations for diagnosis and treatment are missing.

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Consensus Statement | M Reincke, A Albani and others | Consensus on diagnosis and treatment of corticotroph tumor progression | 184:2 | P2

Methods: A systematic literature search was performed focusing on clinical studies and case series (≥5 patients). Definition, cumulative incidence, treatment and long-term outcomes of CTP/NS after BADX were analyzed using descriptive statistics. The results were presented and discussed at an interdisciplinary consensus workshop attended by international pituitary experts in Munich on October 28, 2018.
Results: Data covered definition and cumulative incidence (34 studies, 1275 patients), surgical outcome (12 studies, 187 patients), outcome of radiation therapy (21 studies, 273 patients), and medical therapy (15 studies, 72 patients).
Conclusions: We endorse the definition of CTP-BADX/NS as radiological progression or new detection of a pituitary tumor on thin-section MRI. We recommend surveillance by MRI after 3 months and every 12 months for the first 3 years after BADX. Subsequently, we suggest clinical evaluation every 12 months and MRI at increasing intervals every 2–4 years (depending on ACTH and clinical parameters). We recommend pituitary surgery as first-line therapy in patients with CTP-BADX/NS. Surgery should be performed before extrasellar expansion of the tumor to obtain complete and long-term remission. Conventional radiotherapy or stereotactic radiosurgery should be utilized as second-line treatment for remnant tumor tissue showing extrasellar extension

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Clinical Research Article

Clinical Research Article

Corticotroph Aggressive Pituitary Tumors and Carcinomas Frequently Harbor ATRX Mutations

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Abstract

Context: Aggressive pituitary tumors (APTs) are characterized by unusually rapid growth and lack of response to standard treatment. About 1% to 2% develop metastases being classified as pituitary carcinomas (PCs). For unknown reasons, the corticotroph tumors are overrepresented among APTs and PCs. Mutations in the alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) gene, regulating chromatin remodeling and telomere maintenance, have been implicated in the development of several cancer types, including neuroendocrine tumors.

Objective: To study ATRX protein expression and mutational status of the *ATRX* gene in APTs and PCs.

Design: We investigated ATRX protein expression by using immunohistochemistry in 30 APTs and 18 PCs, mostly of Pit-1 and T-Pit cell lineage. In tumors lacking ATRX immunolabeling, mutational status of the *ATRX* gene was explored.

Results: Nine of the 48 tumors (19%) demonstrated lack of ATRX immunolabelling with a higher proportion in patients with PCs (5/18; 28%) than in those with APTs (4/30;13%). Lack of ATRX was most common in the corticotroph tumors, 7/22 (32%), versus tumors of the Pit-1 lineage, 2/24 (8%). Loss-of-function *ATRX* mutations were found in all 9 ATRX immunonegative cases: nonsense mutations (n = 4), frameshift deletions (n = 4), and large deletions affecting 22-28 of the 36 exons (n = 3). More than 1 *ATRX* gene defect was identified in 2 PCs.

Conclusion: *ATRX* mutations occur in a subset of APTs and are more common in corticotroph tumors. The findings provide a rationale for performing ATRX immunohistochemistry to identify patients at risk of developing aggressive and potentially metastatic pituitary tumors.

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Clinical Research Article

Clinical Research Article

Two Distinctive *POMC* Promoters Modify Gene Expression in Cushing Disease

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Abbreviations: 5′-RACE, 5′-rapid amplification of complementary DNA ends; ACTH, adrenocorticotropin; cDNA, complementary DNA; CpG, dinucleotide 5′-CG-3′; CRH, corticotropin-releasing hormone; EGFR, epidermal growth factor receptor; ELISA, enzyme-linked immunosorbent assay; FFPE, formalin-fixed paraffin-embedded; Pro1, first promoter; Pro2, second promoter; IRB, institutional review board; LIF, leukemia inhibitory factor; mRNA, messenger RNA; pCpGL, CpG-free luciferase reporter plasmid; PCR, polymerase chain reaction; *POMC*, proopiomelanocortin; SAM, S-adenosylmethionine; SCA, silent corticotroph adenoma; SssI, methyltransferase; TET, ten-eleven translocation methylcytosine dioxygenase; *USP8*, ubiquitin-specific protease 8.

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Abstract

Context: Mechanisms underlying pituitary corticotroph adenoma adrenocorticotropin (ACTH) production are poorly understood, yet circulating ACTH levels closely correlate with adenoma phenotype and clinical outcomes.

Objective: We characterized the 5′ ends of proopiomelanocortin (*POMC*) gene transcripts, which encode the precursor polypeptide for ACTH, in order to investigate additional regulatory mechanisms of *POMC* gene transcription and ACTH production.

Methods: We examined 11 normal human pituitary tissues, 32 ACTH-secreting tumors, as well as 6 silent corticotroph adenomas (SCAs) that immunostain for but do not secrete ACTH.

Results: We identified a novel regulatory region located near the intron 2/exon 3 junction in the human *POMC* gene, which functions as a second promoter and an enhancer. In vitro experiments demonstrated that CREB binds the second promoter and regulates its transcriptional activity. The second promoter is highly methylated in SCAs, partially demethylated in normal pituitary tissue, and highly demethylated in pituitary and ectopic ACTH-secreting tumors. In contrast, the first promoter is demethylated in all *POMC*-expressing cells and is highly demethylated only in pituitary ACTH-secreting tumors harboring the ubiquitin-specific protease 8 (*USP8*) mutation. Demethylation patterns of the second promoter correlate with clinical phenotypes of Cushing disease.

Conclusion: We identified a second *POMC* promoter regulated by methylation status in ACTH-secreting pituitary tumors. Our findings open new avenues for elucidating subcellular regulation of the hypothalamic-pituitary-adrenal axis and suggest the second *POMC* promoter may be a target for therapeutic intervention to suppress excess ACTH production.

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Research Article

Research Article

O-GlcNAcylation Is Essential for Rapid *Pomc* Expression and Cell Proliferation in Corticotropic Tumor Cells

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Abbreviations: ACTH, adrenocorticotropin; ALS, amyotrophic lateral sclerosis; CAMKII, Ca2+/calmodulin-dependent protein kinase II; cDNA, complementary DNA; CRH, corticotrophin-releasing hormone; Ctrl, Control; DMSO, Dimethyl sulfoxide; DRB, 5,6-dichlorobenzimidazole 1-beta-D-ribofuranoside; ERK, extracellularly regulated kinase; EThcD-MS, electron-transfer/higherenergy collision dissociation–mass spectronomy; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase; mRNA, messenger RNA; OGA, *O*-GlcNAcase; OGT, *O*-GlcNAc transferase; PCR, polymerase chain reaction; PKA, protein kinase A; POMC, proopiomelanocortin; PRL, prolactin; qPCR, quantitative polymerase chain reaction; siRNA, small interfering RNA; Std, standard; TBS-T, Tris-buffered saline-Tween 20; WGA, wheat germ agglutinin.

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Abstract

Pituitary adenomas have a staggering 16.7% lifetime prevalence and can be devastating in many patients because of profound endocrine and neurologic dysfunction. To date, no clear genomic or epigenomic markers correlate with their onset or severity. Herein, we investigate the impact of the *O*-GlcNAc posttranslational modification in their etiology. Found in more than 7000 human proteins to date, *O*-GlcNAcylation dynamically regulates proteins in critical signaling pathways, and its deregulation is involved in cancer progression and endocrine diseases such as diabetes. In this study, we demonstrated that *O*-GlcNAc enzymes were upregulated, particularly in aggressive adrenocorticotropin (ACTH)-secreting tumors, suggesting a role for *O*-GlcNAcylation in pituitary adenoma etiology. In addition to the demonstration that *O*-GlcNAcylation was essential for their proliferation, we showed that the endocrine function of pituitary adenoma is also dependent on *O*-GlcNAcylation. In corticotropic tumors, hypersecretion of the proopiomelanocortin (POMC)-derived hormone ACTH leads to Cushing disease, materialized by severe endocrine disruption and increased mortality. We demonstrated that *Pomc* messenger RNA is stabilized in an *O*-GlcNAc-dependent manner in response to corticotrophin-releasing hormone (CRH). By affecting *Pomc* mRNA splicing and stability, *O*-GlcNAcylation contributes to this new mechanism of fast hormonal response in corticotropes. Thus, this study stresses the essential role of *O*-GlcNAcylation in ACTH-secreting adenomas' pathophysiology, including cellular proliferation and hypersecretion.

ΥΠΟΦΥΣΗ | ΓΕΩΡΓΙΑ ΝΤΑΛΗ

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Clinical Research Article

Clinical Research Article

Psychotropic Drugs in Patients with Cushing's Disease Before Diagnosis and at Long-Term Follow-Up: A Nationwide Study

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Abstract

Context: Psychiatric symptoms are common in Cushing's disease (CD) and seem only partly reversible following treatment.

Objective: To investigate drug dispenses associated to psychiatric morbidity in CD patients before treatment and during long-term follow-up.

Design: Nationwide longitudinal register-based study.

Setting: University Hospitals in Sweden.

Subjects: CD patients diagnosed between 1990 and 2018 (N = 372) were identified in the Swedish Pituitary Register. Longitudinal data was collected from 5 years before, at diagnosis, and during follow-up. Four matched controls per patient were included. Cross-sectional subgroup analysis of 76 patients in sustained remission was also performed.

Main outcome measures: Data from the Swedish Prescribed Drug Register and the Patient Register.

Results: In the 5-year period before and at diagnosis, use of antidepressants (odds ratio [OR] 2.2 [95% confidence interval (CI) 1.3-3.7]) and 2.3 [1.6-3.5]), anxiolytics [2.9 (1.6-5.3) and 3.9 (2.3-6.6)], and sleeping pills [2.1 (1.2-3.7) and 3.8 (2.4-5.9)] was more common in CD than controls. ORs remained elevated at 5-year follow-up for antidepressants [2.4 (1.5-3.9)] and sleeping pills [3.1 (1.9-5.3)]. Proportions of CD patients using antidepressants (26%) and sleeping pills (22%) were unchanged at diagnosis and 5-year follow-up, whereas drugs for hypertension and diabetes decreased. Patients in sustained remission for median 9.3 years (interquartile range 8.1-10.4) had higher use of antidepressants [OR 2.0 (1.1-3.8)] and sleeping pills [2.4 (1.3-4.7)], but not of drugs for hypertension.

Conclusions: Increased use of psychotropic drugs in CD was observed before diagnosis and remained elevated regardless of remission status, suggesting persisting negative effects on mental health. The study highlights the importance of early diagnosis of CD, and the need for long-term monitoring of mental health.

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Clinical Research Article

Clinical Research Article

Nonfunctioning Pituitary Microadenomas: Should Imaging Interval be Extended? A Large Single-center Cohort Study

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Abbreviations: AI, adrenal insufficiency; GHD, growth hormone deficiency; HRT, hormonal replacement therapy; MRI, magnetic resonance imaging; NFPA, nonfunctioning pituitary adenoma; NFPmA, nonfunctioning pituitary microadenoma; NS, not significant; OHSU, Oregon Health & Science University; PRL, prolactin; PY, person-year.

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Abstract

Context: Characterization of the clinical features and natural history of nonfunctioning pituitary microadenomas (NFPmAs) is limited by heterogeneous and small-scale studies.
Objective: To characterize the clinical presentation and natural history of NFPmAs and evaluate if imaging follow-up interval can be extended.
Methods: Retrospective single-center cohort study (years 2006-2021) of conservatively managed patients with NFPmAs. Initial symptoms, pituitary function, and tumor size were assessed. A change in NFPmA size ≥2 mm, as determined by pituitary or brain magnetic resonance imaging (MRI), was considered significant.
Results: There were 347 patients in the study cohort. Headache (78.4%) and fatigue (70.0%) were commonly reported despite no evidence of mass effect or significant pituitary hypofunction. Pituitary deficiencies at baseline were rare, with hypogonadism being most common (5.1%). During a median imaging follow-up period of 29 months (range 3-154), 8.1% of NFPmAs grew. Growth incidence was 2.1 per 100 person-years with a mean and median time to growth of 38.1 (SD ± 36.4) and 24.5 (interquartile range 12.0-70.8) months, respectively. Tumor growth was mild and not associated with new pituitary deficiencies or visual deficits.
Conclusion: These data indicate that the natural history of NFPmAs is overall benign. Consequently, we propose that the initial MRI follow-up timeline for NFPmAs can be extended up to 3 years unless a lesion is close to the optic chiasm, there are worrisome mass effect symptoms, or new pituitary deficiencies.

Clinical Practice Guideline | A Luger and others | ESE CPG on pituitary adenomas in pregnancy | 185:3 | G1–G33

ESE Clinical Practice Guideline on functioning and nonfunctioning pituitary adenomas in pregnancy

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Abstract

Pregnancies are rare in women with pituitary adenomas, which may relate to hormone excess from secretory subtypes such as prolactinomas or corticotroph adenomas. Decreased fertility may also result from pituitary hormone deficiencies due to compression of the gland by large tumours and/or surgical or radiation treatment of the lesion. Counselling premenopausal women with pituitary adenomas about their chance of conceiving spontaneously or with assisted reproductive technology, and the optimal pre-conception treatment, should start at the time of initial diagnosis. The normal physiological changes during pregnancy need to be considered when interpreting endocrine tests in women with pituitary adenomas. Dose adjustments in hormone substitution therapies may be needed across the trimesters. When medical therapy is used for pituitary hormone excess, consideration should be given to the known efficacy and safety data specific to pregnant women for each therapeutic option. In healthy women, pituitary gland size increases during pregnancy. Since some pituitary adenomas also enlarge during pregnancy, there is a risk of visual impairment, especially in women with macroadenomas or tumours near the optic chiasm. Pituitary apoplexy represents a rare acute complication of adenomas requiring surveillance, with surgical intervention needed in some cases. This guideline describes the choice and timing of diagnostic tests and treatments from the pre-conception stage until after delivery, taking into account adenoma size, location and endocrine activity. In most cases, pregnant women with pituitary adenomas should be managed by a multidisciplinary team in a centre specialised in the treatment of such tumours.

European Journal of Endocrinology (2021) **185**, G1–G33

Table 1 Core recommendations.

	NFA	Prolactinoma	Acromegaly	Cushing's disease
Pre-conception	In women with an NFA near the optic chiasm who are seeking pregnancy, surgery may be considered to reduce the risk of chiasmal compression and to enhance fertility	Aim for normalisation of even mild hyperprolactinaemia with cabergoline at the lowest possible dose to optimise chances to conceive	Consider surgery in active acromegaly before pregnancy	Advise against pregnancy during active Cushing's disease
Pregnancy	Nonfunctioning microadenomas bear a low risk for growth during pregnancy, there is no need for routine monitoring	No indication for prolactin testing Medical treatment should be stopped in most cases upon confirmation of pregnancy Close surveillance is needed in women with a macroprolactinoma	No indication for GH and/or IGF-1 testing Medical treatment should be stopped in most cases upon confirmation of pregnancy	Diagnosis of Cushing's disease and assessment of disease activity is challenging due to placental CRH production and activation of the hypothalamic-pituitary-adrenal axis, circadian rhythm, however, is preserved
Post-pregnancy	We recommend awaiting reassessment of pituitary imaging and function until 3–6 months after delivery	A significant percentage of prolactinomas are biochemically in remission after pregnancy and lactation	Rebound of disease activity shortly after delivery is frequent	Reassessment of disease activity should be performed 2–3 months post-partum

Clinical Study | B Biagetti and others | Predicting the macroprolactinoma response | 185:4 | 587–595

Shrinkage by the third month predicts long-term response of macroprolactinoma after cabergoline

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Abstract

Objective: Transsphenoidal surgery (TSS) is mainly indicated in prolactinomas when dopamine agonist treatment fails. However, there is no established early predictor of cabergoline (CBG) response. The present study was aimed to identify predictors of CBG resistance in order to select patients who may benefit from early TSS.
Design: Retrospective longitudinal study.
Methods: We reviewed the medical record of patients diagnosed with prolactinoma after 2010. Inclusion criteria: macroprolactinomas under CBG treatment with serial prolactin levels and MRI before treatment and 3 and 12 months afterwards. The main outcome was tumour size shrinkage ≥ 50% (using the two largest diameters in sagittal view) after 12 months of CBG (TS_50). The capacity of the most important clinical and biochemical variables in predicting the main outcome was examined.
Results: A total of 185 prolactinomas where included: 124 (67.0%) were microadenomas and 61 (33.0%) were macroadenomas of which 27 patients meet de inclusion criteria; median age (42.5 years; (IQR: 28.0)). The median follow-up was (67.5 months; (IQR: 30.2)). Ten patients (37.0%) underwent surgery after more than 1 year of CBG. The volume reduction at the first MRI (3–4 months) was the unique valuable predictor: (OR: 1.16 (95% CI: 1.02–1.32)) of TS_50. A tumour volume shrinkage of ≥ 30% in the first 3–4 months of CBG therapy predicts TS_50 with an AUC (0.95 (CI: 0.76–0.99)).
Conclusion: Tumour shrinkage in the first 3–4 months after starting treatment with CBG is a good tool for predicting the long-term response and can help clinicians to take more appropriated and personalized decisions.

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Clinical Study | B Baussart and others | Surgery to treat selected microprolactinomas | 185:6 | 783–791

Pituitary surgery as alternative to dopamine agonists treatment for microprolactinomas: a cohort study

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Abstract

Objective: Microprolactinomas are currently treated with dopamine agonists. Outcome information on microprolactinoma patients treated by surgery is limited. This study reports the first large series of consecutive non-invasive microprolactinoma patients treated by pituitary surgery and evaluates the efficiency and safety of this treatment.
Design: Follow-up of a cohort of consecutive patients treated by surgery.
Methods: Between January 2008 and October 2020, 114 adult patients with pure microprolactinomas were operated on in a single tertiary expert neurosurgical department, using an endoscopic endonasal transsphenoidal approach. Eligible patients presented with a microprolactinoma with no obvious cavernous invasion on MRI. Prolactin was assayed before and after surgery. Disease-free survival was modeled using Kaplan–Meier representation. A cox regression model was used to predict remission.
Results: Median follow-up was 18.2 months (range: 2.8–155). In this cohort, 14/114 (12%) patients were not cured by surgery, including ten early surgical failures and four late relapses occurring 37.4 months (33–41.8) after surgery. From Kaplan–Meier estimates, 1-year and 5-year disease free survival was 90.9% (95% CI: 85.6–96.4%) and 81% (95% CI: 71.2–92.1%) respectively. The preoperative prolactinemia was the only significant preoperative predictive factor for remission ($P < 0.05$). No severe complication was reported, with no anterior pituitary deficiency after surgery, one diabetes insipidus, and one postoperative cerebrospinal fluid leakage properly treated by muscle plasty.
Conclusions: In well-selected microprolactinoma patients, pituitary surgery performed by an expert neurosurgical team is a valid first-line alternative treatment to dopamine agonists.

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Clinical Research Article

Clinical Research Article

EGFR/ErbB2-Targeting Lapatinib Therapy for Aggressive Prolactinomas

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Abbreviations: DA, dopamine agonist; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; NCI-CTC, National Cancer Institute Common Terminology Criteria for Adverse Events; PRL, prolactin; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

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Abstract

Context: Approximately 10% to 20% of prolactinomas are resistant to dopamine agonist therapy. The ErbB signaling pathway may drive aggressive prolactinoma behavior.
Objective: We evaluated lapatinib, an ErbB1-epidermal growth factor receptor (EGFR)/ErbB2 or human EGFR2 (HER2) tyrosine kinase inhibitor (TKI), in aggressive prolactinomas.
Design: A prospective, phase 2a multicenter trial was conducted.
Setting: This study took place at a tertiary referral pituitary center.
Patients: Study participants included adults with aggressive prolactinomas showing continued tumor growth despite maximally tolerated dopamine agonist therapy.
Intervention: Intervention included oral lapatinib 1250 mg/day for 6 months.
Main Outcome Measures: The primary end point was 40% reduction in any tumor dimension assessed by magnetic resonance imaging at study end; tumor response was assessed by Response Evaluation Criteria in Solid Tumors criteria. Secondary end points included prolactin (PRL) reduction, correlation of response with EGFR/HER2 expression, and safety.
Results: Owing to rigorous inclusion criteria, of 24 planned participants, only 7 consented and 4 were treated. None achieved the primary end point but 3 showed stable disease,

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The Journal of Clinical Investigation CLINICAL MEDICINE

A randomized controlled trial of the GLP-1 receptor agonist dulaglutide in primary polydipsia

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BACKGROUND. Primary polydipsia, characterized by excessive fluid intake, carries the risk of water intoxication and hyponatremia, but treatment options are scarce. Glucagon-like peptide 1 (GLP-1) reduces appetite and food intake. In experimental models, GLP-1 has also been shown to play a role in thirst and drinking behavior. The aim of this trial was to investigate whether GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia.

METHODS. In this randomized, double-blind, placebo-controlled, 3-week crossover trial, 34 patients with primary polydipsia received weekly dulaglutide (1.5 mg, Trulicity) in one treatment segment and placebo (0.9% sodium chloride) in the other. During the last treatment week, patients attended an 8-hour evaluation visit with free access to water. The primary endpoint was total fluid intake during the evaluation visits. Treatment effects were estimated using linear mixed-effects models. In a subset of 15 patients and an additional 15 matched controls, thirst perception and neuronal activity in response to beverage pictures were assessed by functional MRI.

RESULTS. Patients on dulaglutide reduced their fluid intake by 490 mL (95% CI: −780, −199; $P = 0.002$), from 2950 mL (95% CI: 2435, 3465) on placebo to 2460 mL (95% CI: 1946, 2475) on dulaglutide (model estimates), corresponding to a relative reduction of 17%. Twenty-four-hour urinary output was reduced by −943 mL (95% CI: −1473, −413; $P = 0.001$). Thirst perception in response to beverage pictures was higher for patients with primary polydipsia than for controls, and lower for patients on dulaglutide versus placebo, but functional activity was similar among groups and treatments.

CONCLUSIONS. GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a treatment option for these patients.

TRIAL REGISTRATION. Clinicaltrials.gov NCT02770885.

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Review | C De Herdt and others | Thyrotropin-stimulating pituitary adenoma | 185:2 | R65–R74

ENDOCRINE TUMOURS

Thyrotropin-secreting pituitary adenoma: a structured review of 535 adult cases

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Abstract

Background and aims: Thyrotropin-secreting pituitary adenomas (TSHomas) are a rare entity, occurring in one per million people. We performed a systematic review of 535 adult cases summarizing the clinical, biochemical, hormonal and radiological characteristics of TSHoma. Furthermore, we discussed the current guidelines for diagnosis and treatment.

Methods: A structured research was conducted using Pubmed and Web of Science with the following MeSH terms: 'thyrotropin secreting pituitary adenoma' OR 'TSHoma' OR 'thyrotropinoma.'

Results: Our analysis included 535 cases originating from 18 case series, 5 cohort studies and 91 case reports. The mean age at diagnosis was 46 years. At presentation, 75% had symptoms of hyperthyroidism, 55.5% presented with a goitre and 24.9% had visual field defects. The median TSH at diagnosis was 5.16 (3.20–7.43) mU/L with a mean FT4 of 41.5 ± 15.3 pmol/L. The majority (76.9%) of the TSHomas were macroadenoma. Plurihormonality was seen in 37.4% of the adenoma with a higher incidence in macroadenoma. Surgical resection of the adenoma was performed in 87.7% of patients of which 33.5% had residual pituitary adenoma. Post-operative treatment with a somatostatin analogue (SSA) led to a stable disease in 81.3% of the cases with residual tumour. We noticed a significant correlation between the diameter of the adenoma and residual pituitary adenoma ($r = 0.490$, $P < 0.001$). However, in patients preoperatively treated with an SSA, this correlation was absent.

Conclusion: TSHomas are a rare cause of hyperthyroidism and are frequently misdiagnosed. Based on our structured analysis of case series, cohort studies and case reports, we conclude that the majority of TSHomas are macroadenoma being diagnosed in the fifth to sixth decade of life and presenting with symptoms of hyperthyroidism. Plurihormonalitiy is observed in one-third of TSHomas. Treatment consists of neurosurgical resection and SSA in case of surgical failure.

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Clinical Study | T Verweij and others | CV risk in craniopharyngioma and NFPA patients | 185:6 | 793–801

Cardiovascular risk profile in growth hormone-treated adults with craniopharyngioma compared to non-functioning pituitary adenoma: a national cohort study

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European Journal of Endocrinology

Abstract

Context: Cardiovascular (CV) risk profile might differ between growth hormone-treated patients with craniopharyngioma and non-functioning pituitary adenoma (NFPA), since patients with craniopharyngioma more frequently suffer from hypothalamic metabolic disruption.

Objective: The aim of this study is to investigate the CV risk profile in adult patients with craniopharyngioma compared to NFPA before and after treatment with growth hormone (GH) replacement therapy due to severe GH deficiency.

Design: A sub-analysis of the Dutch National Registry of Growth Hormone Treatment in Adults was performed, in which we compared 291 patients with craniopharyngioma to 778 patients with NFPA. CV risk profile and morbidity were evaluated at baseline and during long-term follow-up within and between both groups.

Results: At baseline, patients with craniopharyngioma demonstrated higher BMI than patients with NFPA, and men with craniopharyngioma showed greater waist circumference and lower HDL compared to men with NFPA. During follow-up, BMI, as well as diastolic blood pressure among patients using antihypertensive drugs, deteriorated in the craniopharyngioma group compared to the NFPA group. Lipid profile improved similarly in both groups over time. No differences were found between groups in the occurrence of diabetes mellitus, cerebrovascular accidents, CV disease, or overall mortality.

Conclusion: This study suggests that overall CV risk profile is worse in craniopharyngioma patients with GH deficiency compared to patients with NFPA. During GH replacement therapy, patients with craniopharyngioma demonstrated an increase in BMI over time, where BMI remained stable in patients with NFPA. Also, diastolic blood pressure did not improve with antihypertensive drugs in craniopharyngioma patients as seen in patients with NFPA.

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ORIGINAL ARTICLE

WILEY

Temporal trends in craniopharyngioma management and long-term endocrine outcomes: A multicentre cross-sectional study

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Abstract

Background: The optimal management of craniopharyngiomas remains controversial.
Objectives: To examine temporal trends in the management of craniopharyngioma with a focus on endocrine outcomes.
Methods: This was a cross-sectional, multicentre study. Patients treated between 1951 and 2015 were identified and divided into four quartiles. Demographics, presentation, treatment and outcomes were collected.
Results: In total, 142 patients with childhood-onset craniopharyngioma (48/142; 34%) and adult-onset disease (94/142; 66%) were included. The median follow-up was 15 years (IQR 5-23 years). Across quartiles, there was a significant trend towards using transsphenoidal surgery ($P < .0001$). The overall use of radiotherapy was not different among the four quartiles ($P = .33$). At the latest clinical review, the incidence of GH, ACTH, gonadotrophin deficiencies and anterior panhypopituitarism fell significantly across the duration of the study. Anterior panhypopituitarism was not affected by treatment modality (surgery vs surgery and radiotherapy) ($P = .23$). There was no difference in the incidence of high BMI (≥25 kg/m^2) among the four quartiles ($P = .14$). BMI was higher in patients who treated with surgery and radiotherapy than those treated with surgery only ($P = .006$). Tumour regrowth occurred in 51 patients (51/142; 36%) with no difference in regrowth among quartiles over the time course of the study ($P = .15$).
Conclusion: We demonstrate a significant reduction in panhypopituitarism in craniopharyngioma patients over time, most likely because of a trend towards more transsphenoidal surgery. However, long-term endocrine sequelae remain common and lifelong follow-up is required.

KEYWORDS
craniopharyngioma, hypopituitarism, obesity, transsphenoidal surgery

Clinical Study | M Le Bras and others | Pituitary adenoma in MEN1 | 185:6 | 863–873

Pituitary adenoma in patients with multiple endocrine neoplasia type 1: a cohort study

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European Journal of Endocrinology

Abstract

Objective: Pituitary adenoma (PA) is one of the three major components of multiple endocrine neoplasia type 1 (MEN1). Recent studies have suggested that MEN1-associated PAs are less aggressive than initially estimated. We propose an analysis of the outcome of PAs with a standard of care treatment in a nationwide cohort of MEN1 patients.
Design: Retrospective observational nationwide cohort study using the MEN1 patient registry from the French Group of Endocrine Tumours (GTE).
Methods: The GTE database population consists of 1435 patients with MEN1. This analysis focused on 551 patients recruited after 2000 with at least 3 years of follow-up. The study outcome was tumour progression of PA defined by an increase in Hardy classification (HC) during follow-up according to referring physician regular reports.
Results: Among 551 MEN1 patients (index and related), 202 (36.7%) had PA, with 114 (56.4%) diagnosed by MEN1-related screening. PAs were defined according to HC as microadenoma (grade I) in 117 cases (57.9%), macroadenoma in 59 (29.2%) with 20 HC grade II and 39 HC grades III–IV and unspecified in 26 (12.8%). They were prolactinomas in 92 cases (45.5%) and non-secreting in 73 (36.1%). After a median follow-up of 3 years among the 137 patients with HC grades I–II, 4 patients (2.9%) presented tumour progression.
Conclusion: PAs in patients with MEN1 are less aggressive than previously thought. Tumour progression is rare with a standard of care monitoring and treatment, especially in related patients who mostly present non-secreting microadenoma. MRI monitoring for asymptomatic MEN1 patients should be reduced accordingly.

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Clinical Study | I Martínez de LaPiscina, N Portillo Najera and others | Sporadic pituitary adenomas in young patients | 185:4 | 485–496

Clinical and genetic characteristics in patients under 30 years with sporadic pituitary adenomas

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*(I Martínez de LaPiscina and N Portillo Najera contributed equally to this work)

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Abstract

Objective: Pituitary adenomas (PA) are rare in young patients, and additional studies are needed to fully understand their pathogenesis in this population. We describe the clinical and genetic characteristics of apparently sporadic PA in a cohort of young patients.

Design: Clinical and molecular analysis of 235 patients (age ≤ 30 years) with PA. Clinicians from several Spanish and Chilean hospitals provided data.

Methods: Genetic screening was performed via next-generation sequencing and comparative genomic hybridization array. Clinical variables were compared among paediatric, adolescent (<19 years) and young adults' (≥19–30 years) cohorts and types of adenomas. Phenotype–genotype associations were examined.

Results: Among the total cohort, mean age was 17.3 years. Local mass effect symptoms were present in 22.0%, and prolactinomas were the most frequent (44.7%). Disease-causing germline variants were identified in 22 individuals (9.3%), more exactly in 13.1 and 4.7% of the populations aged between 0–19 and 19–30 years, respectively; genetically positive patients were younger at diagnosis and had larger tumour size. Healthy family carriers were also identified.

Conclusions: Variants in genes associated with syndromic forms of PAs were detected in a large cohort of apparently sporadic pituitary tumours. We have identified novel variants in well-known genes and set the possibility of incomplete disease penetrance in carriers of *MEN1* alterations or a limited clinical expression of the syndrome. Despite the low penetrance observed, screening of *AIP* and *MEN1* variants in young patients and relatives is of clinical value.

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MORBIDITY

Circulating insulin-like growth factor-I and risk of 25 common conditions: outcome-wide analyses in the UK Biobank study

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Abstract

While there is strong epidemiological evidence that circulating insulin-like growth factor-I (IGF-I) is associated with a higher risk of several cancers, little is known about its association with non-cancer outcomes. We investigated associations of circulating IGF-I with risk of 25 common conditions, other than cancer, in a large British cohort. Study participants were 318,749 middle-aged adults enrolled in the UK Biobank Study. Serum IGF-I concentration was measured in samples collected at baseline (2006–2010), and re-measured in 12,334 participants after an average of 4.3 years. We followed-up participants over an average of 11.5 years by linking to hospital admissions and mortality registries. Multivariable-adjusted Cox regressions estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between circulating IGF-I and 25 common conditions, using the repeated IGF-I measurements to correct for regression dilution bias. After correction for multiple testing ($P < 0.002$), IGF-I was positively associated with carpal tunnel syndrome (HR per 5 nmol/l higher concentration = 1.12, 95% CI 1.08–1.16), and inversely associated with varicose veins (0.90, 0.85–0.95), cataracts (0.97, 0.95–0.99), diabetes (0.92, 0.90–0.95), and iron deficiency anaemia (0.90, 0.86–0.93). The associations for cataracts and diabetes attenuated when restricted to cases diagnosed after five or more years of follow-up, suggesting that these associations were likely affected by reverse causality. Higher IGF-I concentration might be associated with the risk for several conditions, but genetic studies are needed to clarify which associations may be causal.

Keywords Insulin-like growth factor-I · Prospective cohort study · UK Biobank · Risk · Outcome-wide

Introduction

Insulin-like growth factor-I (IGF-I) is a polypeptide hormone that is primarily synthesised in the liver following growth hormone stimulation [1], and promotes tissue growth and development in multiple organ systems by acting as a primary mediator of the effects of growth hormone [2]. Clinically high circulating IGF-I concentration, as in adults with acromegaly, is associated with a higher risk of several diseases [3], particularly higher risks of cardiovascular disease, metabolic disorders (e.g. insulin resistance), biliary diseases (e.g. gallbladder disease), gastrointestinal diseases (e.g. colon polyps), arthropathy, musculoskeletal disorders (e.g. carpal tunnel syndrome), genitourinary diseases (e.g. kidney stones, enlarged prostate [4]), respiratory disease, sleep apnoea, and some cancers [5, 6].

Higher IGF-I concentrations in adults without acromegaly have been shown to also be associated with increased risks of several cancers [7], but corresponding evidence for non-cancer outcomes is inconsistent and/or limited to cross-sectional design. Although some of the available prospective observational and genetic evidence suggests that higher IGF-I levels might be positively associated with type 2 diabetes [8, 9], ischaemic heart disease (IHD) [9–11], hip and knee osteoarthritis [12], enlarged prostate [13], and colon adenomas [14, 15], some studies also reported null [16–24], and inverse [25] associations for these outcomes. These equivocal findings and the lack of available prospective evidence for many non-cancer outcomes likely relates at least

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ΒΑΪΑ ΛΑΜΠΑΔΙΑΡΗ

ΑΝΑΠ. ΚΑΘΗΓΗΤΡΙΑ ΠΑΘΟΛΟΓΙΑΣ-ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ, ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ
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Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes

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ABSTRACT

BACKGROUND

The possible advantage of hybrid closed-loop therapy (i.e., artificial pancreas) over sensor-augmented pump therapy in very young children with type 1 diabetes is unclear.

METHODS

In this multicenter, randomized, crossover trial, we recruited children 1 to 7 years of age with type 1 diabetes who were receiving insulin-pump therapy at seven centers across Austria, Germany, Luxembourg, and the United Kingdom. Participants received treatment in two 16-week periods, in random order, in which the closed-loop system was compared with sensor-augmented pump therapy (control). The primary end point was the between-treatment difference in the percentage of time that the sensor glucose measurement was in the target range (70 to 180 mg per deciliter) during each 16-week period. The analysis was conducted according to the intention-to-treat principle. Key secondary end points included the percentage of time spent in a hyperglycemic state (glucose level, >180 mg per deciliter), the glycated hemoglobin level, the mean sensor glucose level, and the percentage of time spent in a hypoglycemic state (glucose level, <70 mg per deciliter). Safety was assessed.

RESULTS

A total of 74 participants underwent randomization. The mean (±SD) age of the participants was 5.6±1.6 years, and the baseline glycated hemoglobin level was 7.3±0.7%. The percentage of time with the glucose level in the target range was 8.7 percentage points (95% confidence interval [CI], 7.4 to 9.9) higher during the closed-loop period than during the control period (P<0.001). The mean adjusted difference (closed-loop minus control) in the percentage of time spent in a hyperglycemic state was −8.5 percentage points (95% CI, −9.9 to −7.1), the difference in the glycated hemoglobin level was −0.4 percentage points (95% CI, −0.5 to −0.3), and the difference in the mean sensor glucose level was −12.3 mg per deciliter (95% CI, −14.8 to −9.8) (P<0.001 for all comparisons). The time spent in a hypoglycemic state was similar with the two treatments (P=0.74). The median time spent in the closed-loop mode was 95% (interquartile range, 92 to 97) over the 16-week closed-loop period. One serious adverse event of severe hypoglycemia occurred during the closed-loop period. One serious adverse event that was deemed to be unrelated to treatment occurred.

CONCLUSIONS

A hybrid closed-loop system significantly improved glycemic control in very young children with type 1 diabetes, without increasing the time spent in hypoglycemia. (Funded by the European Commission and others; ClinicalTrials.gov number, NCT03784027.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hovorka can be contacted at rh347@cam.ac.uk or at the University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Wellcome Trust–MRC Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom.

*A list of the members of the KidsAP Consortium is provided in the Supplementary Appendix, available at NEJM.org.

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ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΒΑΪΑ ΛΑΜΠΑΔΙΑΡΗ

RESEARCH SUMMARY

Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes

Ware J et al. DOI: 10.1056/NEJMoa2111673

CLINICAL PROBLEM

Management of type 1 diabetes is challenging in very young children. Sensor-augmented insulin-pump therapy has been associated with improvements in glycemic control, but the management burden remains high. Hybrid closed-loop systems, in which an algorithm automatically adjusts basal insulin delivery, have shown promise in older children and adolescents, but data in very young children are limited.

CLINICAL TRIAL

Design: A multicenter, randomized, crossover trial compared a hybrid closed-loop system for insulin delivery with sensor-augmented pump therapy in very young children with type 1 diabetes.

Intervention: 74 children 1 to 7 years of age with type 1 diabetes received 16 weeks of closed-loop insulin delivery followed by 16 weeks of sensor-augmented pump therapy, or vice versa. The primary outcome was the percentage of time spent in the target glucose range (70 to 180 mg per deciliter) during each trial period.

RESULTS

Efficacy: The percentage of time spent in the target range was significantly longer during the closed-loop period than during the sensor-augmented pump period. With closed-loop therapy, the percentage of time spent in a hyperglycemic state was lower, and the glycated hemoglobin and mean sensor glucose levels were also lower. The percentage of time spent in a hypoglycemic state did not differ significantly between the treatments.

Safety: The incidence of adverse events was similar during the two periods. One serious adverse event of severe hypoglycemia occurred during the closed-loop period, and one non–treatment-related serious adverse event occurred during the sensor-augmented pump period. There were no episodes of diabetic ketoacidosis.

LIMITATIONS AND REMAINING QUESTIONS

- Previous insulin-pump use was a prerequisite for inclusion in the trial, but access to insulin-pump therapy is minimal in some regions, which limits the generalizability of the findings.
- Children from ethnic minorities were underrepresented.

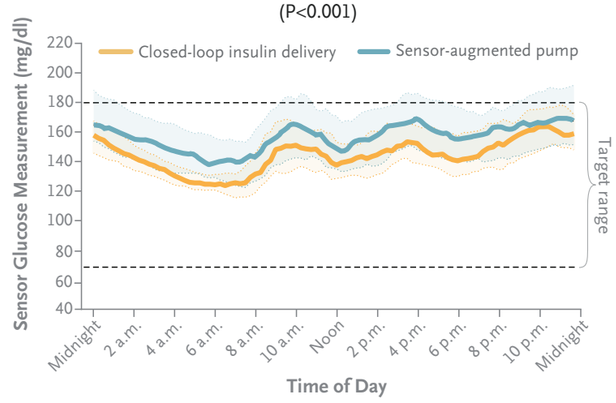
Links: Full Article | NEJM Quick Take

Primary End Point

Percentage of time spent at glucose level 70 to 180 mg/dl during 16-week trial period (P<0.001)

Closed-loop period	71.6±5.9
Sensor-augmented pump period	62.9±9.0

Mean Sensor Glucose Level
(P<0.001)



CONCLUSIONS

In very young children with type 1 diabetes, hybrid closed-loop insulin therapy led to improved glycemic control, as compared with sensor-augmented pump therapy, with no observed increase in the incidence of hypoglycemia.

Articles

A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial

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Lancet 2021; 397: 208–19

*Listed in the appendix (pp 24–25)

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See Online for appendix

Summary

Background Management of type 1 diabetes is challenging. We compared outcomes using a commercially available hybrid closed-loop system versus a new investigational system with features potentially useful for adolescents and young adults with type 1 diabetes.

Methods In this multinational, randomised, crossover trial (Fuzzy Logic Automated Insulin Regulation [FLAIR]), individuals aged 14–29 years old, with a clinical diagnosis of type 1 diabetes with a duration of at least 1 year, using either an insulin pump or multiple daily insulin injections, and glycated haemoglobin (HbA_{1c}) levels of 7·0–11·0% (53–97 mmol/mol) were recruited from seven academic-based endocrinology practices, four in the USA, and one each in Germany, Israel, and Slovenia. After a run-in period to teach participants how to use the study pump and continuous glucose monitor, participants were randomly assigned (1:1) using a computer-generated sequence, with a permuted block design (block sizes of two and four), stratified by baseline HbA_{1c} and use of a personal MiniMed 670G system (Medtronic) at enrolment, to either use of a MiniMed 670G hybrid closed-loop system (670G) or the investigational advanced hybrid closed-loop system (Medtronic) for the first 12-week period, and then participants were crossed over with no washout period, to the other group for use for another 12 weeks. Masking was not possible due to the nature of the systems used. The coprimary outcomes, measured with continuous glucose monitoring, were proportion of time that glucose levels were above 180 mg/dL (>10·0 mmol/L) during 0600 h to 2359 h (ie, daytime), tested for superiority, and proportion of time that glucose levels were below 54 mg/dL (<3·0 mmol/L) calculated over a full 24-h period, tested for non-inferiority (non-inferiority margin 2%). Analysis was by intention to treat. Safety was assessed in all participants randomly assigned to treatment. This trial is registered with ClinicalTrials.gov, NCT03040414, and is now complete.

Findings Between June 3 and Aug 22, 2019, 113 individuals were enrolled into the trial. Mean age was 19 years (SD 4) and 70 (62%) of 113 participants were female. Mean proportion of time with daytime glucose levels above 180 mg/dL (>10·0 mmol/L) was 42% (SD 13) at baseline, 37% (9) during use of the 670G system, and 34% (9) during use of the advanced hybrid closed-loop system (mean difference [advanced hybrid closed-loop system minus 670G system] −3·00% [95% CI −3·97 to −2·04]; p<0·0001). Mean 24-h proportion of time with glucose levels below 54 mg/dL (<3·0 mmol/L) was 0·46% (SD 0·42) at baseline, 0·50% (0·35) during use of the 670G system, and 0·46% (0·33) during use of the advanced hybrid closed-loop system (mean difference [advanced hybrid closed-loop system minus 670G system] −0·06% [95% CI −0·11 to −0·02]; p<0·0001 for non-inferiority). One severe hypoglycaemic event occurred in the advanced hybrid closed-loop system group, determined to be unrelated to study treatment, and none occurred in the 670G group.

Interpretation Hyperglycaemia was reduced without increasing hypoglycaemia in adolescents and young adults with type 1 diabetes using the investigational advanced hybrid closed-loop system compared with the commercially available MiniMed 670G system. Testing an advanced hybrid closed-loop system in populations that are underserved due to socioeconomic factors and testing during pregnancy and in individuals with impaired awareness of hypoglycaemia would advance the effective use of this technology

Funding National Institute of Diabetes and Digestive and Kidney Diseases.

Introduction

Use of technology in the management of type 1 diabetes is becoming an important component of care, often first with a continuous glucose monitor[1] and then an insulin pump as needed, and most recently systems combining the two to automate insulin delivery.[2] The systems currently available in the USA—the MiniMed 670G hybrid closed-loop system (Medtronic, Northridge, CA,

Research

JAMA Pediatrics | Original Investigation

Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and Adolescents With Type 1 Diabetes
A Randomized Clinical Trial

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IMPORTANCE Hybrid closed-loop (HCL) therapy has improved glycemic control in children and adolescents with type 1 diabetes; however, the efficacy of HCL on glycemic and psychosocial outcomes has not yet been established in a long-term randomized clinical trial.

OBJECTIVE To determine the percentage of time spent in the target glucose range using HCL vs current conventional therapies of continuous subcutaneous insulin infusion or multiple daily insulin injections with or without continuous glucose monitoring (CGM).

DESIGN, SETTING, AND PARTICIPANTS This 6-month, multicenter, randomized clinical trial included 172 children and adolescents with type 1 diabetes; patients were recruited between April 18, 2017, and October 4, 2019, in Australia. Data were analyzed from July 25, 2020, to February 26, 2021.

INTERVENTIONS Eligible participants were randomly assigned to either the control group for conventional therapy (continuous subcutaneous insulin infusion or multiple daily insulin injections with or without CGM) or the intervention group for HCL therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was the percentage of time in range (TIR) within a glucose range of 70 to 180 mg/dL, measured by 3-week masked CGM collected at the end of the study in both groups. Secondary outcomes included CGM metrics for hypoglycemia, hyperglycemia, and glycemic variability and psychosocial measures collected by validated questionnaires.

RESULTS A total of 135 patients (mean [SD] age, 15.3 [3.1] years; 76 girls [56%]) were included, with 68 randomized to the control group and 67 to the HCL group. Patients had a mean (SD) diabetes duration of 7.7 (4.3) years and mean hemoglobin A_{1c} of 64 (11) mmol/mol, with 110 participants (81%) receiving continuous subcutaneous insulin infusion and 72 (53%) receiving CGM. In the intention-to-treat analyses, TIR increased from a mean (SD) of 53.1% (13.0%) at baseline to 62.5% (12.0%) at the end of the study in the HCL group and from 54.6% (12.5%) to 56.1% (12.2%) in the control group, with a mean adjusted difference between the 2 groups of 6.7% (95% CI, 2.7%-10.8%; P = .002). Hybrid closed-loop therapy also reduced the time that patients spent in a hypoglycemic (<70 mg/dL) range (difference, −1.9%; 95% CI, −2.5% to −1.3%) and improved glycemic variability (coefficient of variation difference, −5.7%; 95% CI, −10.2% to −0.9%). Hybrid closed-loop therapy was associated with improved diabetes-specific quality of life (difference, 4.4 points; 95% CI, 0.4-8.4 points), with no change in diabetes distress. There were no episodes of severe hypoglycemia or diabetic ketoacidosis in either group.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, 6 months of HCL therapy significantly improved glycemic control and quality of life compared with conventional therapy in children and adolescents with type 1 diabetes.

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Visual Abstract

Supplemental content

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Group Information: The Australian Juvenile Diabetes Research Fund Closed-Loop Research group members appear in Supplement 4.

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Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes

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OBJECTIVE

Advances in diabetes technology have transformed the treatment paradigm for type 1 diabetes, yet the burden of disease is significant. We report on a pivotal safety study of the first tubeless, on-body automated insulin delivery system with customizable glycemic targets.

RESEARCH DESIGN AND METHODS

This single-arm, multicenter, prospective study enrolled 112 children (age 6–13.9 years) and 129 adults (age 14–70 years). A 2-week standard therapy phase (usual insulin regimen) was followed by 3 months of automated insulin delivery. Primary safety outcomes were incidence of severe hypoglycemia and diabetic ketoacidosis. Primary effectiveness outcomes were change in HbA_{1c} and percent time in sensor glucose range 70–180 mg/dL ("time in range").

RESULTS

A total of 235 participants (98% of enrolled, including 111 children and 124 adults) completed the study. HbA_{1c} was significantly reduced in children by 0.71% (7.8 mmol/mol) (mean ± SD: 7.67 ± 0.95% to 6.99 ± 0.63% [60 ± 10.4 mmol/mol to 53 ± 6.9 mmol/mol], $P < 0.0001$) and in adults by 0.38% (4.2 mmol/mol) (7.16 ± 0.86% to 6.78 ± 0.68% [55 ± 9.4 mmol/mol to 51 ± 7.4 mmol/mol], $P < 0.0001$). Time in range was improved from standard therapy by 15.6 ± 11.5% or 3.7 h/day in children and 9.3 ± 11.8% or 2.2 h/day in adults (both $P < 0.0001$). This was accomplished with a reduction in time in hypoglycemia <70 mg/dL among adults (median [interquartile range]: 2.00% [0.63, 4.06] to 1.09% [0.46, 1.75], $P < 0.0001$), while this parameter remained the same in children. There were three severe hypoglycemia events not attributable to automated insulin delivery malfunction and one diabetic ketoacidosis event from an infusion site failure.

CONCLUSIONS

This tubeless automated insulin delivery system was safe and allowed participants to significantly improve HbA_{1c} levels and time in target glucose range with a very low occurrence of hypoglycemia.

ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΒΑΪΑ ΛΑΜΠΑΔΙΑΡΗ

Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial

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Summary

Background People with type 1 diabetes can continuously monitor their glucose levels on demand (intermittently scanned continuous glucose monitoring [isCGM]), or in real time (real-time continuous glucose monitoring [rtCGM]). However, it is unclear whether switching from isCGM to rtCGM with alert functionality offers additional benefits. Therefore, we did a trial comparing rtCGM and isCGM in adults with type 1 diabetes (ALERTT1).

Methods We did a prospective, double-arm, parallel-group, multicentre, randomised controlled trial in six hospitals in Belgium. Adults with type 1 diabetes who previously used isCGM were randomly assigned (1:1) to rtCGM (intervention) or isCGM (control). Randomisation was done centrally using minimisation dependent on study centre, age, gender, glycated haemoglobin (HbA_{1c}), time in range (sensor glucose 3·9–10·0 mmol/L), insulin administration method, and hypoglycaemia awareness. Participants, investigators, and study teams were not masked to group allocation. Primary endpoint was mean between-group difference in time in range after 6 months assessed in the intention-to-treat sample. This trial is registered with ClinicalTrials.gov, NCT03772600.

Findings Between Jan 29 and July 30, 2019, 269 participants were recruited, of whom 254 were randomly assigned to rtCGM (n=127) or isCGM (n=127); 124 and 122 participants completed the study, respectively. After 6 months, time in range was higher with rtCGM than with isCGM (59·6% *vs* 51·9%; mean difference 6·85 percentage points [95% CI 4·36–9·34]; p<0·0001). After 6 months HbA_{1c} was lower (7·1% *vs* 7·4%; p<0·0001), as was time <3·0 mmol/L (0·47% *vs* 0·84%; p=0·0070), and Hypoglycaemia Fear Survey version II worry subscale score (15·4 *vs* 18·0; p=0·0071). Fewer participants on rtCGM experienced severe hypoglycaemia (n=3 *vs* n=13; p=0·0082). Skin reaction was more frequently observed with isCGM and bleeding after sensor insertion was more frequently reported by rtCGM users.

Interpretation In an unselected adult type 1 diabetes population, switching from isCGM to rtCGM significantly improved time in range after 6 months of treatment, implying that clinicians should consider rtCGM instead of isCGM to improve the health and quality of life of people with type 1 diabetes.

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Introduction

The majority of people with type 1 diabetes do not achieve glycated haemoglobin (HbA_{1c}) below 7% (53 mmol/mol)[1,2] and spend a considerable part of the day in hypoglycaemia and hyperglycaemia, exposing them to risk of hypoglycaemic coma, ketoacidosis, and chronic microvascular and macrovascular disease. In recent years, progress has been made in the field of home glucose self-monitoring with the advent of subcutaneous sensors capable of reporting glycaemic levels on demand (intermittently scanned continuous glucose monitoring [isCGM]) or in real time (real-time continuous glucose monitoring [rtCGM]). People on isCGM can check their glucose values by scanning the sensor transmitter with a receiver or smartphone, whereas the transmitter of rtCGM automatically sends a new value to a receiver, smart watch, or smartphone every 1–5 min. In contrast to isCGM, rtCGM has the option of (predictive) alerts for high and low blood glucose levels, but is generally more expensive than isCGM.[3] Several randomised controlled trials comparing the use of CGM with capillary blood glucose measurements, showed that isCGM and rtCGM have a beneficial effect on glycaemic outcomes and quality of life in people with type 1 diabetes treated with multiple daily injections or insulin pump therapy.[4–9] To address the question whether switching from isCGM to rtCGM offers additional benefits, we did a multicentre, non-masked, randomised controlled trial comparing 6-month rtCGM use with 6-month isCGM use in adults with type 1 diabetes who were previously using isCGM.

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ORIGINAL RESEARCH

Hybrid Closed-Loop Systems for the Treatment of Type 1 Diabetes: A Collaborative, Expert Group Position Statement for Clinical Use in Central and Eastern Europe

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ABSTRACT

In both pediatric and adult populations with type 1 diabetes (T1D), technologies such as continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), or sensor-augmented pumps (SAP) can consistently improve glycemic control [measured as glycated hemoglobin (HbA1c) and time in range (TIR)] while reducing the risk of hypoglycemia. Use of technologies can thereby improve quality of life and reduce the burden of diabetes management compared with self-injection of multiple daily insulin doses (MDI). Novel hybrid closed-loop (HCL) systems represent the latest treatment modality for T1D, combining modern glucose sensors and insulin pumps with a linked control algorithm to offer automated insulin delivery in response to blood glucose levels and trends. HCL systems have been associated with increased TIR, improved HbA1c, and fewer hypoglycemic events compared with CSII, SAP, and MDI, thereby potentially improving quality of life for people with diabetes (PwD) while reducing the costs of treating short- and long-term diabetes-related complications. However, many barriers to their use and regional inequalities remain in Central and Eastern Europe (CEE). Published data suggest that access to diabetes technologies is hindered by lack of funding, underdeveloped health technology assessment (HTA) bodies and guidelines, unfamiliarity with novel therapies, and inadequacies in healthcare system capacities. To optimize the use of diabetes technologies in CEE, an international meeting comprising experts in the field of diabetes was held to map the current regional access, to present the current national reimbursement guidelines, and to recommend solutions to overcome uptake barriers. Recommendations included regional and national development of HTA bodies, efficient allocation of resources, and structured education programs for healthcare professionals and PwD. The responsibility of the healthcare community to ensure that all individuals with T1D gain access to modern technologies in a timely and economically responsible manner, thereby improving health outcomes, was emphasized, particularly for interventions that are cost-effective.

Keywords: Advanced hybrid closed-loop; Central and Eastern Europe; Hybrid closed-loop; Position statement; Type 1 diabetes

Key Summary Points

Diabetes technologies can help to improve health outcomes for individuals with type 1 diabetes (T1D) compared with traditional, self-injectable treatments.

However, many barriers remain to their use in Central and Eastern Europe (CEE), including lack of funding, underdeveloped health technology assessment (HTA) bodies and guidelines, unfamiliarity with novel therapies, and inadequacies in healthcare system capacities.

To overcome these barriers, the present position statement recommended the continued regional and national development of HTA bodies, more efficient allocation of resources, and structured education programs for healthcare professionals and people with diabetes.

The expert group wished to emphasize the responsibility of the healthcare community to ensure that all individuals with T1D gain timely access to modern, cost-effective technologies to improve health outcomes while providing value for money for healthcare payers.

The present position statement should be used to inform development of updated guidance in the CEE region for the reimbursement of efficacious diabetes technologies, including novel hybrid closed-loop systems.

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Table 1 Recommendations for use of current diabetes technologies

Technology	Recommendation	Evidence level[a]
CSII	CSII should be considered as a treatment option for all children and adults with T1D who are able to safely manage the device	A
	A well-trained multidisciplinary specialist team is crucial for safe and effective patient selection, education, and management	A
	Individuals should be adequately educated on CSII use through a comprehensive pump management education program	A
	In people on MDI who are not achieving glycemic targets, CSII with or without CGM may be used to improve HbA1c	B
	CSII with or without CGM may be used instead of MDI to improve treatment satisfaction, quality of life, and other health-related outcomes	C
	Individuals on CSII should undergo periodic evaluation to determine whether CSII is effective	E
CGM	CGM should be considered in children and adults with T1D on CSII or MDI	A
	Real-time CGM with high sensor adherence may be used to improve HbA1c regardless of the insulin delivery method	B
	The benefits of CGM correlate with adherence to the ongoing use of the device	B
	CGM in conjunction with MDI can lower HbA1c and reduce hypoglycemia in adults with T2D who are not meeting glycemic targets	B
	CGM may be used in pregnant women with T1D to improve glycemic control and neonatal outcomes	B
	CGM with alarms should be considered in patients with frequent hypoglycemia, previous hypoglycemic seizures, hypoglycemia unawareness, or when fear of hypoglycemia is high	B
	Real-time CGM is preferred in those with frequent hypoglycemic episodes or hypoglycemia unawareness	B
SAP	SAP can be considered in children and adults to improve glycemic control	A
	The benefits correlate with adherence to the ongoing use of the system	A
	SAP with automatic low glucose suspend may be considered for patients with T1D at high risk for hypoglycemia to prevent episodes of hypoglycemia and reduce their severity	B

CGM continuous glucose monitoring, *CSII* continuous subcutaneous insulin infusion, *HbA1c* glycated hemoglobin, *MDI* multiple daily insulin, *SAP* sensor-augmented pump, *T1D* type 1 diabetes, *T2D* type 2 diabetes

[a] A grading system developed by the American Diabetes Association was used to classify the evidence that forms the basis for the recommendations. Recommendations are assigned ratings of A (clear evidence from well-conducted, generalizable randomized controlled trials that were adequately powered, including evidence from a meta-analysis that incorporated quality ratings in the analysis); B (evidence from a well-conducted prospective cohort study or registry, or from a well-conducted meta-analysis of cohort studies); or C (evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results, or from case series or case reports). Expert opinion (E) is a separate category for recommendations in which there is no evidence from clinical trials

ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΒΑΪΑ ΛΑΜΠΑΔΙΑΡΗ

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ORIGINAL RESEARCH

The Cost-Effectiveness of an Advanced Hybrid Closed-Loop System in People with Type 1 Diabetes: a Health Economic Analysis in Sweden

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ABSTRACT

Introduction: Swedish National Diabetes Registry data show a correlation of improved glycemic control in people with type 1 diabetes (T1D) with increased use of diabetes technologies over the past 25 years. However, novel technologies are often associated with a high initial outlay. The aim of the present study was to evaluate the long-term cost-effectiveness of the advanced hybrid closed-loop (AHCL) MiniMed 780G system versus intermittently scanned continuous glucose monitoring (isCGM) plus self-injection of multiple daily insulin (MDI) or continuous subcutaneous insulin infusion (CSII) in people with T1D in Sweden.

Methods: Outcomes were projected over patients' lifetimes using the IQVIA CORE Diabetes Model (v9.0). Clinical data, including changes in glycated hemoglobin (HbA1c) and hypoglycemia rates, were sourced from observational studies and a randomized crossover trial. Modeled patients were assumed to receive the treatments for their lifetimes, with HbA1c kept constant following the application of treatment effects. Costs were accounted from a societal perspective and expressed in Swedish krona (SEK). Utilities and days off work estimates were taken from published sources.

Results: The MiniMed 780G system was associated with an improvement in life expectancy of 0.16 years and an improvement in quality-adjusted life expectancy of 1.95 quality-adjusted life years (QALYs) versus isCGM plus MDI or CSII. These clinical benefits were due to a reduced incidence and a delayed time to onset of diabetes-related complications. Combined costs were estimated to be SEK 727,408 (EUR 72,741) higher with MiniMed 780G, with treatment costs partially offset by direct cost savings from the avoidance of diabetes-related complications and indirect cost savings from the avoidance of lost workplace productivity. The MiniMed 780G system was associated with an incremental cost-effectiveness ratio of SEK 373,700 per QALY gained.

Conclusions: Based on a willingness-to-pay threshold of SEK 500,000 per QALY gained, the MiniMed 780G system was projected to be cost-effective versus isCGM plus MDI or CSII for the treatment of T1D in Sweden.

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Cost-effectiveness analysis of an Advanced Hybrid Closed Loop insulin delivery system in people with type 1 diabetes in Greece

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Abstract

Introduction Usage of automated insulin delivery systems are increasing for the treatment of people with type 1 diabetes (T1D). This study compared long-term cost-effectiveness of the Advanced Hybrid Closed Loop MiniMed 780G (AHCL) system versus sensor augmented pump (SAP) system with predictive low glucose management (PLGM), or multiple daily injections (MDI) plus intermittently-scanned continuous glucose monitoring (isCGM) in people with T1D in Greece. Methods Analyses were performed using the IQVIA CORE Diabetes Model, with clinical input data sourced from various studies. In the AHCL versus SAP plus PLGM analysis, patients were assumed to have 7.5% baseline HbA1c, when comparing AHCL with MDI plus isCGM baseline HbA1c was assumed to be 7.8%. HbA1c was reduced to 7.0% following AHCL treatment initiation, but remained at baseline levels in the comparator arms. Analyses were performed from a societal perspective over a lifetime time horizon. Future costs and clinical outcomes were discounted at 1.5% per annum. Results AHCL was associated with increased quality-adjusted life expectancy of 0.284 quality-adjusted life years (QALYs), and EUR 10,173 lower mean total lifetime costs with SAP plus PLGM. Compared with MDI plus isCGM, AHCL was associated with increased quality-adjusted life expectancy of 2.708 QALYs, EUR 76,396 higher mean total lifetime costs, and an ICER of EUR 29,869 per QALY. Extensive sensitivity analysis confirmed the robustness of results. Conclusions Over patient lifetime, the MiniMed 780G system is likely to be cost saving compared with the SAP plus PLGM system and cost-effective compared with MDI plus isCGM in people with T1D in Greece.

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ORIGINAL ARTICLE

WILEY

Efficacy and safety of liraglutide in type 1 diabetes by baseline characteristics in the ADJUNCT ONE and ADJUNCT TWO randomized controlled trials

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Abstract

Aim: To evaluate 26 weeks of liraglutide treatment in type 1 diabetes (T1D) by subgroups in the ADJUNCT ONE and ADJUNCT TWO trials.

Materials and Methods: ADJUNCT ONE and ADJUNCT TWO were randomized controlled phase 3 trials in 1398 and 835 participants with T1D treated with liraglutide (1.8, 1.2, or 0.6 mg) or placebo (adjuncts to insulin). This post hoc analysis evaluated treatment effects by subgroups: HbA1c (< or ≥8.5%), body mass index (BMI; < or ≥27 kg/m^2), and insulin regimen (basal bolus or continuous subcutaneous insulin infusion).

Results: In both trials at week 26, reductions in HbA1c, body weight, and daily insulin dose did not differ significantly ($P > .05$) by baseline HbA1c or BMI. Risk of clinically significant hypoglycaemia or hyperglycaemia with ketosis did not differ significantly ($P > .05$) by baseline HbA1c, BMI, or insulin regimen. At week 26 in ADJUNCT ONE, these risks did not differ ($P > .05$) between treatment groups. Placebo-adjusted reductions in HbA1c, body weight, and insulin dose (−0.30%-points, −5.0 kg, and −12%, respectively, with liraglutide 1.8 mg), were significant ($P < .05$), greater than at week 52, and similar to those in ADJUNCT TWO (−0.35%, −4.8 kg, and −10%, respectively, with liraglutide 1.8 mg).

Conclusions: In ADJUNCT ONE and ADJUNCT TWO, the efficacy and glycaemic safety of liraglutide did not depend on subgroups, leaving residual beta-cell function as the only identified variable impacting the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in T1D. These findings support a role for GLP-1 RAs as adjuncts to insulin in T1D, warranting further study.

KEYWORDS
clinical trial, incretin therapy, liraglutide, type 1 diabetes

Prior presentation/publication: Parts of these data have been accepted as an abstract and were presented as a poster at the American Diabetes Association (ADA) - 81st Annual Scientific Session, 25-29 June 2021, and the corresponding abstract has been published by ADA (Dejgaard et al. Diabetes 2021; 70(Suppl 1): doi: 10.2337/db21-675-P).

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ORIGINAL ARTICLE

WILEY

Reducing the need for carbohydrate counting in type 1 diabetes using closed-loop automated insulin delivery (artificial pancreas) and empagliflozin: A randomized, controlled, non-inferiority, crossover pilot trial

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Abstract

Aim: To assess whether adding empagliflozin to closed-loop automated insulin delivery could reduce the need for carbohydrate counting in type 1 diabetes (T1D) without worsening glucose control.

Materials and Methods: In an open-label, crossover, non-inferiority trial, 30 adult participants with T1D underwent outpatient automated insulin delivery interventions with three random sequences of prandial insulin strategy days: carbohydrate counting, simple meal announcement (no carbohydrate counting) and no meal announcement. During each sequence of prandial insulin strategies, participants were randomly assigned empagliflozin (25 mg/day) or not, and crossed over to the comparator. Mean glucose for carbohydrate counting without empagliflozin (control) was compared with no meal announcement with empagliflozin (in the primary non-inferiority comparison) and simple meal announcement with empagliflozin (in the conditional primary non-inferiority comparison).

Results: Participants were aged 40 ± 15 years, had 27 ± 15 years diabetes duration and HbA1c of 7.6% ± 0.7% (59 ± 8 mmol/mol). The system with no meal announcement and empagliflozin was not non-inferior (and thus reasonably considered inferior) to the control arm (mean glucose 10.0 ± 1.6 vs. 8.5 ± 1.5 mmol/L; non-inferiority p = .94), while simple meal announcement and empagliflozin was non-inferior (8.5 ± 1.4 mmol/L; non-inferiority p = .003). Use of empagliflozin on the background of automated insulin delivery with carbohydrate counting was associated with lower mean glucose, corresponding to a 14% greater time in the target range. While no ketoacidosis was observed, mean fasting ketones levels were higher on empagliflozin (0.22 ± 0.18 vs. 0.13 ± 0.11 mmol/L; p < .001).

Conclusions: Empagliflozin added to automated insulin delivery has the potential to eliminate the need for carbohydrate counting and improves glycaemic control in conjunction with carbohydrate counting, but does not allow for the elimination of meal announcement.

KEYWORDS
continuous glucose monitoring, empagliflozin, insulin pump therapy, randomized trial, SGLT2 inhibitor, type 1 diabetes

ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΒΑΪΑ ΛΑΜΠΑΔΙΑΡΗ

1 | INTRODUCTION

In type 1 diabetes (T1D) management, the carbohydrate content of meals is the main determinant of prandial insulin requirement.[1,2] Consequently, accurate carbohydrate counting is recommended for people with T1D[1,2] and is associated with better glycaemic control.[3] However, accurate carbohydrate counting is challenging for people with diabetes, is associated with an average counting error approximating 20%, and does not eliminate postprandial hypoglycaemia.[4] Moreover, the need for carbohydrate counting may also negatively influence dietary choices as people with diabetes may prefer prepackaged processed foods to whole foods such as whole grains and fruits, simply because they are accompanied by nutrition labels that more clearly state the amount of carbohydrates.[5] Carbohydrate counting is particularly challenging when eating out, simply because the carbohydrate content of meals may not be readily accessible or accurate.

Closed-loop automated insulin delivery (the artificial pancreas) is a clinical strategy that automates insulin delivery through an insulin pump based on glucose sensor readings and a dosing algorithm.[6] Commercially available systems are termed 'hybrid automated insulin delivery systems' as they automate basal insulin delivery but require the user to estimate prandial insulin.[7–9] Early automated insulin delivery studies attempted to eliminate carbohydrate counting by omitting prandial insulin boluses and instead relied on glucose sensor readings to provide meal-related insulin requirements.[10,11] However, because of delays in subcutaneous insulin absorption[12] compared with meal glucose absorption,[13] this approach results in significant postprandial hyperglycaemia.[10,11] An alternative approach that would avoid carbohydrate counting but necessitates announcing the meal to the system, is to give a partial prandial bolus that is dependent on body weight.[10,14] Although systems adopting this approach achieve better postprandial control compared with complete omission of the prandial insulin bolus,[10] they lead to higher postprandial excursions compared with carbohydrate-matched bolus delivery.[14] Consequently, all automated insulin delivery systems that outperformed conventional pump therapy required either carbohydrate counting[7,8,15] or meal-size categorization based on carbohydrate content, in which the user must choose if the meal is small, medium or large regarding the carbohydrate content.[16–18]

Sodium-glucose co-transporter inhibitors (SGLTis) may represent a pharmacological strategy to improve the glycaemic performance of automated insulin delivery systems by reducing postprandial glycaemic exposure.[19,20] These agents inhibit glucose reabsorption in the kidney, which allows more glucose to be excreted in the urine and thus lowers blood glucose levels through an insulin-independent mechanism.[21] Extensive T1D phase 3 clinical trials have been conducted with SGLTis, showing reduction in HbA1c, weight and blood pressure without increasing hypoglycaemia.[22,23] Moreover, post hoc analysis of recent randomized trials suggests renal protection with SGLTis in individuals with type 1 diabetes and albuminuria.[24] However, because of the mechanism of action, SGLTis can induce ketosis and potentiate diabetic ketoacidosis. Although not approved in the United States or Canada, low doses of agents from the SGLTi class have been approved for use in people with type 1 diabetes in the European Union and in Japan. We assessed whether adding empagliflozin, a highly selective SGLTi,[25] to closed-loop automated insulin delivery systems, can reduce the need for carbohydrate counting without degrading glucose control.

2 | METHODS

2.1 | Participants

From July 2018 to November 2019, participants were enrolled at Mount Sinai Hospital, Toronto, Ontario, and the Research Institute of McGill University Health Centre, Montreal, Quebec, Canada. Participants were adults aged 18-65 years, diagnosed with T1D for more than 1 year, had used an insulin pump for more than 3 months and had an HbA1c of 10% or less. Exclusion criteria included renal insufficiency, use of non-insulin antihyperglycaemic drugs (e.g. glucagon-like peptide-1 [GLP-1] analogues), use of loop diuretics, pregnancy, diabetic ketoacidosis in the last 3 months, history of lower limb amputation, recent history of genital or urinary infection, and recent history of leg or foot infection. All participants provided written informed consent. The study was approved by the local ethics committees and Health Canada.

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ORIGINAL ARTICLE

Comparison of treatment with insulin degludec and glargine U100 in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia: The HypoDeg randomized, controlled, open-label, crossover trial

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Abstract

Aim: To investigate whether the long-acting insulin analogue insulin degludec compared with insulin glargine U100 reduces the risk of nocturnal symptomatic hypoglycaemia in patients with type 1 diabetes (T1D).

Methods: Adults with T1D and at least one episode of nocturnal severe hypoglycaemia during the last 2 years were included in a 2-year prospective, randomized, open, multicentre, crossover trial. A total of 149 patients were randomized 1:1 to basal-bolus therapy with insulin degludec and insulin aspart or insulin glargine U100 and insulin aspart. Each treatment period lasted 1 year and consisted of 3 months of run-in or crossover followed by 9 months of maintenance. The primary endpoint was the number of blindly adjudicated nocturnal symptomatic hypoglycaemic episodes. Secondary endpoints included the occurrence of severe hypoglycaemia. We analysed all endpoints by intention-to-treat.

Results: Treatment with insulin degludec resulted in a 28% (95% CI: 9%-43%; $P = .02$) relative rate reduction (RRR) of nocturnal symptomatic hypoglycaemia at level 1 (≤3.9 mmol/L), a 37% (95% CI: 16%-53%; $P = .002$) RRR at level 2 (≤3.0 mmol/L), and a 35% (95% CI: 1%-58%; $P = .04$) RRR in all-day severe hypoglycaemia compared with insulin glargine U100.

Conclusions: Patients with T1D prone to nocturnal severe hypoglycaemia have lower rates of nocturnal symptomatic hypoglycaemia and all-day severe hypoglycaemia with insulin degludec compared with insulin glargine U100.

KEYWORDS
basal insulin, hypoglycaemia, insulin analogues, phase IV study, randomized trial, type 1 diabetes

1 | INTRODUCTION

Hypoglycaemia is the primary side effect of insulin therapy in type 1 diabetes and a daily source of concern for patients and their relatives.[1,2] Nocturnal hypoglycaemia, in particular, is feared by many patients, and their effort to reduce the risk may result in overnight hyperglycaemia, which is a significant contributor to poor glycaemic control, and ultimately a potential driver of microvascular complications.[3-6] Therefore, reducing nocturnal hypoglycaemia is a cornerstone to improve overall glycaemic control and treatment outcomes in type 1 diabetes.

During the night, a significant cause of hypoglycaemia is inappropriate nocturnal insulin action because of an unphysiological action profile and variable absorption of basal insulin. Even although the first-generation long-acting insulin analogues glargine U100 and detemir, in comparison with NPH insulin, consistently reduce the risk of nocturnal hypoglycaemia in patients with type 1 diabetes, nocturnal hypoglycaemia remains a significant clinical problem.[7-9] The newer long-acting insulin analogue degludec displays a further 25% relative rate reduction (RRR) of nocturnal hypoglycaemia compared with insulin glargine U100 in the phase 3 trials in patients with type 1 diabetes at a low risk of hypoglycaemia.[10] This reduction is confirmed in a trial including subgroups of patients at an increased risk of hypoglycaemia.[11] However, no data exist on patients specifically prone to nocturnal severe hypoglycaemia.

Therefore, the HypoDeg trial aims to investigate whether the rate of nocturnal symptomatic hypoglycaemia is lower with insulin degludec U100 compared with insulin glargine U100 in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The HypoDeg trial was an investigator-initiated, 2-year, crossover study conducted in a prospective, randomized, open, blinded endpoint (PROBE) design, carried out at 10 centres in Denmark. Each 1-year treatment period consisted of 3 months of run-in or crossover, used for insulin dose adjustment and stabilization of treatment regimens, followed by 9 months of maintenance. A detailed description of the study design has been published previously.[12]

Patients were eligible if they had been diagnosed clinically with type 1 diabetes for more than 5 years, were aged 18 years or older, and reported one or more episodes of nocturnal severe hypoglycaemia in the previous 2 years (defined by the need for treatment assistance from another person). Pertinent exclusion criteria were: history of primary and secondary adrenal insufficiency, growth hormone deficiency or untreated hypothyroidism, unstable macrovascular disease, history of malignancy, drug or alcohol abuse, and HbA1c more than 86 mmol/mol (>10%).[12] Because the use of continuous glucose monitoring (CGM) was very limited in Denmark at this time we decided only to include people using self-monitored blood glucose (SMBG) as control of glycaemia.

We identified participants by either a screening questionnaire, which was mailed to the patients, or completed by the patients in the outpatient clinics, or by opportunistic screening in the clinics.

The study was approved by the Regional Committee on Biomedical Research Ethics (#H-3-2014-101), the Danish Medicines Agency (#2014071615), and the Danish Data Protection Agency (I-suite no: 02945; #NOH-2014-018), and was registered at www.

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Review

Type 1 Diabetes Mellitus in the SARS-CoV-2 Pandemic: Oxidative Stress as a Major Pathophysiological Mechanism Linked to Adverse Clinical Outcomes

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Abstract: Recent reports have demonstrated the association between type 1 diabetes mellitus (T1DM) and increased morbidity and mortality rates during coronavirus disease (COVID-19) infection, setting a priority of these patients for vaccination. Impaired innate and adaptive immunity observed in T1DM seem to play a major role. Severe, life-threatening COVID-19 disease is characterized by the excessive release of pro-inflammatory cytokines, known as a "cytokine storm". Patients with T1DM present elevated levels of cytokines including interleukin-1a (IL), IL-1β, IL-2, IL-6 and tumor necrosis factor alpha (TNF-α), suggesting the pre-existence of chronic inflammation, which, in turn, has been considered the major risk factor of adverse COVID-19 outcomes in many cohorts. Even more importantly, oxidative stress is a key player in COVID-19 pathogenesis and determines disease severity. It is well-known that extreme glucose excursions, the prominent feature of T1DM, are a potent mediator of oxidative stress through several pathways including the activation of protein kinase C (PKC) and the increased production of advanced glycation end products (AGEs). Additionally, chronic endothelial dysfunction and the hypercoagulant state observed in T1DM, in combination with the direct damage of endothelial cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may result in endothelial and microcirculation impairment, which contribute to the pathogenesis of acute respiratory syndrome and multi-organ failure. The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) receptors in pancreatic b-cells permits the direct destruction of b-cells, which contributes to the development of new-onset diabetes and the induction of diabetic ketoacidosis (DKA) in patients with T1DM. Large clinical studies are required to clarify the exact pathways through which T1DM results in worse COVID-19 outcomes.

Keywords: inflammation; immunity; oxidative stress; SARS-CoV-2; type 1 diabetes mellitus; hyperglycemia; endothelial dysfunction; ACE2

1. Introduction

Coronavirus disease (COVID-19) is a newly recognized infection that was first reported in Wuhan, China in December 2019 and has rapidly spread worldwide. COVID-19 is caused by a novel enveloped RNA beta-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. On 11 March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 as a pandemic after recording 118,000 cases

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DTT

LETTER TO THE EDITOR

Glycemic Control of Patients with Type 1 Diabetes Using an Insulin Pump Before and During the COVID-19–Associated Quarantine

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Dear Editor,

THE UNPRECEDENTED EXPERIENCE of the COVID-19 lockdown altered the normality and daily routine of a great proportion of the global population, including patients with type 1 diabetes (DM1). Currently, very few and conflicting data exist regarding the influence of the COVID-19–related quarantine on the glycemic control of these people. The aim of this analysis is to compare glycemic control as obtained by continuous glucose monitoring (CGM) in adults with DM1 using a CGM-augmented insulin pump with or without a closed-loop system, before and during the lockdown period.

Consecutive adult patients with DM1 were recruited at their first postlockdown appointment at the insulin pump outpatient clinic of the participating hospitals (see first three affiliations). CGM recordings up to three months before that visit were downloaded and analyzed. CGM-derived glycemic metrics, defined according to the international consensus on time in range (TIR) recommendations,[1] from three phases were compared: phase 1, the 15-day period immediately before the lockdown date; phase 2, the 15-day period immediately after the lockdown (early lockdown); and phase 3, the 15-day period after phase 2 (late lockdown). $TIR_{70–180}$, times below ($TBR_{<70}$/$TBR_{<54}$) and above range ($TAR_{>180}$/$TAR_{>250}$), average glucose (AvgGlu), and glucose management index (GMI) were compared between the two postlockdown periods and the prelockdown period, using a paired testing statistical approach. All patients signed an informed consent to allow for CGM data download. The study was performed according to the declaration of Helsinki principles and was approved by the ethics committees of all participating hospitals.

A total of 46 patients (16 men), using a CGM device for >80% of the requested time periods, (mean age 38.2 [standard deviation: 12.9] years, median DM1 duration 19.5 [interquartile range: 12–28] years), were included. Thirty-six patients had been using a closed loop system designed to ''suspend before low'' (Medtronic MiniMed 640G/Enlite[a]), whereas 10 had been using an open loop system with various types of insulin pump and the same flush CGM device (Freestyle libre, Abbott[b]).

The comparisons between CGM-obtained glycemic metrics are given in Table 1. $TIR_{70–180}$ was significantly longer in late lockdown, as compared with prelockdown phase. Overall, glucose values tended to be lower during both quarantine phases, as indicated by the lower AvgGlu, the lower GMI, the longer $TBR_{<70}$, the shorter $TAR_{>180}$ and $TAR_{>250}$, and the longer times spent in automatic suspension (in closed-loop users) (Table 1). After applying Bonferroni adjustment for multiple comparisons, only the GMI and the time in suspension mode remained statistically significantly different during the two quarantine periods. No significant difference was observed among the three periods regarding the dose of insulin (either basal or bolus) and the amount of consumed carbohydrates. None of the patients was ever diagnosed with COVID-19.

Our retrospective analysis shows that adults with DM1 treated by advanced technology systems did not experience a deterioration of glycemic control during the quarantine period. On the contrary, CGM-obtained indices during both the early and the late quarantine phases pointed toward lower glucose values. Importantly, in patients using a ''sustain before low'' system, the time spent in automatic suspension increased by ∼30%–40% during the total lockdown period, indicating a higher tendency toward hypoglycemia and lower insulin needs. In this sense, it seems reasonable to

[a]The only closed-loop system available in the Greek market.
[b]The only CGMS fully reimbursed by the national security system in Greece.

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Table 1. Continuous Glucose Monitorings—Obtained Glycemic Metrics Between the Two Postlockdown and the Prelockdown Periods

CGM metrics	*Prelockdown*	*Lockdown days 1–15*	*Lockdown days 16–30*	*Comparison prelockdown/lockdown days 1–15*	*Comparison prelockdown/lockdown days 16–30*
$TIR_{70–180}$ (%)	66.3 (16.4)	68.3 (16.1)	68.9 (15.2)	0.17	0.025
$TBR_{<70}$ (%)[a]	3.6 (5.9)	4.8 (6.5)	3.9 (5.3)	0.05	0.61
$TBR_{<54}$ (%)[a]	0.1 (0.0–0.6)	0.2 (0.0–1.0)	0.3 (0.0–0.8)	0.10	0.09
$TAR_{>180}$ (%)	30.0 (17.3)	26.8 (17.2)	27.1 (16.2)	0.049	0.04
$TAR_{>250}$ (%)	6.6 (8.5)	4.5 (5.6)	5.8 (9.1)	0.036	0.42
AvgGlu	159.5 (33.3)	152.5 (31.4)	153.6 (32.4)	0.005	0.02
CV (%)	32.9 (5.1)	32.2 (5.2)	32.1 (4.0)	0.33	0.20
GMI (%)	7.2 (0.9)	6.9 (0.8)	6.9 (1.1)	0.007	0.007
Suspension mode[a] (min/day)	105.6 (76.0)	130.5 (72.3)	138.7 (79.4)	0.016	<0.001
Insulin dose (U/day)					
Basal	22.2 (11.7)	21.9 (10.3)	22.3 (11.1)	0.66	0.90
Bolus	26.8 (15.6)	26.7 (17.2)	27.0 (19.6)	0.91	0.85
Total	49.0 (25.2)	48.6 (25.5)	49.3 (28.8)	0.71	0.84
CHO consumed (g/day)	158.6 (79.7)	154.7 (69.4)	153.5 (71.6)	0.53	0.47

[a]Nonparametric test used (median interquartile range).

AvgGlu, Average glucose value; CGM, continuous glucose monitoring; CHO, carbohydrates; CV, coefficient of variation; GMI, glucose management index; Susp. time, mean time spent in automatic suspension mode daily; TAR, time above range; TBR, time below range; TIR, time in range.

hypothesize that closed-loop systems offered protection against hypoglycemia to their users. Hitherto, in two reports from Italy[2,3] (a country heavily affected by COVID-19), glucose control improved slightly during the quarantine to a very similar extent as to our report. In another study from India, however, in DM1 patients not using advanced insulin delivery and/or glucose monitoring systems, glucose control deteriorated.[4] It seems plausible that the direction of glycemic control during such a disastrous situation may differ depending on several parameters related to the catastrophe itself and its consequences as well as on the individual characteristics of the patient.

The population of our study is characterized by good diabetes education, use of advanced technology, good glycemic control, and a feeling of security due to the very low incidence of COVID-19 in Greece. This combination of events might have been responsible for tilting the balance of glycemia toward lower values. Important limitations of this analysis are its retrospective design, the use of different pumps/CGM devices, and its reflection of a single health care system.

In conclusion, in a country with low prevalence of COVID-19 but early implementation of quarantine measures, patients with DM1 did not experience a deterioration of glycemic control. Lower glycemic levels were observed during quarantine, as well as a tendency toward hypoglycemia that was successfully anticipated by an increase of the automatic insulin suspension time of the closed loop systems.

Authors' Contributions

Conception and design of the study were by S.L.; provision of study materials or patients were by A.B., V.L., A.P., A.K, A.S., A.M., and S.L.; collection and assembly of data were carried out by A.B., V.L., A.P., A.K, A.S., A.M., and S.L.; article writing was carried out by A.B., V.L., S.L.; and final approval of the article was by all authors.

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Early left ventricular systolic dysfunction in asymptomatic patients with type 1 diabetes: a single-center, pilot study

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ABSTRACT

Aims: Prevalence and risk factors of pre-symptomatic left ventricular systolic dysfunction (LVSD) in individuals with type 1 diabetes (T1D) have not been adequately studied. The present cross-sectional study assessed the prevalence of early LVSD in asymptomatic patients with type 1 diabetes and investigated potential risk factors.
Methods: Consecutive patients with T1D, free of cardiovascular disease and significant evident microvascular complications were examined. LVSD was assessed by speckle-tracking echocardiography and calculation of global longitudinal strain (GLS). Abnormal GLS was defined as a value>-18.7%. We looked for possible associations between the presence of LVSD and patient demographic, clinical and laboratory characteristics, as well as with autonomic nervous system (ANS) function and arterial stiffness.
Results: We enrolled 155 T1D patients (29.7% men, age 36.7 ± 13.1 years, diabetes duration 19.1 ± 10.0 years, HbA1c 7.5 ± 1.4% [58 ± 15 mmol/mol]). Early LVSD was prevalent in 53 (34.2%) patients. Multivariable analysis identified male gender (OR:4.14; 95% CI:1.39–12.31, $p = 0.011$), HbA1c (OR:1.59 per 1% increase; 95% CI:1.11–2.28, $p = 0.011$), glomerular filtration rate (GFR, OR:0.97; 95% CI:0.95–0.99, $p = 0.010$) and BMI (OR:1.19; 95% CI:1.06–1.34, $p = 0.003$) as independent predictors of LVSD presence.
Conclusions: Early subclinical LVSD is a common finding in asymptomatic patients with T1D, free of macrovascular and significant microvascular complications. Apart from chronic hyperglycemia, increased adiposity may be implicated in its etiology. Further investigation is warranted to identify patients at high risk for whom early screening is required and to determine possible associations between risk markers identified in the present analysis and long-term outcomes.

1. Introduction

Despite recent improvements in outcomes of cardiovascular disease (CVD) in type 1 diabetes,[1] young patients experience a > 10-fold increased risk of CVD morbidity and mortality compared to the age-adjusted general population.[2] Although rates of coronary heart disease and CVD in type 1 diabetes may be declining overtime faster than in the general population,[1] the condition is still strongly linked to CVD outcomes, at an even higher rate than type 2 diabetes according to a recent analysis of >10 million individuals in the UK National Health Service.[3] It is also linked to a higher incidence of heart failure (HF) than type 2 diabetes, across most of the life course.[4] Furthermore, diabetes has been associated with worse HF prognosis, independently of the presence of coronary heart disease or left ventricular ejection fraction.[5] Nonetheless, the existence of a so-called "diabetic cardiomyopathy" as a distinct clinical entity is still a matter of debate and is usually defined as "ventricular dysfunction in the absence of coronary artery disease and hypertension".[6] No specific strategy has been shown to more effectively treat HF related to diabetes. The sodium-glucose cotransporter-2 inhibitors (SGLT-2i), a new class of glucose-lowering medications to treat type 2 diabetes, have been shown to exert beneficial effects regarding HF outcomes irrespectively of the presence of diabetes, thus indicating that their prevailing mechanisms of action are not related to their glucose-lowering effect.[7]

The most common echocardiographic findings in asymptomatic patients with diabetes are related to left ventricular diastolic dysfunction.[8] Left ventricular systolic dysfunction (LVSD) in patients with diabetes is less frequently described in the literature.[9] This disparity, however, is most probably attributable to the limited diagnostic accuracy of

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REVIEW
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Stress Hyperglycemia in Children and Adolescents as a Prognostic Indicator for the Development of Type 1 Diabetes Mellitus

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Hyperglycemia is a common manifestation in the course of severe disease and is the result of acute metabolic and hormonal changes associated with various factors such as trauma, stress, surgery, or infection. Numerous studies demonstrate the association of adverse clinical events with stress hyperglycemia. This article briefly describes the pathophysiological mechanisms which lead to hyperglycemia under stressful circumstances particularly in the pediatric and adolescent population. The importance of prevention of hyperglycemia, especially for children, is emphasized and the existing models for the prediction of diabetes are presented. The available studies on the association between stress hyperglycemia and progress to type 1 diabetes mellitus are presented, implying a possible role for stress hyperglycemia as part of a broader prognostic model for the prediction and prevention of overt disease in susceptible patients.

Keywords: stress hyperglycemia, type 1 diabetes mellitus, autoantibodies, inflammation, environmental factors

Introduction

The term stress hyperglycemia (SH) refers to a transient increase in plasma glucose levels (usually above 150 mg/dl) during acute illness or physical or psychological stress, which subsides when the stressful condition resolves (1). Specifically, according to the latest American Diabetes Association and American Association of Clinical Endocrinologists consensus, stress hyperglycemia is defined as any transient inpatient plasma glucose levels > 140 mg/dl (fasting plasma glucose of >126 mg/dl or random plasma glucose > 200 mg/dl) without evidence of previous diabetes (2). Common causes in children include febrile infections and seizures, trauma, cardiac surgery and burns, and its incidence in the pediatric population admitted to the hospital is quite remarkable. Almost 3.8-5% of non-diabetic children presenting to the emergency department have glucose levels >150 mg/dl, while about 20-35% of critically ill children surpass the cut-off point of 200 mg/dl in the intensive care unit (ICU) (3). In most patients, hyperglycemia is mild to moderate, with blood glucose concentrations ranging between 150 and 299 mg/dl, however, values of 300 mg/dl or higher have also been reported in smaller cohorts, especially in the ICU setting.

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AACE Guideline

American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus

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predictive low-glucose suspend

ABSTRACT

Objective: To provide evidence-based recommendations regarding the use of advanced technology in the management of persons with diabetes mellitus to clinicians, diabetes-care teams, health care professionals, and other stakeholders.
Methods: The American Association of Clinical Endocrinology (AACE) conducted literature searches for relevant articles published from 2012 to 2021. A task force of medical experts developed evidence-based guideline recommendations based on a review of clinical evidence, expertise, and informal consensus, according to established AACE protocol for guideline development.
Main Outcome Measures: Primary outcomes of interest included hemoglobin A1C, rates and severity of hypoglycemia, time in range, time above range, and time below range.
Results: This guideline includes 37 evidence-based clinical practice recommendations for advanced diabetes technology and contains 357 citations that inform the evidence base.
Recommendations: Evidence-based recommendations were developed regarding the efficacy and safety of devices for the management of persons with diabetes mellitus, metrics used to aide with the assessment of advanced diabetes technology, and standards for the implementation of this technology.
Conclusions: Advanced diabetes technology can assist persons with diabetes to safely and effectively achieve glycemic targets, improve quality of life, add greater convenience, potentially reduce burden of

Disclaimer: The American Association of Clinical Endocrinology medical guidelines for clinical practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on clinical evidence. In areas of uncertainty, or when clarification is required, expert opinion and professional judgment were applied.

This guideline is a working document that reflects the state of the field at the time of publication. Because rapid changes are expected in this area, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made considering local resources and individual patient circumstances.

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The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a writing group to develop a consensus statement on the management of type 1 diabetes in adults. The writing group has considered the rapid development of new treatments and technologies and addressed the following topics: diagnosis, aims of management, schedule of care, diabetes self-management education and support, glucose monitoring, insulin therapy, hypoglycemia, behavioral considerations, psychosocial care, diabetic ketoacidosis, pancreas and islet transplantation, adjunctive therapies, special populations, inpatient management, and future perspectives. Although we discuss the schedule for follow-up examinations and testing, we have not included the evaluation and treatment of the chronic microvascular and macrovascular complications of diabetes as these are well-reviewed and discussed elsewhere. The writing group was aware of both national and international guidance on type 1 diabetes and did not seek to replicate this but rather aimed to highlight the major areas that health care professionals should consider when managing adults with type 1 diabetes. Though evidence-based where possible, the recommendations in the report represent the consensus opinion of the authors.

SECTION 1: INTRODUCTION AND RATIONALE FOR THE CONSENSUS REPORT

Type 1 diabetes is a condition caused by autoimmune damage of the insulin-producing β-cells of the pancreatic islets, usually leading to severe endogenous insulin deficiency. Type 1 diabetes accounts for approximately 5–10% of all cases of diabetes. Although the incidence peaks in puberty and early adulthood, new-onset type 1 diabetes occurs in all age-groups and people with type 1 diabetes live for many decades after onset of the disease, such that the overall prevalence of type 1 diabetes is higher in adults than in children, justifying our focus on type 1 diabetes in adults (1). The global prevalence of type 1 diabetes is 5.9 per 10,000 people, while the incidence has risen rapidly over the last 50 years and is currently estimated to be 15 per 100,000 people per year (2).

Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations

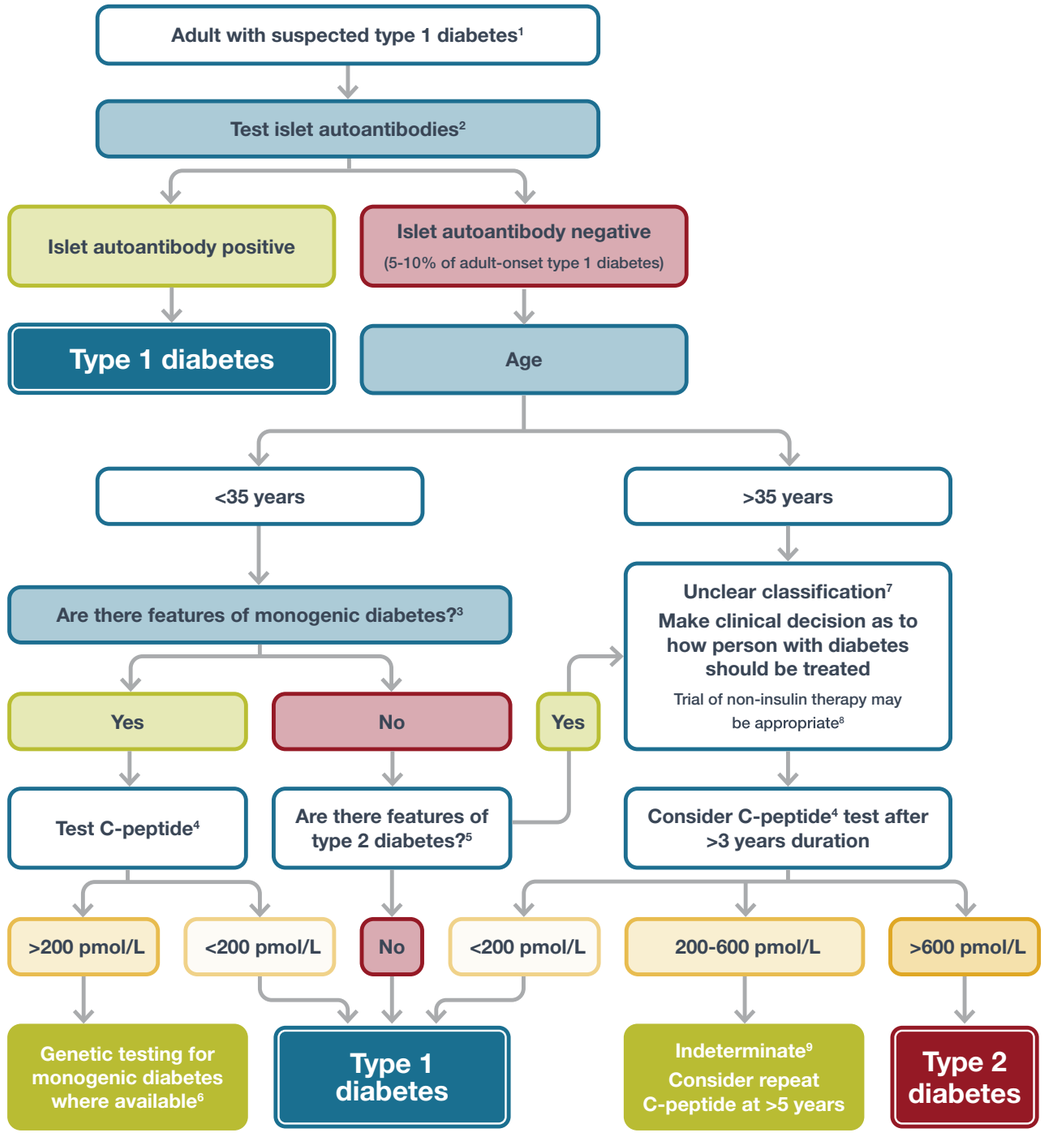

Figure 1—Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations. [1]No single clinical feature confirms type 1 diabetes in isolation. The most discriminative feature is younger age at diagnosis (<35 years), with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and glucose >20 mmol/L (>360 mg/dL) at presentation also being informative. Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases are weak discriminators. [2]GAD should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA2) and/or zinc transporter 8 (ZNT8) where these tests are available. In those diagnosed below the age of 35 years who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes since 5–10% of people with type 1 diabetes do not have antibodies. [3]Monogenic diabetes is suggested by the presence of one or more of the following features: HbA_{1c} <58 mmol/mol (7.5%) at diagnosis, one parent with diabetes, features of specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model

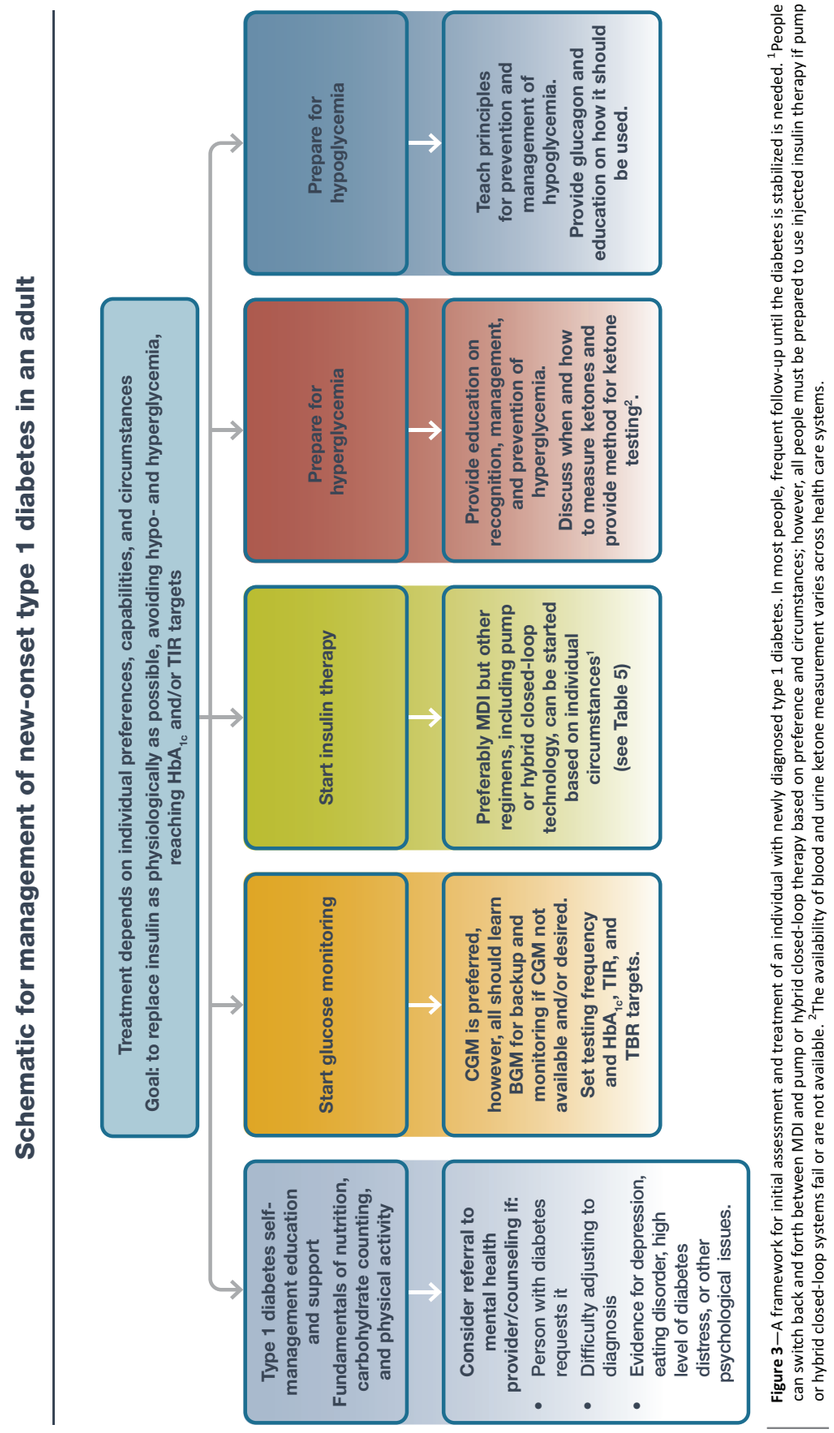

Figure 3—A framework for initial assessment and treatment of an individual with newly diagnosed type 1 diabetes. In most people, frequent follow-up until the diabetes is stabilized is needed. [1]People can switch back and forth between MDI and pump or hybrid closed-loop therapy based on preference and circumstances; however, all people must be prepared to use injected insulin therapy if pump or hybrid closed-loop systems fail or are not available. [2]The availability of blood and urine ketone measurement varies across health care systems.

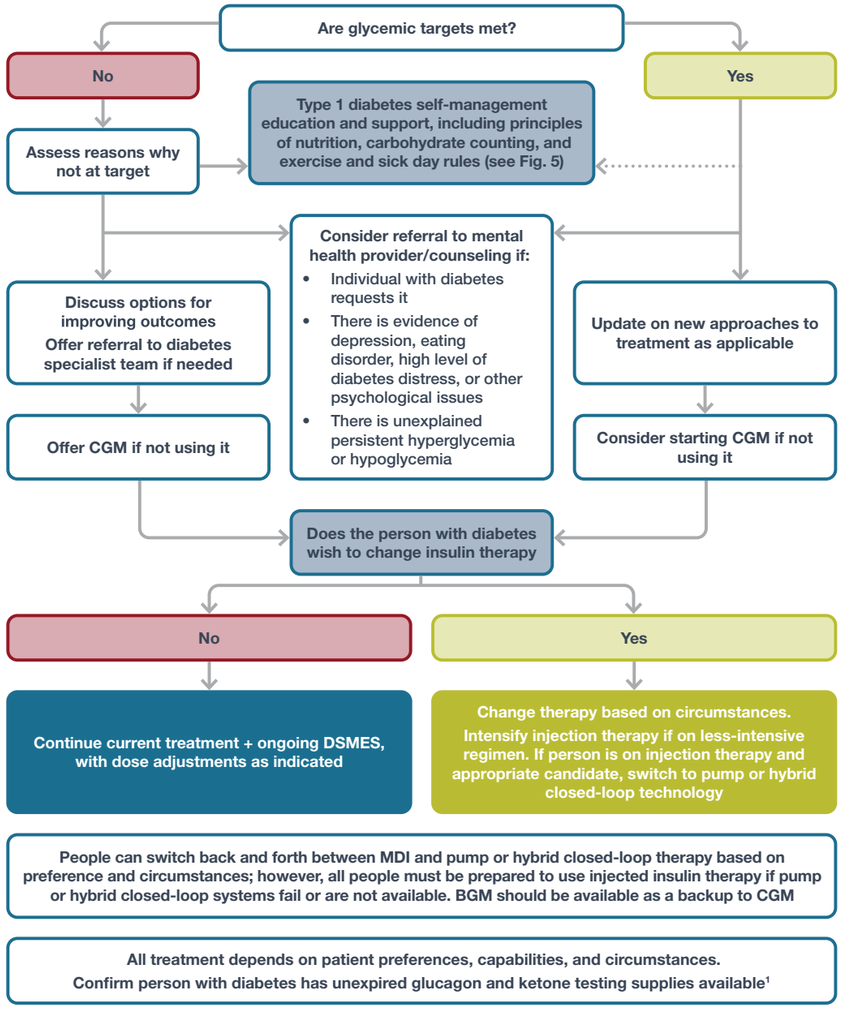

Fig. 4—A framework for the follow-up treatment of an individual with type 1 diabetes. [1]The availability of blood and urine ketone measurement varies across health care systems.

for those with a lower risk for cardiovascular disease (10-year risk of <15%). A lower target of <130/80 mmHg is recommended for those at higher cardiovascular disease risk or with evidence of microvascular complications, particularly renal disease. ACE inhibitors or angiotensin receptor blockers are recommended first-line therapies.

Similar to the situation for blood pressure, there is a paucity of trials of lipid-lowering therapy in people with type 1 diabetes, but an observational study reported that lipid-lowering therapy is associated with a 22–44% reduction in the risk of cardiovascular disease and death among individuals with type 1 diabetes without a prior history of cardiovascular disease (48). Based on type 2 diabetes guidelines, moderate-intensity statins should be considered for people aged over 40 years, and in those aged between 20–39 years with additional atherosclerotic cardiovascular disease risk factors or when the 10-year cardiovascular risk estimated by one of the risk calculators suitable for people with type 1 diabetes exceeds 10% (49–51). Additional agents, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, may be needed.

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes[1]

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Figure 6—Choices of insulin regimens in people with type 1 diabetes. CGM improves outcomes with injected or infused insulin and is superior to BGM. Inhaled insulin may be used in place of injectable prandial insulin in the U.S.. [1]The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; RAA, rapid-acting insulin analog; URAA: ultra-rapid-acting insulin analog.

while others do not wish to wear a device or inject multiple times per day. In these cases, subcutaneous regimens of human short-acting (regular) and NPH insulin or premixed insulin, with BGM as frequently as feasible, may be used at a cost of higher glucose variability with higher risk of hypoglycemia and less flexibility of lifestyle. Figure 6 shows advantages and disadvantages of more- or less-physiological insulin replacement regimens, while Table 5 provides details on various regimens that might be employed.

Mode of Delivery

There are several options for the mode of insulin delivery, and the choice of device should be individualized. Hybrid closed-loop systems are the most effective means of maintaining glucose in the normal range in people with type 1 diabetes (90,91).

MDI therapy can be administered using vials and insulin syringes or insulin pens, with the latter providing more convenience with regard to dosing, but may be at higher cost. Smaller gauge and shorter needles provide almost painless injections. Contrary to common wisdom, skin thickness is not significantly increased in individuals who have overweight or obesity. Needles as short as 4 mm, injected at a 90° angle, enter the subcutaneous space with minimal risk of intramuscular injection in most adults (92). The use of longer needles increases the risk of intramuscular injection. MDI regimens may be enhanced with emerging technology, such as bolus calculators and memory-enabled pens that keep track of insulin doses.

Different insulin pumps for subcutaneous insulin delivery are available in many countries. The primary mechanical differences between pumps are whether they utilize external tubing to connect to an infusion set or a pod directly applied to the skin and controlled via a wireless connection to a controller. Current pumps include bolus calculators programmed with personalized insulin:carbohydrate ratio and correction factors.

Hybrid closed-loop systems comprise an insulin pump, continuous glucose sensor, and a control algorithm. The algorithm controls basal insulin delivery and, in some cases, correction boluses, based on CGM data, while the user still boluses manually for meals (90,91).

Some people with type 1 diabetes are using "do-it-yourself," user-driven, open-source artificial insulin delivery systems, which use commercially available CGM systems and pumps, with software algorithms that communicate with both and can reverse-engineer the pump control of basal and corrective doses (93). Regulatory bodies do not allow health care professionals to prescribe these systems, but health care professionals should respect an individual's right to make informed choices about their care and continue to offer support to the people using these systems.

ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ

ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

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ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ «ΛΑΪΚΟ»

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

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*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

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Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

RESULTS

Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

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*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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REVIEW

A novel diabetes typology: towards precision diabetology from pathogenesis to treatment

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Abstract
The current classification of diabetes, based on hyperglycaemia, islet-directed antibodies and some insufficiently defined clinical features, does not reflect differences in aetiological mechanisms and in the clinical course of people with diabetes. This review discusses evidence from recent studies addressing the complexity of diabetes by proposing novel subgroups (subtypes) of diabetes. The most widely replicated and validated approach identified, in addition to severe autoimmune diabetes, four subgroups designated severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes subgroups. These subgroups display distinct patterns of clinical features, disease progression and onset of comorbidities and complications, with severe insulin-resistant diabetes showing the highest risk for cardiovascular, kidney and fatty liver diseases. While it has been suggested that people in these subgroups would benefit from stratified treatments, RCTs are required to assess the clinical utility of any reclassification effort. Several methodological and practical issues also need further study: the statistical approach used to define subgroups and derive recommendations for diabetes care; the stability of subgroups over time; the optimal dataset (e.g. phenotypic vs genotypic) for reclassification; the transethnic generalisability of findings; and the applicability in clinical routine care. Despite these open questions, the concept of a new classification of diabetes has already allowed researchers to gain more insight into the colourful picture of diabetes and has stimulated progress in this field so that precision diabetology may become reality in the future.

Keywords Clustering · Complications · Diabetes subgroups · Personalised medicine · Precision medicine · Reclassification · Review

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Abbreviations

ADOPT	A Diabetes Outcome Progressive Trial
AHEAD	Action for Health in Diabetes
ANDIS	All New Diabetics in Scania
ANGPTL8	Angiopoietin-like protein 8
CAN	Cardiovascular autonomic neuropathy
CASP-8	Caspase-8
CKD	Chronic kidney disease
DSPN	Distal sensorimotor polyneuropathy
EN-RAGE	S100 calcium-binding protein A12
GDS	German Diabetes Study
GLP-1RA	Glucagon-like peptide-1 receptor agonist
hsCRP	High-sensitivity C-reactive protein
MARD	Mild age-related diabetes
MOD	Mild obesity-related diabetes

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ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

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ABSTRACT

BACKGROUND
Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

METHODS
In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS
Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS
Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

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Drs. Anker and Butler contributed equally to this article.

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ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.

METHODS

In this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m^2 of body-surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2. All the patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).

CONCLUSIONS

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

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CLINICAL RESEARCH

Finerenone in Predominantly Advanced CKD and Type 2 Diabetes With or Without Sodium-Glucose Cotransporter-2 Inhibitor Therapy

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Introduction: FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease) investigated the nonsteroidal, selective mineralocorticoid receptor (MR) antagonist finerenone in patients with CKD and type 2 diabetes (T2D). This analysis explores the impact of use of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) on the treatment effect of finerenone.

Methods: Patients (N = 5674) with T2D, urine albumin-to-creatinine ratio (UACR) of 30 to 5000 mg/g and estimated glomerular filtration rate (eGFR) of 25 to <75 ml/min per 1.73 m^2 receiving optimized renin-angiotensin system (RAS) blockade were randomized to finerenone or placebo. Endpoints were change in UACR and a composite kidney outcome (time to kidney failure, sustained decrease in eGFR ≥40% from baseline, or renal death) and key secondary cardiovascular outcomes (time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) (ClinicalTrials.gov, NCT02540993).

Results: Of 5674 patients, 259 (4.6%) received an SGLT-2i at baseline. Reduction in UACR with finerenone was found with or without use of SGLT-2i at baseline, with ratio of least-squares means of 0.69 (95% CI = 0.66–0.71) and 0.75 (95% CI -= 0.62–0.90), respectively ($P_{interaction}$ = 0.31). Finerenone also significantly reduced the kidney and key secondary cardiovascular outcomes versus placebo; there was no clear difference in the results by SGLT-2i use at baseline ($P_{interaction}$ = 0.21 and 0.46, respectively) or at any time during the trial. Safety was balanced with or without SGLT-2i use at baseline, with fewer hyperkalemia events with finerenone in the SGLT-2i group (8.1% vs. 18.7% without).

Conclusion: UACR improvement was observed with finerenone in patients with CKD and T2D already receiving SGLT-2is at baseline, and benefits on kidney and cardiovascular outcomes appear consistent irrespective of use of SGLT-2i.

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KEYWORDS: albuminuria; chronic kidney disease; finerenone; sodium-glucose cotransporter-2 inhibitors; type 2 diabetes

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Diabetes is the ptleading cause of kidney failure in many countries,[1] with approximately 30% to 50% of adults with T2D having CKD.[2,3] In patients with T2D, recommendations include a comprehensive

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Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure

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ABSTRACT

OBJECTIVES The purpose of this paper was to investigate the effects of dapagliflozin in chronic kidney disease (CKD) patients, with and without heart failure (HF).

BACKGROUND Patients with CKD, with and without type 2 diabetes, were enrolled in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial. Some patients had HF at baseline.

METHODS A total of 4,304 participants were randomized to dapagliflozin 10 mg daily or placebo. The primary composite endpoint was ≥50% decline in estimated glomerular filtration rate, end-stage kidney disease, or kidney/cardiovascular death. Secondary endpoints were a kidney composite (primary endpoint minus cardiovascular death), the composite of cardiovascular death/HF hospitalization, and all-cause death. Analysis of outcomes according to HF history was prespecified.

RESULTS HF patients (n = 468; 11%) were older and had more coronary disease, atrial fibrillation, and type 2 diabetes. Mean estimated glomerular filtration rate was similar in patients with and without HF. Rates of HF hospitalization/cardiovascular death and death from any cause were higher in HF patients, but the secondary kidney failure outcome occurred at the same rate in people with and without HF. Dapagliflozin reduced the risk of the primary outcome equally in patients with HF (HR: 0.58 [95% CI: 0.37-0.91]) and without HF (HR: 0.62 [95% CI: 0.51-0.75]) (*P* interaction = 0.59). The proportional risk-reductions were similar in patients with and without HF for the cardiovascular death/HF hospitalization composite (HR: 0.68 [95% CI: 0.44-1.05] vs HR: 0.70 [95% CI: 0.51-0.97], respectively; *P* interaction = 0.90), and all-cause death (HR: 0.56 [95% CI: 0.34-0.93] vs HR: 0.73 [95% CI: 0.54-0.97], respectively; *P* interaction = 0.39), although absolute risk reductions were larger in HF patients. Adverse event rates were low and did not differ among patients with or without HF.

CONCLUSIONS Dapagliflozin reduced the risk of kidney failure and cardiovascular death/HF hospitalization and prolonged survival in CKD patients with or without type 2 diabetes, independently of history of HF. (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease [DAPA-CKD]; NCT03036150) (J Am Coll Cardiol HF 2021;■:■-■) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial

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Summary

Background Semaglutide is an effective treatment for type 2 diabetes; however, 20–30% of patients given semaglutide 1·0 mg do not reach glycaemic treatment goals. We aimed to investigate the efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in adults with inadequately controlled type 2 diabetes on a stable dose of metformin with or without a sulfonylurea.

Methods We did a 40-week, randomised, active-controlled, parallel-group, double-blind, phase 3B trial (SUSTAIN FORTE) at 125 outpatient clinics in ten countries. Participants (≥18 years) with inadequately controlled type 2 diabetes (HbA_{1c} 8·0–10·0%) with metformin and with or without sulfonylurea were randomly assigned (1:1) by an interactive web-response system to 2·0 mg or 1·0 mg once-weekly semaglutide. Participants, site personnel, the clinical study group, and investigators were masked to the randomised treatment. Outcomes included change from baseline at week 40 in HbA_{1c} (primary outcome) and bodyweight (secondary confirmatory outcome), evaluated through trial product estimand (no treatment discontinuation or without rescue medication) and treatment policy estimand (regardless of treatment discontinuation or rescue medication) strategies. This study is registered with ClinicalTrials.gov, NCT03989232; EudraCT, 2018-004529-96; and WHO, U1111-1224-5162.

Findings Between June 19 and Nov 28, 2019, of 1515 adults assessed for eligibility, 961 participants (mean age 58·0 years [SD 10·0]; 398 [41%] women) were included. Participants were randomly assigned to once-weekly semaglutide 2·0 mg (n=480 [50%]) or 1·0 mg (n=481 [50%]); 462 (96%) patients in the semaglutide 2·0 mg group and 471 (98%) in the semaglutide 1·0 mg group completed the trial. Mean baseline HbA_{1c} was 8·9% (SD 0·6; 73·3 mmol/mol [SD 6·9]) and BMI was 34·6 kg/m² (SD 7·0). Mean change in HbA_{1c} from baseline at week 40 was –2·2 percentage points with semaglutide 2·0 mg and –1·9 percentage points with semaglutide 1·0 mg (estimated treatment difference [ETD] –0·23 percentage points [95% CI –0·36 to –0·11]; p=0·0003; trial product estimand) and –2·1 percentage points with semaglutide 2·0 mg and –1·9 percentage points with semaglutide 1·0 mg (ETD –0·18 percentage points [–0·31 to –0·04]; p=0·0098; treatment policy estimand). Mean change in bodyweight from baseline at week 40 was –6·9 kg with semaglutide 2·0 mg and –6·0 kg with semaglutide 1·0 mg (ETD –0·93 kg [95% CI –1·68 to –0·18]; p=0·015; trial product estimand) and –6·4 kg with semaglutide 2·0 mg and –5·6 kg with semaglutide 1·0 mg (ETD –0·77 kg [–1·55 to 0·01]; p=0·054; treatment policy estimand). Gastrointestinal disorders were the most commonly reported adverse events (163 [34%] in the 2·0 mg group and 148 [31%] in the 1·0 mg group). Serious adverse events were similar between treatment groups, reported for 21 (4%) participants given semaglutide 2·0 mg and 25 (5%) participants given semaglutide 1·0 mg. Three deaths were reported during the trial (one in the semaglutide 1·0 mg group and two in the semaglutide 2·0 mg group).

Interpretation Semaglutide 2·0 mg was superior to 1·0 mg in reducing HbA_{1c}, with additional bodyweight loss and a similar safety profile. This higher dose provides a treatment intensification option for patients with type 2 diabetes treated with semaglutide in need of additional glycaemic control.

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Introduction

GLP-1 receptor agonists are an established treatment option for type 2 diabetes, providing effective glycaemic lowering by stimulating insulin secretion and inhibiting the release of glucagon in a glucose-dependent manner.[1,2] They also decrease bodyweight by reducing appetite and food intake.[1,2] Owing to structural differences between the available GLP-1 receptor agonists, differences exist in the efficacy profile within the class regarding improvements in glycaemia and bodyweight and cardiovascular risk reduction.[1,2]

Once-weekly subcutaneous semaglutide, a GLP-1 receptor agonist, is available for the treatment of type 2 diabetes in two doses: 0·5 mg and 1·0 mg.[3,4] The efficacy

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

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ABSTRACT

BACKGROUND

The efficacy and safety of sodium–glucose cotransporter 2 inhibitors such as sotagliflozin in preventing cardiovascular events in patients with diabetes with chronic kidney disease with or without albuminuria have not been well studied.

METHODS

We conducted a multicenter, double-blind trial in which patients with type 2 diabetes mellitus (glycated hemoglobin level, ≥7%), chronic kidney disease (estimated glomerular filtration rate, 25 to 60 ml per minute per 1.73 m^2 of body-surface area), and risks for cardiovascular disease were randomly assigned in a 1:1 ratio to receive sotagliflozin or placebo. The primary end point was changed during the trial to the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The trial ended early owing to loss of funding.

RESULTS

Of 19,188 patients screened, 10,584 were enrolled, with 5292 assigned to the sotagliflozin group and 5292 assigned to the placebo group, and followed for a median of 16 months. The rate of primary end-point events was 5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.63 to 0.88; P<0.001). The rate of deaths from cardiovascular causes per 100 patient-years was 2.2 with sotagliflozin and 2.4 with placebo (hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.35). For the original coprimary end point of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, the hazard ratio was 0.84 (95% CI, 0.72 to 0.99); for the original coprimary end point of the first occurrence of death from cardiovascular causes or hospitalization for heart failure, the hazard ratio was 0.77 (95% CI, 0.66 to 0.91). Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with placebo.

CONCLUSIONS

In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events. (Funded by Sanofi and Lexicon Pharmaceuticals; SCORED ClinicalTrials.gov number, NCT03315143.)

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

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide in Children and Adolescents with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Metformin is the regulatory-approved treatment of choice for most youth with type 2 diabetes early in the disease. However, early loss of glycemic control has been observed with metformin monotherapy. Whether liraglutide added to metformin (with or without basal insulin treatment) is safe and effective in youth with type 2 diabetes is unknown.

METHODS

Patients who were 10 to less than 17 years of age were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide (up to 1.8 mg per day) or placebo for a 26-week double-blind period, followed by a 26-week open-label extension period. Inclusion criteria were a body-mass index greater than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin). All the patients received metformin during the trial. The primary end point was the change from baseline in the glycated hemoglobin level after 26 weeks. Secondary end points included the change in fasting plasma glucose level. Safety was assessed throughout the course of the trial.

RESULTS

Of 135 patients who underwent randomization, 134 received at least one dose of liraglutide (66 patients) or placebo (68 patients). Demographic characteristics were similar in the two groups (mean age, 14.6 years). At the 26-week analysis of the primary efficacy end point, the mean glycated hemoglobin level had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo, for an estimated treatment difference of –1.06 percentage points (P<0.001); the difference increased to –1.30 percentage points by 52 weeks. The fasting plasma glucose level had decreased at both time points in the liraglutide group but had increased in the placebo group. The number of patients who reported adverse events was similar in the two groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and gastrointestinal adverse events were higher with liraglutide.

CONCLUSIONS

In children and adolescents with type 2 diabetes, liraglutide, at a dose of up to 1.8 mg per day (added to metformin, with or without basal insulin), was efficacious in improving glycemic control over 52 weeks. This efficacy came at the cost of an increased frequency of gastrointestinal adverse events. (Funded by Novo Nordisk; Ellipse ClinicalTrials.gov number, NCT01541215.)

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

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplementation and Prevention of Type 2 Diabetes

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ABSTRACT

BACKGROUND

Observational studies support an association between a low blood 25-hydroxyvitamin D level and the risk of type 2 diabetes. However, whether vitamin D supplementation lowers the risk of diabetes is unknown.

METHODS

We randomly assigned adults who met at least two of three glycemic criteria for prediabetes (fasting plasma glucose level, 100 to 125 mg per deciliter; plasma glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg per deciliter; and glycated hemoglobin level, 5.7 to 6.4%) and no diagnostic criteria for diabetes to receive 4000 IU per day of vitamin D_3 or placebo, regardless of the baseline serum 25-hydroxyvitamin D level. The primary outcome in this time-to-event analysis was new-onset diabetes, and the trial design was event-driven, with a target number of diabetes events of 508.

RESULTS

A total of 2423 participants underwent randomization (1211 to the vitamin D group and 1212 to the placebo group). By month 24, the mean serum 25-hydroxyvitamin D level in the vitamin D group was 54.3 ng per milliliter (from 27.7 ng per milliliter at baseline), as compared with 28.8 ng per milliliter in the placebo group (from 28.2 ng per milliliter at baseline). After a median follow-up of 2.5 years, the primary outcome of diabetes occurred in 293 participants in the vitamin D group and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). The hazard ratio for vitamin D as compared with placebo was 0.88 (95% confidence interval, 0.75 to 1.04; P=0.12). The incidence of adverse events did not differ significantly between the two groups.

CONCLUSIONS

Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D_3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; D2d ClinicalTrials.gov number, NCT01942694.)

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular effects of ertugliflozin, an inhibitor of sodium–glucose cotransporter 2, have not been established.

METHODS

In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

RESULTS

A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cannon at Brigham and Women's Hospital, 360 Longwood Ave., 7th Fl., Boston, MA 02115, or at cpcannon@bwh.harvard.edu.

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

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Complications in Youth-Onset Type 2 Diabetes

TODAY Study Group*

ABSTRACT

BACKGROUND

The prevalence of type 2 diabetes in youth is increasing, but little is known regarding the occurrence of related complications as these youths transition to adulthood.

METHODS

We previously conducted a multicenter clinical trial (from 2004 to 2011) to evaluate the effects of one of three treatments (metformin, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention) on the time to loss of glycemic control in participants who had onset of type 2 diabetes in youth. After completion of the trial, participants were transitioned to metformin with or without insulin and were enrolled in an observational follow-up study (performed from 2011 to 2020), which was conducted in two phases; the results of this follow-up study are reported here. Assessments for diabetic kidney disease, hypertension, dyslipidemia, and nerve disease were performed annually, and assessments for retinal disease were performed twice. Complications related to diabetes identified outside the study were confirmed and adjudicated.

RESULTS

At the end of the second phase of the follow-up study (January 2020), the mean (±SD) age of the 500 participants who were included in the analyses was 26.4±2.8 years, and the mean time since the diagnosis of diabetes was 13.3±1.8 years. The cumulative incidence of hypertension was 67.5%, the incidence of dyslipidemia was 51.6%, the incidence of diabetic kidney disease was 54.8%, and the incidence of nerve disease was 32.4%. The prevalence of retinal disease, including more advanced stages, was 13.7% in the period from 2010 to 2011 and 51.0% in the period from 2017 to 2018. At least one complication occurred in 60.1% of the participants, and at least two complications occurred in 28.4%. Risk factors for the development of complications included minority race or ethnic group, hyperglycemia, hypertension, and dyslipidemia. No adverse events were recorded during follow-up.

CONCLUSIONS

Among participants who had onset of type 2 diabetes in youth, the risk of complications, including microvascular complications, increased steadily over time and affected most participants by the time of young adulthood. Complications were more common among participants of minority race and ethnic group and among those with hyperglycemia, hypertension, and dyslipidemia. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov numbers, NCT01364350 and NCT02310724.)

The members of the writing committee (Petter Bjornstad, M.D., Kimberly L. Drews, Ph.D., Sonia Caprio, M.D., Rose Gubitosi-Klug, M.D., Ph.D., David M. Nathan, M.D., Bereket Tesfaldet, M.S., Jeanie Tryggestad, M.D., Neil H. White, M.D., and Philip Zeitler, M.D., Ph.D.) assume responsibility for the overall content and integrity of this article.

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

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ΜΗ ΙΝΣΟΥΛΙΝΟ-ΕΞΑΡΤΩΜΕΝΟΣ ΣΑΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ | ΝΙΚΟΛΑΟΣ ΤΕΝΤΟΛΟΥΡΗΣ

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Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018

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Abstract

BACKGROUND—Documenting current trends in diabetes treatment and risk-factor control may inform public health policy and planning.

METHODS—We conducted a cross-sectional analysis of data from adults with diabetes in the United States participating in the National Health and Nutrition Examination Survey (NHANES) to assess national trends in diabetes treatment and risk-factor control from 1999 through 2018.

RESULTS—Diabetes control improved from 1999 to the early 2010s among the participants but subsequently stalled and declined. Between the 2007–2010 period and the 2015–2018 period, the percentage of adult NHANES participants with diabetes in whom glycemic control (glycated hemoglobin level, <7%) was achieved declined from 57.4% (95% confidence interval [CI], 52.9 to 61.8) to 50.5% (95% CI, 45.8 to 55.3). After major improvements in lipid control (non–high-density lipoprotein cholesterol level, <130 mg per deciliter) in the early 2000s, minimal improvement was seen from 2007–2010 (52.3%; 95% CI, 49.2 to 55.3) to 2015–2018 (55.7%; 95% CI, 50.8 to 60.5). From 2011–2014 to 2015–2018, the percentage of participants in whom blood-pressure control (<140/90 mm Hg) was achieved decreased from 74.2% (95% CI, 70.7 to 77.4) to 70.4% (95% CI, 66.7 to 73.8). The percentage of participants in whom all three targets were simultaneously achieved plateaued after 2010 and was 22.2% (95% CI, 17.9 to 27.3) in 2015–2018. The percentages of participants who used any glucose-lowering medication or any blood-pressure–lowering medication were unchanged after 2010, and the percentage who used statins plateaued after 2014. After 2010, the use of combination therapy declined in participants with uncontrolled blood pressure and plateaued for those with poor glycemic control.

CONCLUSIONS—After more than a decade of progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adult NHANES participants with diabetes, while lipid control leveled off. (Funded by the National Heart, Lung, and Blood Institute.)

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Dr. Coresh reports owning stock options in Healthy.io; and Dr. Selvin, receiving lecture fees from Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

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

ΔΙΑΤΡΟΦΗ

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Applying Sports Nutrition Research for Enhancing Public Health

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Professor of Nutrition, Emeritus, Georgia State University, USA

Presentation:

This presentation has 7 sections, including the introduction, information related to 'weight' assessment, issues related to the assessment of the energy cost of activity, the misperception of labeling certain foods as 'perfect', the multiple dietary factors associated with hyperinsulinemia, the misuse of nutrient supplements, and issues related to within-day energy balance. The section abstracts and associated references are listed below.

Introduction Abstract

The introduction establishes the relationship between sports nutrition research and how it can be applied for enhancing public health, while it points out the many nutritional myths that have been in the public sphere for both athletes and the public at large. It also points out the common nutritional failures for both athletes and the general public, including a failure to provide energy and nutrients in a way that they can be optimally used by tissues, and a tendency to excessively emphasize some fuels as more critical for both performance and health than others. Protein, for instance, tends to be emphasized over carbohydrates, but neither athletes nor the general public have an appropriate understanding of how much should be consumed, and how to best consume it to achieve the optimal anabolic effect. Importantly, the well-established problems associated with achieving an optimal nutritional state in athletes mirror the common problems observed in the general public. Of particular concern is that the many nutritional misunderstandings about nutrition tend to elevate obesity risk and associated cardiometabolic disorders. This is largely due to a failure to consume foods/beverages in a way that dynamically satisfies tissue requirements for nutrients, even if the total daily intake of nutrients appears adequate.

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Issues of 'Weight' Abstract

One of the major failures observed in both athletes and non-athletes is the use of body mass (i.e., weight) as a primary indicator of well-being. Doing so fails to discriminate between the status of lean mass vs. fat mass, or to determine how these mass components have changed. In addition, the terminology used for labeling individuals as 'obese' or 'overweight' via the weight:height index (BMI), can be misleading as the term 'obese' refers to having too much body fat, while neither 'weight' nor 'BMI' make a direct determination of body fatness. Athletes are encouraged to increase musculature to enhance their strength:weight ratio, and the resulting elevated musculature per unit height often inappropriately may place them in an 'obese' category using 'BMI'. In non-athlete children, the low sensitivity to detecting excess body fatness fails to identify over 25% of children who are obese because of their normal weight:height ratio. There is also a common belief that only consuming excess food will make you fat, but data clearly indicate that individuals who diet (i.e., consume a lower caloric intake than they are accustomed to) to lose weight become more fat because of the excess catabolism of fat-free mass. In addition, once adaptive thermogenesis occurs several months following the 'diet', there is a faster rate of fat recovery relative to fat-free mass recovery, resulting in the same 'weight' the individual had prior to the 'diet', but a weight that is constituted of more fat mass and lower lean mass. This weight rebound is associated with greater risk of both cardiovascular and renal diseases. Athletes in subjectively scored appearance sports (i.e., diving, gymnastics, figure skating, etc.) are very weight conscious, and are predisposed to 'dieting' if they are told they need to lose 'weight'. This inevitable weight cycling may predispose them to increased risk for eating disorders and low bone mineral density that places them at high fracture risk. The common recommendation, therefore, to eat less and exercise more may make matters worse for whoever follows this strategy for achieving the desired weight.

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Energy Cost of Exercise Abstract

One of the difficulties for determining how much food (i.e., how many calories) an individual should consume is extremely difficult to determine because the greater the exercise the more individuals find a way to burn less energy to do the exercise. This improved energy efficiency is likely a genetic survival mechanism that treats energy/food as precious. Regular physical activity improves oxygen delivery and

greater exercise efficiency, making it difficult to calculate energy utilization via standard means and increasing the risk that the determined value is inaccurate.

Energy Cost of Exercise References

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Misperception of 'Perfect Food' Abstract

It is common for both athletes and non-athletes to think of certain foods as 'perfect', resulting in their overconsumption. The excessive emphasis on a single food inevitably results in the inadequate consumption of other foods, with malnutrition as the inevitable outcome. Consider, for instance, that it is common for people to eat the same breakfast virtually every morning. This has two problems associated with it, including a failure to expose tissues with all the nutrients they require and failing to avoid excess tissue exposure to a potentially toxic substance contained in the regularly consumed foods. One strategy for assuring better nutrient exposure is to vary the colors of foods consumed, as each different color is associated with different nutrients/phytonutrients.

Misperception of 'Perfect Food' References

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Sugar Intake and Food Patterns Associated with Hyperinsulinemia Abstract

Many athletes are resistant to consuming sports beverages because they contain sugar and are fearful that the sugar will elevate their body fat level. Athletes should be trained to understand that sugar-containing sports beverages are intended to be consumed in small amounts during physical activity to avoid thirst, rather than waiting for thirst to occur followed by a large consumption of sports beverage all at once. While it is true that a high bolus of sugar consumption of sugar has a hyperinsulinemic effect that is likely to elevate body fatness, it is also true that there are other important factors that are associated with hyperinsulinemia. For instance, waiting too long to eat may result in low blood sugar and eating in a low blood sugar state results in hyperinsulinemia, regardless of what foods are consumed. Also, the appetite stimulating hormone ghrelin is only turned off with a normoinsulinemic response to eating, resulting in a sustained appetite that causes individuals to eat too much in a meal. Insulin is also elevated exponentially to the caloric load of the meal, so allowing low blood sugar to occur inevitably results in fat elevating hyperinsulinemia.

Sugar Intake and Food Patterns Associated with Hyperinsulinemia References

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Nutrient Supplement Issues Abstract

Nutrient supplements are common in both athlete and non-athlete populations. Studies now clearly indicate that both athletes and the general public would do better with a lower reliance on supplements and higher reliance of food to obtain needed nutrients. Studies of athletes have found that a significant proportion of supplements targeting this population contain illegal substances not listed on the label. In addition, the level of nutrient content of many supplements far exceeds tissue capability to absorb it, with repeating daily intakes resulting in decreased tissue uptake. A study monitoring dietary supplements and mortality rate in older women found a higher mortality risk for all supplements (multivitamins, vitamin B6, iron, folate, zinc…) with only calcium supplementation demonstrating a lower mortality risk for this population. Studies of folate have found that there is a completely different mortality risk related to how folate intake is distributed during the day. For instance, individuals who consume the recommended daily intake (400 mcg) in a single dose are likely to have elevated cancer risk, while those who consume the same amount distributed during the day in four 100 mcg doses have lower cancer risk.

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Within-Day Energy Balance Issues Abstract

It is important to consider the problems associated with the traditional strategy for determining energy balance, often referred to as 'Energy-In vs. Energy-Out' and determined over a 24-hour period. This traditional view of energy balance suggests that if, over a 24-hour period, 3,000 Calories are consumed and 3,000 Calories are expended the person is in perfect energy balance and 'weight' will stay the same. However, because energy balance occurs in real time (i.e., the pancreas doesn't wait until the end of the day to determine how much insulin to produce), this traditional view of energy balance fails to provide essential information. Studies clearly demonstrate that decreased meal frequency, even when 24-hour energy balance is achieved, is associated with higher body fat and lower lean mass. Athletes, because of their elevated energy expenditure during physical activity, can more easily achieve a severe negative energy balanced state, with negative consequences, than non-athletes. However, studies of non-athletes also clearly demonstrate that meal-skipping, which results in a severe negative energy balance, is also associated with higher body fat and more cardiometabolic risk factors. A recent consensus statement by the International Olympic Committee has established a term for this condition, which is referred to as 'Relative Energy Deficiency in Sport (RED-S)', and has determined that this condition (i.e., not having sufficient energy to do the physical task required), results in higher disease risks and multiple negative performance outcomes. Studies have also demonstrated that the state of energy balance, in real time, can influence how nutrients are used. For instance, a good energy balance and appropriate distribution of protein has a much better anabolic outcome than consuming the same amount of protein that is poorly distributed or consumed when in a negative energy balanced state. It is important to consider that both nutrient and energy balance must be considered in real time, with both intakes that are excessive or inadequate in real time causing problems that can negatively impact body composition and health.

Within-Day Energy Balance Issues References

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ΕΠΙΝΕΦΡΙΔΙΑ

ΚΡΥΣΤΑΛΛΕΝΙΑ ΑΛΕΞΑΝΔΡΑΚΗ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ ΑΚΑΔΗΜΑΪΚΟΣ ΥΠΟΤΡΟΦΟΣ, ΙΑΤΡΙΚΗ ΣΧΟΛΗ, Ε.Κ.Π.Α.

Επινεφρίδια
ΠΡΟΕΔΡΟΣ: Δήμητρα Βασιλειάδη
ΟΜΙΛΗΤΗΣ: Κρυσταλλένια Αλεξανδράκη

Endocrine-Related Cancer | M Araujo-Castro *et al.* | Complications in pheochromocytoma surgery | **28**:11 | **695**–703

RESEARCH

Risk factors for intraoperative complications in pheochromocytomas

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Background
Unicentric studies and/or with a limited number of patients (pts) included, not generalizability of results

Purpose identify presurgical and surgical risk factors for intraoperative complications in pts with pheochromocytomas

Methods Retrospective study; pts with pheochromocytomas; surgery in 10 Spanish hospitals; 2011 ⟶ 2021
Intraoperative Complications: intraoperative hypertensive crisis, intraoperative bleeding, prolonged hypotensive episode, arrhythmias, hemodynamic instability, others

Results
162 surgeries (159 pts); mean age 51.6±16.4 years (yrs) old; 52.8% women; median tumour size 40 mm (range 10–110)
- Laparoscopic adrenalectomy - 148 pts vs open adrenalectomy - 14 pts
- Presurgical α- and β-blockade in 95.1% and 51.9%, respectively

33.3% pts (54) ≥1 intraoperative complications
- Pts pre-treated with doxazosin required intraoperative hypotensive treatment more commonly than pts pre-treated with other antihypertensive drugs (51.1% vs 26.5%, *P*=0.002)

Most common hypertensive crisis in 21% → prolonged hypotension 20% → hemodynamic instability 10.5%

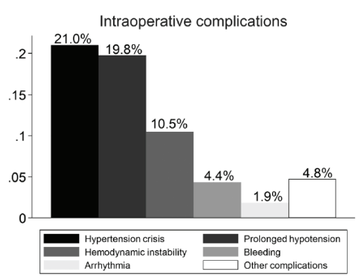

Table 2 Presurgical and surgical risk factors of intraoperative complications.

Variable	Complications (*n* = 53)	No complications (*n* = 109)	OR (95% CI), *P* value
Female sex	55.6% (*n* = 30)	51.9% (*n* = 56)	*OR* = 0.81 (0.42–1.57), *P* = 0.531
Age	53.3 ± 16.98	50.4 ± 16.14	*OR* = 1.01 (0.99–1.03), *P* = 0.301
Any comorbidity	50% (*n* = 27)	37.0% (*n* = 40)	*OR* = 1.7 (0.88–3.29), *P* = 0.115
Diabetes	33.3% (*n* = 18)	21.3% (*n* = 23)	*OR* = 1.8 (0.89–3.83), *P* = 0.101
Hypertension	59.3% (*n* = 32)	61.1% (*n* = 66)	*OR* = 0.93 (0.48–1.80), *P* = 0.820
Obesity	16.7% (*n* = 9)	14.3% (*n* = 15)	*OR* = 1.2 (0.49–2.95), *P* = 0.693
Cardiovascular disease	16.7% (*n* = 9)	12.0% (*n* = 13)	*OR* = 0.93 (0.58–1.50), *P* = 0.767
Cerebrovascular disease	5.6% (*n* = 3)	3.7% (*n* = 4)	*OR* = 1.53 (0.33–7.09), *P* = 0.592
BMI, kg/m²	25.6 ± 4.9	26.1 ± 4.9	*OR* = 0.98* (0.91–1.05), *P* = 0.560
Presurgical systolic BP	120.7 ± 24.37	118.6 ± 13.7	*OR* = 1.01* (0.99–1.03), *P* = 0.492
Presurgical diastolic BP	72.8 ± 11.7	70.9 ± 9.5	*OR* = 1.02* (0.99–1.05), *P* = 0.284
Presurgical HR	76.6 ± 14.0	72.0 ± 11.7	*OR* = 1.03* (1.00–1.07), *P* = 0.031
Presurgical BP > 130/80	41.5% (*n* = 22)	24.0% (*n* = 23)	*OR* = 2.25 (1.10–4.63), *P* = 0.027
Adrenergic tumours	16.7% (*n* = 9)	29.6% (*n* = 32)	*OR* = 0.48 (0.21–1.09), *P* = 0.066
Urine metanephrine (µg/24 h)	4857.4 ± 10 723.7	1629.6 ± 3517.2	*OR* = 1.01 for each 100 µg/24 h (1.00–1.02), *P* = 0.026
Urine normetanephrine (µg/24 h)	3853.9 ± 4889.1	1882.9 ± 3019.2	*OR* = 1.00 for each 100 µg/24 h (1.00–1.03), *P* = 0.025
Urine epinephrine (µg/24 h)	90.9 ± 209.33	86.6 ± 147.56	*OR* = 1.02 for each 100 µg/24 h (0.81–1.27), *P* = 0.897
Urine norepinephrine (µg/24 h)	1400.7 ± 3509.74	484.5 ± 667.078	*OR* = 1.02 for each 100 µg/24 h (1.00–1.05), *P* = 0.056
Plasmatic metanephrine (µg/dL)	390.8 ± 549.25	399.1 ± 799.44	*OR* = 1.00 for each 10 µg/dL (0.99–1.01), *P* = 0.972
Plasmatic normetanephrine(µg/dL)	1091.6 ± 997.57	1122.63 ± 1784.80	*OR* = 1.00 for each 10 µg/dL (0.99–1.00), *P* = 0.949
Tumour size (mm)	57.3 ± 47.33	38.5 ± 17.29	*OR* = 1.4 for each 10 mm (1.16–1.68), *P* < 0.001
Tumour > 50 mm	43.1% (*n* = 22)	28.0% (*n* = 30)	*OR* = 1.09 (0.97–3.91), *P* = 0.061
Open adrenalectomy	11.1% (*n* = 6)	7.4% (*n* = 8)	*OR* = 1.56 (0.51–4.76), *P* = 0.437
Doxazosin pre-treatment	73.1% (*n* = 38)	52.8% (*n* = 56)	*OR* = 2.21 (1.10–4.42), *P* = 0.0023
Absence of presurgical treatment	3.7% (*n* = 2)	5.6% (*n* = 6)	*OR* = 0.65 (0.13–3.35), *P* = 0.600
Beta-blockers	42.6% (*n* = 23)	56.5% (*n* = 61)	*OR* = 0.57 (0.30–1.11), *P* = 0.095
Not presurgical hydrocortisone (*n* = 140)	92.0% (*n* = 46)	74.4% (*n* = 67)	*OR* = 3.95 (1.28–12.17), *P* = 0.008

- Intraoperative complications more common with higher urine metanephrine (OR=1.01 for each 100 µg/24 h, P=0.026), normetanephrine (OR=1.00 for each 100 µg/24 h, P=0.025), larger tumours (higher content of catecholamines + need for greater surgical manipulation) (OR=1.4 for each 10 mm, P<0.001), insufficient blood pressure (BP) control > 130/80 mmHg (OR=2.25, P=0.027), pre-treated doxazosin (OR=2.20, P=0.023), no perioperative hydrocortisone (HC) (OR=3.95, P=0.008)
- No intraoperative deaths

Limitations
- ✓ Retrospective review of data
- ✓ Variability of anaesthetic and surgical management between medical centres

Strengths
- ✓ Large series of records from consecutive patients in 10 tertiary hospitals
- ✓ Precise definition of complications before data collection and analysis
- ✓ Multicentric nature increases the external validity

Conclusion
- ✓ Intraoperative complications in pheochromocytoma: common and potentially life-threatening
- ✓ Higher metanephrine and normetanephrine levels, larger tumour size, insufficient BP control before surgery, pre-treatment with doxazosin, lack of treatment with perioperative HC associated with higher risk of intraoperative complications

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ORIGINAL ARTICLE

Surgical outcomes in the pheochromocytoma surgery. Results from the PHEO-RISK STUDY

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Purpose To identify presurgical and surgical risk factors for postsurgical complications in the pheochromocytoma surgery

Methods Retrospective study of pheochromocytomas pts submitted to surgery; 10 Spanish hospitals; 2011⟶2021
Postoperative complications were classified according to Clavien-Dindo scale: hypertensive crisis, hypotension episode, hypoglycaemia, acute renal failure, postsurgical ileus, others

Results

162 surgeries (159 pts)

- Preoperative antihypertensive blockade performed in 95.1%; doxazosin monotherapy (43.8%) most frequent regimen. Pts pre-treated doxazosin required intraoperative hypotensive treatment more frequently (49.4% vs 25.0%, P=0.003) than phenoxybenzamine
- No differences rate of intraoperative and postsurgical complications
- Phenoxybenzamine longer hospital stay (12.2 ± 11.16 vs 6.2 ± 6.82, P<0.001) than doxazosin

Table 2 Presurgical antihypertensive regimens, blood pressure levels and intraoperative complications

Pre-treatment regimen, %	Pre-treatment SBP/DBP	SBP/DBP before surgery	Intraoperative hypertensive crisis	Intraoperative hypotensive crisis	Hemodynamic instability
Doxazosin monotherapy ($n=71$)	133.3 ± 21.8/ 79.9 ± 12.9	117.8 ± 10.4/ 70.6 ± 10.4	15.5% ($n=11$)	16.9% ($n=12$)	11.3% ($n=8$)
PHENO monotherapy ($n=39$)	128.7 ± 22.5/ 77.4 ± 14. 2	113.1 ± 23.1/ 70.9 ± 10.6	18.0% ($n=7$)	18.0% ($n=7$)	7.7% ($n=3$)
Doxazosin + PHENO ($n=5$)	123.0 ± 24.5/ 81.8 ± 19.8	120.0 ± 18.3/ 77.5 ± 9.6	80.0% ($n=4$)	40.0% ($n=2$)	20.0% ($n=1$)
Doxazosin + amlodipine ($n=15$)	159.5 ± 31.0/ 94.3 ± 16.3	124.3 ± 18.2/ 71.5 ± 8.6	46.7% ($n=7$)	53.3% ($n=8$)	20.0% ($n=3$)
PHENO + amlodipine ($n=6$)	144.3 ± 27.4/ 86.7 ± 17.9	122.0 ± 18.1/ 73.8 ± 7.2	33.3% ($n=2$)	33.3% ($n=6$)	16.7% ($n=1$)
Other regimens ($n=24$)	139.5 ± 34.8/ 81.2 ± 19.8	122.0 ± 16.3/ 74.9 ± 9.8	45.5% ($n=10$)	40.9% ($n=9$)	27.3% ($n=6$)

PHENO phenoxybenzamine, *SBP/DBP* systolic blood pressure/diastolic blood pressure

Variable	OR [95% CI], *p* value
Female sex	OR = 1.48 [0.67–3.25], $P=0.326$
Age >65 years	OR = 2.43 [1.05–5.62], $P=0.042$
Diabetes	OR = 3.17 [1.39–7.23] $P=0.007$
Hypertension	OR = 2.15 [0.90–5.15], $P=0.076$
Severe hypertension (SBP >180 and/or DBP >100 mmHg)	OR = 1.64 [0.41–6.54], $P=0.501$
Obesity	OR = 1.2 [0.49–2.95], $P=0.693$
Cardiovascular disease	OR = 0.93 [0.51–1.70], $P=0.800$
Cerebrovascular disease	OR = 6.32 [1.34–29.88], $P=0.022$
BMI, kg/in2	OR = 0.98 for each kg/m^2 [0.88–1.09] $P=0.720$
Presurgical BP >130/80	OR = 1.48 [0.60–3.69], $P=0.403$
Fasting plasma glucose	OR = 1.13 for each 10 mg/dl [1.03–1.25], $P=0.013$
Urinary free metanephrine (μg/24 h)	OR = 1.01 for each 100 mcg/24 h [1.00–1.02], $P=0.010$
Urinary free normetanephrine (μg/24 h)	OR = 1.01 for each 100 mcg/24 h [1.00–1.03], $P=0.088$
Plasma free metanephrine levels (μg/dl)	OR = 1.00 for each 10 mcg/dl [0.98–1.01], $P=0.743$
Plasma free normetanephrine (μg/dl)	OR = 1.00 for each 10 mcg/dl [0.98–1.01], $P=0.279$
Urinary epinephrine (μg/24 h)	OR = 1.20 for each 100 mcg/24 h [0.95–1.50], $P=0.125$
Urinary norepinephrine (μg/24 h)	OR = 1.08 for each 100 mcg/24 h [1.02–1.15], $P<0.001$
Tumour size >50 mm	OR = 2.70 [1.21–6.02], $P=0.016$
Open adrenalectomy	OR = 1.79 [0.52–6.15], $P=0.370$
Doxazosin pre-treatment	OR = 0.78 [0.35–1.76], $P=0.554$
Beta-blockers	OR = 0.61 [0.28–1.35], $P=0.219$
Intraoperative complications	OR = 1.94 [0.87–4.33], $P=0.107$
Use of intraoperative vasoactive drugs	OR = 1.25 [0.54–2.89], $P=0.601$
Use of intraoperative hypotensive drugs	OR = 0.90 [0.40–2.01], $P=0.798$

Results

- Hypertension resolution in 78.7%
- Biochemical cure in 96.6%
- 31 pts (19.1%) had postsurgical complications; prolonged hypotension the most common, in 9.9% (16), followed by hypoglycaemia in 6 pts and acute renal failure in 4 pts
- 13% of complications score ≥3 in the Clavien-Dindo scale

Postsurgical complications more common in pts with diabetes, cerebrovascular disease, higher plasma glucose levels, higher urinary free metanephrine and norepinephrine, and pheochromocytomas > 5 cm

Limitations:

- ✓ Retrospective review of data
- ✓ Variability of anaesthetic and surgical management between medical centres

Strengths:

- ✓ Large series of records from consecutive pts in 10 tertiary hospitals
- ✓ Precise definition of complications before data collection and analysis

Conclusion

Preoperative medical treatment and postsurgical monitoring of pheochromocytoma: pts with diabetes, cerebrovascular disease, higher levels of plasma glucose and urine free metanephrine and norepinephrine, with pheochromocytomas >5 cm, due to the higher risk of postsurgical complications

Clinical Study | K Zawadzka and others | α-Blockade: pretreatment for pheochromocytoma | 184:6 | 751–760

Selective vs non-selective alpha-blockade prior to adrenalectomy for pheochromocytoma: systematic review and meta-analysis

Karolina Zawadzka[1], Krzysztof Więckowski[1], Piotr Małczak[1,2], Michał Wysocki[1,2], Piotr Major[1,2], Michał Pędziwiatr[1,2] and Magdalena Pisarska-Adamczyk[1,2]

European Journal of Endocrinology (2021) 184, 751–760

Objective

- ✓ α-adrenergic blockade 1st choice of preoperative treatment in pts with functional pheochromocytoma and sympathetic paraganglioma
- ✓ No consensus whether selective or non-selective α-blockade superior for preventing perioperative hemodynamic instability and complications

Design Compare selective and non-selective alpha-blockade: systematic review with meta-analysis

Methods MEDLINE, Embase, Web of Science and Cochrane Library searched for eligible studies. Randomized and observational studies comparing selective vs non-selective α-blockade in pheochromocytoma and sympathetic paraganglioma surgery in adults. Data on perioperative hemodynamic parameters and postoperative outcomes were extracted.

Results

11 studies [1 RCT and 10 observational]- 1344 pts: 578 pretreated with the selective α-blocker (SAB) [terazosin, prazosin, doxazosin]; 766 pretreated with non-selective alpha-blocker (NAB) [phenoxybenzamine]

- Pts receiving SAB higher maximum intraoperative systolic BP (SBP) (weighted mean difference, WMD: 12.14 mmHg , 95%CI: 6.06–18.21, *P*<0.0001) vs NAB
- Group pretreated with SAB, more frequently intraoperative vasodilators (OR: 2.46 , 95%CI 1.44–4.20, *P*=0.001)
- Pts treated with SAB lower minimum intraoperative SBP (WMD: −2.03 mmHg, 95% CI: −4.06 to −0.01, *P*=0.05) and shorter length of hospital stay (WMD: −0.58 days, 95% CI: −1.12 to −0.04, *P*=0.04)
- Operative time, overall morbidity and mortality did not differ between the groups

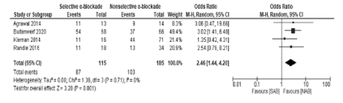

Figure 6
Pooled estimates of intraoperative usage of vasodilators comparing SAB vs NAB. df, degrees of freedom.

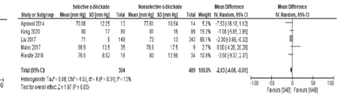

Figure 4
Pooled estimates of minimum intraoperative systolic blood pressure comparing SAB vs NAB. df, degrees of freedom.

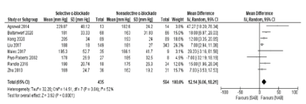

Figure 2
Pooled estimates of maximum intraoperative systolic blood pressure comparing SAB vs NAB. df, degrees of freedom.

Limitations

- ✓ Heterogeneity in preoperative treatment strategies (goals and dosage)
- ✓ Included studies characterized by moderate or low quality

Conclusions

This meta-analysis shows **NAB more effective in preventing intraoperative BP fluctuations** while maintaining comparable risk of both intraoperative and postoperative hypotension and overall morbidity

Maternal and fetal outcomes in phaeochromocytoma and pregnancy: a multicentre retrospective cohort study and systematic review of literature

Lancet Diabetes Endocrinol 2021; 9: 13–21

*Irina Bancos, Elizabeth Atkinson, Charis Eng, William F Young Jr, Hartmut P H Neumann, on behalf of the International Pheochromocytoma and Pregnancy Study Group**

Background Phaeochromocytoma or paraganglioma (PPGL) in pregnant women → severe complications and death ~ catecholamine excess

Purpose Identify factors ~ maternal and fetal outcomes in women with PPGL during pregnancy

Methods Multicentre, retrospective study; patients with PPGL and pregnancy; 1/1/1980 → 31/12/2019; International Pheochromocytoma and Pregnancy Registry; systematic review 2005 - 2019 > 5 cases.

- ✓ Inclusion criteria: pregnancy and PPGL before or during pregnancy or within 12 months post-partum
- ✓ Eligible pts retrospective study and systematic review included
- ✓ Outcomes of interest: maternal or fetal death; maternal severe cardiovascular complications of catecholamine excess

Findings Systematic review 7 studies (63 pregnancies: 55 pts) eligibility criteria and quality 197 pregnancies (-11 overlap?) 186 pts Registry→ **249 pregnancies in 232** PPGL pts. Diagnosis PPGL *before* 37 (15%), *during* 134 (54%), *after* 78 (31%). Genetic predisposition: 95/144 (66%)

- ✓ Unrecognised PPGL during pregnancy (OR 27·0; 95% CI 3·5–3473·1), abdominal/ pelvic location (11·3; 1·5–1440·5), catecholamine excess >10ULN (4·7; 1·8–13·8)**~adverse outcomes**
- ✓ During pregnancy, α-adrenergic blockade ~fewer adverse outcomes (3·6; 1·1–13·2 for no α-adrenergic blockade *vs* α-adrenergic blockade)
- ✓ Surgery during pregnancy not ~better outcomes (0·9; 0·3–3·9 for no surgery *vs* surgery).

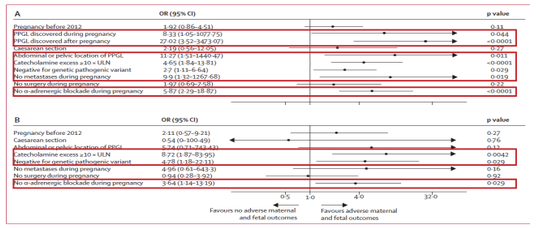

Figure 2: Factors associated with adverse maternal and fetal outcomes

	(n=197)	(n=33)	
Age at pregnancy, years	29 (25–46)	29 (19–40)	0·40
Year of pregnancy (n=195)	2012 (1980–2019)	2006 (1982–2019)	0·043
Time of PPGL discovery			
Before pregnancy	35 (18%)	0	0·0001
During pregnancy	106 (54%)	12 (36%)	..
Gestation week	26 (6–38)	25 (10–28)	..
After pregnancy	56 (28%)	21 (64%)	..
Location of PPGL			
Abdominal or pelvic	169 (86%)	33 (100%)	0·021
Other locations	28 (14%)	0	..
Time of delivery or miscarriage (n=228)			
<32 weeks	15 (8%)	19 (59%)	<0·0001
≥32 weeks	181 (92%)	13 (41%)	..
Type of delivery in term pregnancies (n=156)			
Vaginal	62 (42%)	2 (22%)	0·24
Caesarean section	85 (58%)	7 (78%)	..
Tumour size, mm (n=186)	51 (13–310)	51 (20–158)	0·67
Degree of catecholamine excess (n=187)			
2 x ULN	33 (20%)	2 (8%)	0·0027
5 x ULN	31 (19%)	2 (8%)	..
10 x ULN	26 (16%)	1 (4%)	..
>10 x ULN	72 (44%)	20 (80%)	..
Metastases present during pregnancy			
No	172 (87%)	33 (100%)	0·030
Yes	25 (13%)	0	..
Positive for genetic disease (n=149)			
No	36 (39%)	12 (52%)	0·026
Yes	90 (71%)	11 (48%)	..

Data are n (%) or median (range). Data are reported for each pregnancy, after excluding non-functioning PPGL, pregnancies terminated through elective abortion, and ongoing pregnancies. For categories with missing data, the number of patients with available data is indicated. PPGL=phaeochromocytoma and paraganglioma. ULN=upper limit of normal.

Table 3: Factors associated with adverse maternal and fetal outcomes in pregnancy with PPGL

Limitations:

- ✓ Retrospective design
- ✓ Inclusion of convenient sample of pts, non-systematic reporting of data, selection, and information bias
- ✓ Period of enrolment several decades: advances in obstetric care and the understanding of PPGL

Strengths:

- ✓ Largest known cohort of pregnant women with PPGL
- ✓ Systematically searched multiple databases and obtained published data on individual pts not included in the registry → the most complete evidence base to date and providing more generalisable inferences

Interpretation

- ✓ Unrecognised and untreated PPGL ~substantially higher risk of either maternal or fetal complications
- ✓ Appropriate case detection and counselling for premenopausal women at risk for PPGL could prevent adverse pregnancy-related outcomes

Loss of *KDM1A* in GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome: a multicentre, retrospective, cohort study

Lancet Diabetes Endocrinol 2021; 9: 813-24

Fanny Chasseloup, Isabelle Bourdeau*, Antoine Tabarin, Daniela Regazzo, Charles Dumontet, Nataly Ladurelle, Lucie Tosca, Larbi Amazit, Alexis Proust, Raphael Scharfmann, Tiphaine Mignot, Frédéric Fiore, Stylianos Tsagarakis, Dimitra Vassiliadi, Dominique Maiter, Jacques Young, Anne-Lise Lecoq, Vianney Deméocq, Sylvie Salenave, Hervé Lefebvre, Lucie Cloix, Philippe Emy, Rachel Dessailloud, Delphine Vezzosi, Carla Scaroni, Mattia Barbot, Wouter de Herder, François Pattou, Martine Tétreault, Gilles Corbeil, Margot Dupeux, Benoit Lambert, Gérard Tachdjian, Anne Guiochon-Mantel, Isabelle Beau, Philippe Chanson, Say Viengchareun, André Lacroix, Jérôme Bouligand, Peter Kamenický*

Background Ectopic expression of the glucose-dependent insulinotropic polypeptide (GIP) receptor-dependent primary bilateral macronodular adrenal hyperplasia (PBMAH) with Cushing's syndrome (CS) by aberrant expression of the GIP receptor adrenal lesions. Bilateral nature suggests germline genetic predisposition.

AIM identify the genetic driver event responsible for GIP-dependent PBMAH with CS

Methods Multicentre, retrospective, cohort study hospitals (France, Canada, Italy, **Greece**, Belgium, Netherlands). Blood/adrenal samples pts unilateral or bilateral adrenalectomy GIP-dependent PBMAH with CS. Adrenal samples pts with PBMAH adrenalectomy overt or mild CS without evidence of and those with GIP-dependent unilateral adrenocortical adenomas (control groups). Whole genome, whole exome, targeted next generation sequencing (NGS), copy number analyses of blood and adrenal DNA from pts with familial or sporadic disease. RNA sequencing on adrenal samples and functional analyses of the identified genetic defect in the human adrenocortical cell line H295R.

Findings 17 pts with GIP-dependent PBMAH with CS. Median age pts 43·3 (95%CI 38·8–47·8) yrs and most pts (15 [88%]) women

- ✓ We identified **germline heterozygous pathogenic** or most likely **inactivating** pathogenic variants in the *KDM1A* gene in all 17 pts: not reported in gnomAD or in the 1000 Genomes Project databases
- ✓ Recurrent deletion in the short p arm of chromosome 1 harboring the *KDM1A* locus in adrenal lesions of these pts
- ✓ 0/29 pts in the control groups *KDM1A* germline or somatic alterations
- ✓ ARMC5 and KDM1A mutually exclusive driver events
- ✓ Concomitant **genetic inactivation** of both *KDM1A* alleles → **loss of *KDM1A* expression** in adrenal lesions → Global gene expression analysis showed **GIP receptor upregulation** with a log2 fold change of 7·99 (95%CI 7·34–8·66; $p=4{\cdot}4 \times 10^{-125}$), and differential regulation of several other G protein-coupled receptors in GIP-dependent PBMAH samples vs control samples
- ✓ In vitro pharmacological inhibition and inactivation of KDM1A by CRISPR-Cas9 genome editing → ↑ GIP receptor transcripts and protein in human adrenocortical H295R cells

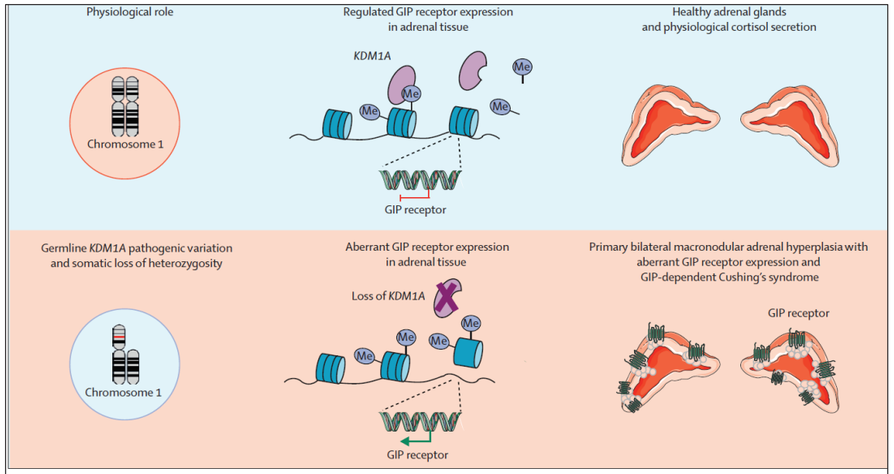

Figure 5: **Pathophysiology of GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome**
A free medical art server, Servier Medical Art, was used for some components of the figure. GIP=glucose-dependent insulinotropic polypeptide.

	Sex	Age, years	Adrenal histology	24 h urinary free cortisol, μg per 24 h	Morning plasma corticotropin, pg/mL	Morning plasma cortisol, μg/dL	Post-prandial plasma cortisol, μg/dL	References (patient reported)
Patient 1	Man	54	Primary bilateral macronodular adrenal hyperplasia and myelolipoma	294	<1	9	33	Unpublished
Patient 2	Woman	42	Primary bilateral macronodular adrenal hyperplasia	463	<1	5	35	Lecoq et al[7] (patient 13)
Patient 3	Woman	47	Primary bilateral macronodular adrenal hyperplasia and myelolipoma	512	2	7	23	Unpublished
Patient 4	Woman	55	Primary bilateral macronodular adrenal hyperplasia	43	<15	3	28	Lecoq et al[7] (patient 7)
Patient 5	Man	35	Primary bilateral macronodular adrenal hyperplasia	372	15	5	27	Lecoq et al[7] (patient 8)
Patient 6	Woman	43	Primary bilateral macronodular adrenal hyperplasia	213	<1	5	26	Lecoq et al[7] (patient 12)
Patient 7	Woman	43	Primary bilateral macronodular adrenal hyperplasia	230	5	15	40	Lecoq et al[7] (patient 9)
Patient 8	Woman	30	Primary bilateral macronodular adrenal hyperplasia	450	5	9	25	Unpublished
Patient 9	Woman	61	Primary bilateral macronodular adrenal hyperplasia and myelolipoma	319	<1	8	38	Larose et al[9]
Patient 10	Woman	33	Primary bilateral macronodular adrenal hyperplasia	390	1	10	36	Lecoq et al[7] (patient 6)
Patient 11	Woman	45	Primary bilateral macronodular adrenal hyperplasia	525	<5	6	35	Lecoq et al[7] (patient 10)
Patient 12	Woman	54	Primary bilateral macronodular adrenal hyperplasia	707	<5	16	76	Lecoq et al[7] (patient 11)
Patient 13	Woman	42	Primary bilateral macronodular adrenal hyperplasia and myelolipoma	6*	8	3	22	Unpublished
Patient 14	Woman	41	Primary bilateral macronodular adrenal hyperplasia	7*	<5	7	22	Unpublished
Patient 15	Woman	34	Unknown	5*	<5	6	25	Unpublished
Patient 16	Woman	35	Primary bilateral macronodular adrenal hyperplasia	8*	<5	7	20	Albiger et al[10] (patient 1)
Patient 17	Woman	42	Primary bilateral macronodular adrenal hyperplasia	498	4	6	27	Karapanou et al[11] (patient 1)

Patient 1 is shown as patient 10 (III) in figure 1A and patients 2 and 3 are shown as patients 1 (II) and 1 (I) in figure 1B. *Upper limit of normal. Conversions to International System of Units: μg per 24 h is equivalent to 2·76 nmol/L, pg/mL is equivalent to 0·22 pmol/L; μg/dL is equivalent to 27·6 nmol/L.

Table: Patient characteristics

Implications of all the available evidence

Uncovering a common genetic mechanism of GIP-dependent primary bilateral macronodular adrenal hyperplasia represents a substantial advancement in the field of adrenal Cushing's syndrome. This finding will enable genetic testing and counselling of patients and earlier detection of the disease, which is important because *KDM1A* pathogenic variants predispose to myelomas or monoclonal gammopathy of undetermined significance. Further, this novel role of *KDM1A* as an epigenetic regulator of GIP receptor expression and that of several other G protein-coupled receptors can have pharmacological implications. Targeting KDM1A by inhibitors could possibly be applied beyond the field of adrenal hyperplasia—eg, in the field of endocrine and metabolic diseases—and warrants further investigation.

Interpretation

- ✓ GIP-dependent PBMAH with CS results from a two-hit inactivation of *KDM1A*, consistent with tumour suppressor gene model of tumorigenesis → **genetic disease**
- ✓ Genetic testing and counselling offered to pts and 1st-degree relatives
- ✓ Carriers KDM1A pathogenic variants: clinical examination and biochemical screening including fasting and post-prandial plasma cortisol, urinary free cortisol (UFC) excretion, and serum protein electrophoresis to detect *monoclonal gammopathy*

Annals of Internal Medicine — ORIGINAL RESEARCH

Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors

Ann Intern Med. doi:10.7326/M21-1737

A Cross-Sectional Multicenter Study

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Background

- ✓ Benign adrenal tumors commonly discovered on cross-sectional imaging
- ✓ Mild autonomous cortisol secretion (MACS) regularly diagnosed, **but** effect on cardiometabolic disease in affected persons: ill defined

Objective 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/ tertiary centers (2011-2016) **Participants** 1305 prospectively recruited persons with benign adrenal tumors **Measurements** Cortisol excess defined = clinical assessment + 1-mg overnight dexamethasone-suppression test (cortisol: <50 nmol/L, nonfunctioning adrenal tumor [NFAT]; 50 - 138 nmol/L, possible MACS [MACS-1]; >138 nmol/L + absence of typical clinical CS, definitive MACS [MACS-2]). Net steroid production assessed by multisteroid profiling 24-hour urine by tandem mass spectrometry.

Results: 1305 participants, **49.7%** NFAT (649; 64.1% women), **34.6%** MACS-1 (451; 67.2% women), **10.7%** MACS-2 (140; 73.6% women), **5.0**% CS (65; 86.2% women).

- ✓ Prevalence and severity of hypertension higher in MACS-2 and CS than NFAT (adjusted prevalence ratios [aPRs]: MACS-2, 1.15 [95% CI, 1.04 to 1.27]; CS, 1.37 [CI, 1.16 to 1.62]; aPRs ≥3 antihypertensives: MACS-2, 1.31 [CI, 1.02 to 1.68], CS, 2.22 [CI, 1.62 to 3.05])
- ✓ Type 2 diabetes more prevalent CS than NFAT (aPR, 1.62 [CI, 1.08 to 2.42]); more likely insulin therapy for MACS-2 (aPR, 1.89 [CI, 1.01 to 3.52]), CS (aPR, 3.06 [CI, 1.60 to 5.85]).

Table 2. Cardiometabolic Disease Burden in Benign Adrenocortical Tumors With Different Degrees of Cortisol Excess*

Cardiometabolic Outcome	NFAT (n = 649)	MACS-1 (n = 451)	MACS-2 (n = 140)	Adrenal CS (n = 65)
Hypertension, n (%)	416 (64.1)	339 (75.2)	107 (76.4)	47 (72.3)
Unadjusted PR (95% CI)	-	1.17 (1.08-1.27)	1.19 (1.07-1.33)	1.13 (0.96-1.33)
aPR (95% CI)	-	1.07 (0.99-1.16)	1.15 (1.04-1.27)	1.37 (1.16-1.62)
Treatment with ≥3 antihypertensives, n (%)†	142 (34.3)	132 (39.1)	46 (43.0)	27 (57.4)
Unadjusted PR (95% CI)	-	1.14 (0.94-1.38)	1.25 (0.97-1.63)	1.68 (1.26-2.23)
aPR (95% CI)	-	1.12 (0.92-1.37)	1.31 (1.02-1.68)	2.22 (1.62-3.05)
Dysglycemia, n (%)‡	321 (49.5)	243 (53.9)	77 (55.0)	32.4 (49.8)
Unadjusted PR (95% CI)	-	1.09 (0.97-1.23)	1.11 (0.91-1.35)	1.01 (0.75-1.34)
aPR (95% CI)	-	1.00 (0.89-1.13)	1.07 (0.89-1.29)	1.23 (0.92-1.65)
Type 2 diabetes, n (%)	171 (26.4)	145 (32.2)	47 (33.7)	20 (31.5)
Unadjusted PR (95% CI)	-	1.22 (1.00-1.49)	1.27 (0.95-1.72)	1.19 (0.80-1.78)
aPR (95% CI)	-	1.10 (0.91-1.33)	1.23 (0.92-1.64)	1.62 (1.08-2.42)
Insulin treatment, n (%)§	29 (16.9)	37 (25.8)	15 (32.6)	8 (41.0)
Unadjusted PR (95% CI)	-	1.53 (0.92-2.56)	1.94 (1.05-3.59)	2.44 (1.25-4.76)
aPR (95% CI)	-	1.45 (0.83-2.52)	1.89 (1.01-3.52)	3.06 (1.60-5.85)
Dyslipidemia, n (%)	187 (28.8)	161 (35.7)	50 (35.9)	10 (15.7)
Unadjusted PR (95% CI)	-	1.24 (1.04-1.47)	1.24 (0.96-1.60)	0.54 (0.30-0.97)
aPR (95% CI)	-	1.08 (0.91-1.29)	1.18 (0.91-1.52)	0.76 (0.43-1.32)

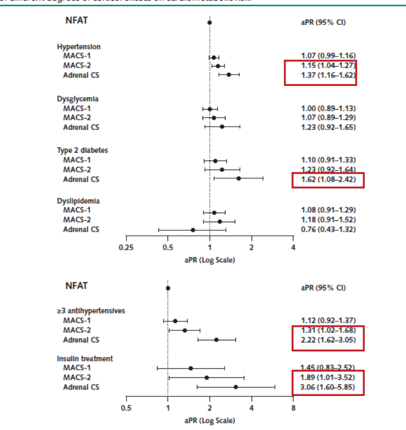
aPR = adjusted prevalence ratio; CS = Cushing syndrome; MACS-1 = possible mild autonomous cortisol secretion; MACS-2 = definitive mild autonomous cortisol secretion; NFAT = nonfunctioning adrenal tumor; PR = prevalence ratio.
* A series of Poisson regression models with robust variance was used to investigate the cardiometabolic burden of 1305 persons from the EURINE-ACT study. Unadjusted and adjusted PRs are reported; adjusted models included age, sex, and body mass index (BMI) as covariates. Missing outcome data were replaced via multiple imputation, using chained equations with age, sex, and BMI as covariates. Imputations for treatment with ≥3 antihypertensives, type 2 diabetes, and insulin treatment were conditional to persons with hypertension, dysglycemia, and type 2 diabetes, respectively.
† Considering only participants with a diagnosis of hypertension (n = 909).
‡ Includes participants with prediabetes and type 2 diabetes.
§ Considering only participants with a diagnosis of type 2 diabetes (n = 383).

ΕΠΙΝΕΦΡΙΔΙΑ | ΚΡΥΣΤΑΛΛΕΝΙΑ ΑΛΕΞΑΝΔΡΑΚΗ

Results

- ✓ Bilateral tumors and MACS → ↑ cardiometabolic burden
- ✓ Urinary multisteroid profiling revealed ↑ glucocorticoid (GC) excretion from NFAT over MACS-1 and MACS-2 to CS [**gradually progressive continuum**], whereas androgen excretion ↓
- ✓ No characteristic (tumor diameter, 1mg-DST results, ACTH, DHEAS, 24-hour UFC) correlated clinically with cardiometabolic disease

Figure 3. Effect of different degrees of cortisol excess on cardiometabolic risk.



Poisson regression models with robust variance were fitted to explore cardiometabolic risk in persons with MACS and adrenal CS versus persons with NFATs. aPRs (adjusted for age, sex, and BMI) and 95% CIs are reported. aPR = adjusted prevalence ratio; CS = Cushing syndrome; MACS = mild autonomous cortisol secretion; MACS-1 = possible MACS; MACS-2 = definitive MACS; NFAT = nonfunctioning adrenal tumor. **Top.** aPRs for hypertension, dysglycemia, type 2 diabetes, and dyslipidemia. **Bottom.** aPRs for treatment with 3 or more antihypertensives (in participants with hypertension) and insulin (in participants with type 2 diabetes).

Limitations

- ✓ Cross-sectional design: possible selection bias

Strengths

- ✓ Prospective recruitment
- ✓ Large sample size
- ✓ Standardized classification of different degrees of cortisol excess
- ✓ 24-hour urine multisteroid profiling by a centralized tandem mass spectrometry assay

Conclusion MACS [no typical features of CS] = cardiometabolic risk condition, predominantly affects women and warrants regular assessment for hypertension and type 2 diabetes

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Clinical Research Article
ENDOCRINE SOCIETY

Clinical Research Article

An Open-label Phase I/IIa Clinical Trial of 11β-HSD1 Inhibitor for Cushing's Syndrome and Autonomous Cortisol Secretion

Satoko Oda,[1,*] Kenji Ashida,[1,2,*] Makiko Uchiyama,[3] Shohei Sakamoto,[1] Nao Hasuzawa,[1,2] Ayako Nagayama,[2] Lixiang Wang,[1,4] Hiromi Nagata,[1] Ryuichi Sakamoto,[1] Junji Kishimoto,[3] Koji Todaka,[3] Yoshihiro Ogawa,[1] Yoichi Nakanishi,[3] and Masatoshi Nomura[1,2]

Context 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors → antimetabolic and antisarcopenic effects in CS and autonomous cortisol secretion (ACS) pts

Objective Confirm efficacy and safety of S-707106 (11β-HSD1 inhibitor) administered to CS and ACS pts

Design 24-week single-center, open-label, single-arm, dose-escalation, investigator initiated clinical trial on a database **Setting** 2 University Hospital **Pts** 16 pts with inoperable or recurrent CS and ACS, with mildly impaired glucose tolerance (IGT) **Intervention** Oral administration 200mg S-707106 after dinner, daily, 24 weeks (wks) (insufficient improvement in oral glucose tolerance test (OGTT) results at 12 wks→ 200 mg twice daily for the residual 12 weeks). **Main Outcome Measures** Rate of participants responding to glucose tolerance impairment, defined as those showing 25% reduction in the area under the curve (AUC) of OGTT at 24 wks

Results

- S-707106 administration not achieve primary endpoint of this clinical trial (>20% of responsive participants: 1 pt not 3).
- AUC glucose ↓ by **−7.1%** [SD, 14.8 (90%CI −14.8 to −1.0), *P* = 0.033] and **−2.7%** [14.5 (−10.2 to 3.4), *P*=0.18] at **12** and **24** wks, respectively.
- ↓AUC glucose significantly in participants with high BMI. Body fat percentage ↓ by **−2.5%** [1.7 (−3.3 to −1.8), *P* < 0.001] and body muscle percentage ↑by **2.4%** [1.6 (1.7 to 3.1), *P* < 0.001].
- ALT; ALT/AST significantly ↓ by 12- and 24-week; γ-GT significantly ↓ after 24 wks
- Eicosapentaenoic acid (EPA), EPA/arachidonic acid (AA) significantly ↓after the 24-wk
- Cushing QOL scores significantly improved at 24 wks
- Systemic eruption in 1 pt cured by S-707106 discontinuation; 2 pts [1 (pyelonephritis) and urinary tract infection] due to CS.

  - Inhibited 11β-HSD1 activity to 1/10 without adrenal insufficiency (AI) development
  - Attenuated insulin resistance
  - ↓ body fat mass and ↑ skeletal muscle mass, demonstrated by anthropometrical changes→ improvement in liver adiposity

Table 2. Changes in glucose metabolism parameters following 11β-HSD1 inhibitor administration: FAS analysis

Variables [reference range]	Baseline [n = 15]	12 weeks [n = 14]		24 weeks [n = 14]	
	Mean ± SD	Mean ± SD	*P*-value[a]	Mean ± SD	*P*-value[a]
FPG (mg/dL) [70-109]					
Value	106.6 ± 19.0	107.6 ± 17.1	0.93	105.6 ± 17.7	0.56
HbA1c (NGSP %) [4.6-6.2]					
Value	6.23 ± 0.50	6.15 ± 0.49		6.15 ± 0.50	
Change value	NA	−0.08 ± 0.24	0.29	−0.07 ± 0.23	0.26
1,5-AG (μg/mL) [male: 14.9-44.7; female: 12.4-28.8]					
Value	15.22 ± 4.19	13.31 ± 4.71	0.0497	13.92 ± 4.23	0.12
AUC glucose (mg/dL × h)					
Value	388.13 ± 90.41	359.49 ± 57.69		375.51 ± 50.22	
Percentage change value	NA	−7.10 ± 14.81 (90% CI: −14.8– −1.0)	0.033[b]	−2.66 ± 14.52 (90% CI: −10.2–3.4)	0.18[b]
Peak PG during 75-g OGTT (mg/dL)					
Value	229.0 ± 53.6	215.6 ± 34.0	0.15	226.1 ± 34.6	0.57
Insulinogenic index					
Value	0.58 ± 0.50	0.57 ± 0.51	0.39	0.53 ± 0.68	0.89
HOMA-IR					
Value	2.85 ± 1.28	2.54 ± 1.76		2.01 ± 0.97	
Change value	NA	−0.38 ± 1.11	0.22	−0.91 ± 0.82	0.0011

Values are presented as means ± SD. Peak plasma glucose levels are measured during the 75-g OGTT. $P < 0.05$ is considered significant and presented in bold.
Abbreviations: AUC, area under the curve; FAS, full analysis set; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test.
[a]Each value is compared with baseline values based on the paired *t*-test.
[b]*P*-values for the percentage change value in the AUC of glucose were calculated with the 1-sided paired *t*-test.

Limitations

- ✓ Small pt number
- ✓ Short study duration
- ✓ Enrollment of participants with mildly IGT with low HbA1c levels

Conclusions

S-707106 = effective insulin sensitizer and antisarcopenic and antiobesity [↓ body fat mass, ↑skeletal muscle mass, possibly improved liver adiposity] medication for these pts

Clinical Study | F Vogel and others | Postoperative IGF-I predicts outcome of Cushing-associated myopathy | 184:6 | 813–821

Patients with low IGF-I after curative surgery for Cushing's syndrome have an adverse long-term outcome of hypercortisolism-induced myopathy

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European Journal of Endocrinology (2021) **184**, 813–821

Background GC excess ⟶ muscle atrophy and weakness in pts with endogenous CS. Insulin-like growth factor I (IGF-I) is known to have protective effects on muscle loss.

Hypothesis Individual serum IGF-I predictive for long-term myopathy outcome in endogenous CS before and after curative surgery

Patients and methods

Prospective longitudinal study 31 pts with florid CS [23 pituitary; 8 adrenal] ; analyzed IGF-I and IGF binding protein 3 (IGFBP 3) at the time of diagnosis and following surgical remission over a period of up to 3 yrs

Assessed: muscle strength by grip strength measurements using a hand grip dynamometer and muscle mass by bio-impedance measurements

Findings

Individual serum IGF-I in the postoperative phase strongly predictive of long-term grip strength outcome (rs = 0.696, *P* ≤ 0.001).

- ✓ **Preoperative** IGF-I during florid phase of CS did not predict long-term muscle function outcome (rs = 0.285, *P* = 0.127).
- ✓ **IGF-I/IGFBP 3 at 6 months** correlated with normalized grip strength after 1, 2 and 3 yrs as well as with lean body cell mass after 2 and 3 yrs
- ✓ **Changes of individual IGF-I SDS from the time of florid hypercortisolism to 6 months after surgery** also correlated with normalized grip strength at 3 yrs (rs = 0.493, P = 0.007)

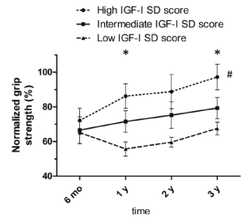

Figure 2
Course of age and gender corrected grip strength (normalized grip strength, % of normal controls) in patients after curative surgery for Cushing's syndrome (mo = months; y = years). Division into three groups was made according to the IGF-I SDS at the time of 6 months after surgery (High IGF-I SDS: IGF-I SDS > 1.4, *n* = 10; Intermediate IGF-I SDS: IGF-I SDS < 1.4 and > −0.4, *n* = 9; Low IGF-I SDS: IGF-I SDS ≤ −0.4, *n* = 10). *n* = 29. Comparisons were performed by Mann-Whitney-*U*-Test and Wilcoxon signed rank test. Higher percentage indicates greater muscle strength. Data are given as mean ± s.e.m.; $P < 0.05$ was considered statistically significant. *$P < 0.05$ High IGF-I SDS vs Low IGF-I SDS, #$P < 0.05$ 3 years follow-up vs 6 months follow-up.

- ✓ Pts with high IGF-I s.d. scores (SDS; >1.4) → improvement in **grip strength** follow-up period (*P*=0.009) ⟶ Pts with lower IGF-I SDS(≤−0.4) → worse outcome with persisting muscle dysfunction
- ✓ Lower IGF-I concentrations 6-months after successful surgery ~ associated with a **lower muscle mass** (≡ lean body cell mass) after 3 yrs (rs = 0.404, *P*=0.033)

Postoperative IGF-I predicts outcome of Cushing-associated myopathy | 184:6 | 816

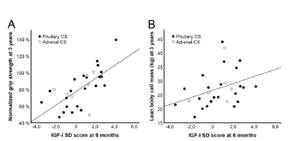

Figure 1
(A) Relationship between IGF-I SDS 6 months after surgical cure of Cushing's syndrome (CS) and age and gender corrected grip strength (normalized grip strength, % of normal controls) after 3 years in remission. Line indicates estimated linear regression line. *n* = 29, Spearman's coefficient 0.696, $R^2 = 0.446$, $P \leq 0.001$. (B) Relationship between IGF-I SDS 6 months after surgery and lean body cell mass as surrogate for muscle mass measured by bio-impedance after 3 years in remission. Line indicates estimated linear regression line. *n* = 28, Spearman's coefficient 0.404, $R^2 = 0.126$, $P = 0.033$.

Limitations

- ✓ Small pts number

Conclusion Lower individual IGF-I concentrations 6 months after curative surgery for CS ~ adverse long-term myopathy outcome and IGF-I might be essential for muscle regeneration in the early phase after correction of hypercortisolism

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Clinical Research Article

Clinical Research Article

Plasma Cortisol and Risk of Atrial Fibrillation: A Mendelian Randomization Study

Susanna C. Larsson,[1,2] Wei-Hsuan Lee,[3] Stephen Burgess,[3,4] and Elias Allara[3]

Context: Atrial fibrillation (AF), cardiac arrhythmias, related risk factors common in pts with CS. Hypercortisolism may be associated with AF, association not yet ascertained causally

Objective determine whether plasma cortisol is causally ~ with AF using a 2-sample Mendelian randomization (MR) design

Methods: 3 genetic variants in *SERPINA1/SERPINA6* locus; functionally associated with plasma cortisol identified in CORtisol NETwork consortium (12597 participants). Summary-level genome-wide association study (GWAS) data for associations between cortisol-associated variants and AF obtained from GWAS meta-analysis 6 studies (60620 AF cases; 970216 noncases) and FinnGen consortium (17325 AF cases; 97214 noncases). Fixed-effects inverse-variance weighted approach accounting for genetic correlations between variants for analysis. Multivariable MR analyses: assess potential mediating effects of SBP and waist circumference (WC) (for central obesity). Summary-level GWAS data for SBP and WC obtained respectively from International Consortium of BP (757601 participants) and Genetic Investigation of Anthropometric Traits consortium (232101 participants).

Table 1. Characteristics of the single nucleotide polymorphisms used to proxy plasma cortisol levels and their associations with AF

				Plasma cortisol		AF in GWAS meta-analysis[a]			AF in FinnGen		
SNP	Chr	Gene	EA	Beta (SE)[b]	*P*	Beta	SE	*P*	Beta	SE	*P*
rs12589136	14	*SERPINA6*	T	0.10 (0.015)	3.3×10^{-12}	0.011	0.008	.175	0.016	0.020	.418
rs11621961	14	*SERPINA6*	T	−0.08 (0.013)	4.0×10^{-8}	−0.017	0.007	.018	−0.019	0.017	.272
rs2749527	14	*SERPINA1*	T	−0.08 (0.013)	5.2×10^{-11}	−0.021	0.007	.002	−0.024	0.016	.143

Abbreviations: AF, atrial fibrillation; Chr, chromosome; EA, effect allele; GWAS, genome-wide association study; SE, standard error; SNP, single nucleotide polymorphism.
[a]Includes data from 6 studies, including The Nord-Trøndelag Health Study, deCODE, the Michigan Genomics Initiative, DiscovEHR, UK Biobank, and the AFGen Consortium.
[b]The beta coefficients and corresponding standard errors represent the age- and sex-adjusted cortisol z-score change in morning plasma cortisol per additional effect allele in 12 597 participants of European ancestries.

Results

- ✓ Meta-analysis of results from 2 data sources, OR of AF per 1 SD ↑ of plasma cortisol was 1.20 (95%CI 1.06-1.35) ⟶ genetically predicted
- ✓ Association attenuated when adjusting for genetically predicted SBP and WC (OR 0.99, 95%CI 0.72-1.38)

- ❑ MR study first to utilize genetic variants associated with cortisol to examine causal association with AF
- ❑ Genetic predisposition to higher plasma cortisol is associated with an ↑ risk of AF

Limitations

- ✓ Single-nucleotide polymorphism (SNPs) selected only explain 0.54% variation in morning plasma cortisol
- ✓ Only European cohorts ⟶ limits applicability to non-European populations

Strengths

- ✓ Compared with observational studies, MR is less prone to biases
- ✓ Highlight potential relevance of hypercortisolemia to AF and provide mechanistic insight into this association

Conclusion Evidence derived from the MR study suggests a positive association between plasma cortisol and risk of AF, likely mediated through SBP and WC

AF monitoring in pts with CS + potential risk of AF caused by sustained hypercortisolemia in general populations

Clinical Study | D Li and others | Fractures in adrenal adenomas | 184:4 | 597–606

Risk of bone fractures after the diagnosis of adrenal adenomas: a population-based cohort study

Dingfeng Li[1], Ravinder Jeet Kaur[1], Catherine D Zhang[1], Andreas Ebbehoj[2], Sumitabh Singh[1], Elizabeth J Atkinson[3], Sara J Achenbach[3], Walter Rocca[4,5,6], Sundeep Khosla[1] and Irina Bancos[1]

European Journal of Endocrinology (2021) 184, 597–606

- ❑ Small studies reported ↑ prevalence/ incidence of asymptomatic vertebral fractures: pts with NFAT/ adenomas MACS
- ❑ Risk symptomatic fractures at vertebrae, and at other sites remains unknown

Objective determine prevalence/ incidence symptomatic site-specific fractures in pts with adrenal adenomas

Design Population-based cohort study, USA, 1995–2017
Methods Pts adrenal adenoma and age/sex -matched referent subjects. Pts overt hormone excess excluded. Main outcomes measures: prevalence and incidence of bone fractures

Results 1004 pts adrenal adenomas, 582 (58%) women, median age diagnosis 63 yrs (20–96)

- ✓ At diagnosis: pts higher prevalence previous fractures (any fracture: 47.9% vs 41.3%, *P* = 0.003, vertebral fracture: 6.4% vs 3.6%, *P*=0.004, combined osteoporotic sites: 16.6% vs 13.3%, *P*=0.04)
- ✓ Median follow-up 6.8 yrs (0–21.9). After adjusting for age, sex, BMI, tobacco use, prior history of fracture, common causes of secondary osteoporosis, pts with adenoma hazard ratio **1.27 (95%CI: 1.07–1.52)** developing new fracture during follow-up
- ✓ Cumulative incidence new fractures any site at 6 months after index date higher pts with adenoma throughout passive follow-up (13.7% vs 8.8% at 5-year, 27.3% vs 18.4% at 10-year and 32.8% vs 31.8% at 15-year of follow-up, P=0.007)
- ✓ Using time to first fracture after index date as an endpoint, pts with adenoma demonstrated higher risk of fractures with a crude HR 1.4 (95%CI: 1.2–1.7).
- ✓ No difference bisphosphonate therapy

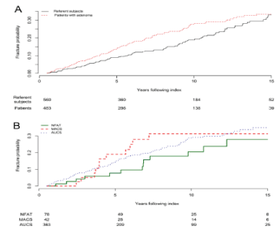

Figure 2
Cumulative incidence of new bone fractures. (A) Cumulative incidence of new bone fractures of any site in patients with adenoma vs referent subjects, starting at 6 months following the index date. After excluding participants who had fractures prior to this starting point, 483 patients with adrenal adenoma and 560 referent subjects entered the analysis. The numbers of participants who completed 5-, 10-, and 15-year passive follow-up period were shown in the figure. (B) Cumulative incidence of new bone fractures of any site in patients with mild autonomous cortisol secretion (MACS), non-functioning adrenal tumors (NFAT), and adenomas with unknown cortisol secretion (AUCS), starting at 6 months following the index date. After excluding participants who had fractures prior to this starting point, 42 patients with MACS, 78 patients with NFAT, and 363 patients with AUCS entered the analysis. The numbers of participants who completed 5-, 10-, and 15-year passive follow-up period were shown in the figure. The curves have been adjusted by age and sex difference between each group.

Table 4 Comparison of subgroups of patients with adrenal adenomas classified by cortisol secretion and age and sex matched referent subjects. Data are presented as *n* (%) or as %.

Variable	Patients with AUCS (*n* = 782)	Referent subjects (*n* = 782)	*P* value	Patients with MACS (*n* = 81)	Referent subjects (*n* = 81)	*P* value	Patients with NFAT (*n* = 141)	Referent subjects (*n* = 141)	*P* value
Prevalence of fractures before the index date[1]									
Any fracture	386 (49.4)	329 (42.1)	0.004	36 (44.4)	36 (44.4)	1.00	59 (41.8)	50 (35.5)	0.27
Hip fracture	27 (3.5)	20 (2.6)	0.30	1 (1.2)	0 (0)	0.32	1 (0.7)	0 (0)	0.32
Vertebral fracture	50 (6.4)	33 (4.2)	0.06	6 (7.4)	3 (3.7)	0.30	8 (5.7)	0 (0)	0.004
Distal forearm fracture	76 (9.7)	69 (8.8)	0.54	6 (7.4)	9 (11.1)	0.42	12 (8.5)	12 (8.5)	1.00
Any osteoporotic site	136 (17.4)	112 (14.3)	0.09	13 (16.0)	10 (12.3)	0.49	18 (12.8)	12 (8.5)	0.25
History of bisphosphonate therapy within 5 years prior to the index date	80 (10.2)	63 (8.1)	0.14	6 (7.4)	7 (8.6)	0.77	5 (3.5)	8 (5.7)	0.39
Cumulative incidence of fractures, 10 years[2]									
Any fracture	28.3	19.2	0.008	30.3	14.1	0.13	20.0	15.8	0.29
Hip fracture	2.8	2.3	0.93	3.2	4.6	0.54	1.3	3.5	0.29
Vertebral fracture	3.9	3.8	0.20	3.8	0	0.39	1.0	5.5	0.20
Distal forearm fracture	3.1	3.1	0.78	4.8	0	0.997	2.6	4.4	0.52
Any osteoporotic site	8.1	7.8	0.49	9.1	3.3	0.17	5.4	11.5	0.22
Cumulative incidence of new bisphosphonate therapy, 10 years following the index date	10.7	11.4	0.96	13.6	10.9	0.09	12.1	7.7	0.27

[1]Index date: diagnosis date or matched date; 2 Fractures are defined as new if they occurred after 6 months after the index date; subjects with a prior fracture at that site are not included in the estimates.
AUCS, adenoma with unknown cortisol secretion; MACS, mild autonomous cortisol secretion; NFAT, non-functioning adrenal tumor.

Table 2 Comparison of patients with adrenal adenoma and age and sex matched referent subjects. Data are presented as *n* (%) or median (range).

Variable	Patients (*n* = 1004)	Referent subjects (*n* = 1004)	*P* value
Sex, female	582 (58.0)	582 (58.0)	1.00
Age at the index date,[1] years	62.8 (20.5–96.4)	62.7 (20.5–95.5)	0.98
Race, Caucasian	939 (93.5)	945 (94.1)	0.58
Post-secondary education	608 (62.6)	633 (69.0)	0.004
BMI at the index date, kg/m^2	29.9 (10.3–81.0)	28.0 (16.7–60.2)	<0.001
Tobacco use prior to the index date	652 (70.1)	434 (53.6)	<0.001
Years of medical record prior to the index date[2]	40.0 (0.02–82.2)	39.5 (0.09–78.6)	0.46
Bone mineral density (BMD)			
BMD available at the index date[3]	155 (15.4)	113 (11.3)	–
Bone mineral density at the index date, g/cm^2			
Femoral neck	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.03[3]
Total hip	0.9 (0.59–1.4)	0.9 (0.5–1.3)	0.02[3]
Lumbar spine	1.1 (0.5–1.5)	1.0 (0.7–1.6)	0.47
Prevalence of fracture prior to the index date			
Any fracture	481 (47.9)	415 (41.3)	0.003
Hip fracture	29 (2.9)	20 (2.0)	0.19
Vertebral fracture	64 (6.4)	36 (3.6)	0.004
Distal forearm fracture	94 (9.4)	90 (9.0)	0.76
Any osteoporotic site	167 (16.6)	134 (13.3)	0.04
Patients with history of bisphosphonate therapy within 5 years prior to the index date	91 (9.1)	78 (7.8)	0.29
Duration of follow-up, years	6.8 (0–21.9)	7.2 (0–21.9)	–
Cumulative incidence of new fracture,[4] 10 years, %			
Any fracture	27.3	18.4	0.007
Hip fracture	2.6	2.7	0.84
Vertebral fracture	3.5	3.6	0.33
Distal forearm fracture	3.2	3.0	0.63
Any osteoporotic site	8.0	7.8	0.60
Cumulative incidence of new bisphosphonate therapy, at 10 years following the index date, %	11.1	10.9	0.37

[1]Index date: diagnosis date or matched date. [2]Available past medical records within the Rochester Epidemiology Project infrastructure prior to the index date. [3]After adjusting for age, BMI, and sex, BMDs were similar between patients and referent subjects. BMD was available only for 155 patients and 113 referent subjects. [4]Fractures are defined as new if they occurred after 6 months after the index date; subjects with a prior fracture at that site are not included in the estimate.

Limitations

- ✓ Results may not generalizable to other populations with different socioeconomic/ ethnic characteristics
- ✓ Factors not captured as markers of bone metabolism, medications other than biphosphonates or GCs, family history of osteoporosis, alcohol use
- ✓ Laboratory-confirmed MACS or NFAT relatively small sample size

Strengths

- ✓ First large population-based study from unselected community subjects with comparisons to age and sex matched referent subjects
- ✓ Highlight potential relevance of hypercortisolemia to AF and provide mechanistic insight into this association

Conclusions

Pts with adrenal adenomas higher prevalence of fractures (any; vertebral; at combined osteoporotic sites) at diagnosis and ↑ 27% risk develop new fractures compared to referent subjects after adjusting for sex, age, BMI, tobacco use, prior history of fracture, common causes of secondary osteoporosis.
Pts with adenomas: baseline hormonal workup and evaluation of bone health; receive appropriate therapy and monitoring

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doi:10.1210/clinem/dgab005
Clinical Research Article

Clinical Research Article

^{18}F-FDG-PET/CT Evaluation of Indeterminate Adrenal Masses in Noncancer Patients

Xin He,[1] Elaine M. Caoili,[2] Anca M. Avram,[3] Barbra S. Miller,[4] and Tobias Else[1]

Context Adrenal tumors in noncancer pts common

Objective Evaluate performance of 18F-fluorodeoxyglucose positron emission tomography computed tomography (18F-FDG-PET/CT) in distinguishing between benign and malignant adrenal tumors

Design Retrospective chart review 2010-2019 **Setting** Academic institution **Pts** 117 noncancer pts, defined no history of cancer or with cancer in remission for ≥5 yrs, completed 18F-FDG-PET/CT to evaluate adrenal masses, with pathologic diagnoses or imaging follow-up (≥12 months) **Intervention** 18F-FDG-PET/CT of 117 indeterminate adrenal masses **Main Outcome Measures** Receiver operator curve (ROC) characteristic of ratios of adrenal lesion standardized uptake value (SUV)max to liver SUVmean and of adrenal lesion SUVmax to aortic arch blood pool SUVmean were constructed

Results 70 benign and 47 malignant masses (35 adrenocortical carcinomas [ACCs], 12 adrenal metastases)

- ✓ Malignant masses higher median liver SUV and blood pool SUV ratios than benign masses (6.2 and 7.4 vs 1.4 and 2.0, *P*<0.001)
- ✓ Median liver and blood pool SUV ratios of ACC (6.1 and 7.3, respectively) and metastases (6.7 and 7.7, respectively) higher (1.4 and 2.2, *P*<0.05 for all comparisons)
- ✓ Optimal liver SUV ratio to discern between benign and malignant masses 2.5, yielding 85% sensitivity, 90% specificity; 7 false negative results (3 ACCs)
- ✓ Optimal blood pool SUV ratio 3.4, yielding 83% sensitivity, 90% specificity, 8 false negative results (4 ACCs)
- ✓ 10% benign lesions 18F-FDG-PET positive; 15% malignant lesions 18F-FDG-PET negative

Table 3. Imaging characteristics of benign versus malignant tumors

Imaging characteristic	Benign tumors (n = 70)	Malignant tumors (n = 47)	*P* value
Largest dimension, cm, median (range)	4.5 (0.7-17.9)	8.6 (2.2-19.3)	<.001
Well-defined margins (%)	67/70 (96%)	35/47 (74%)	.001
Homogeneous (%)	10/70 (14%)	6/47 (13%)	1.000
CT washout >60% (%)	1/4 (25%)	4/4 (100%)	.143
Calcifications (%)	27/70 (39%)	12/47 (26%)	.205
Cyst / necrosis (%)	35/70 (50%)	35/47 (74%)	.014
Macroscopic fat (%)	16/70 (23%)	2/47 (4%)	.008
Adrenal lesion SUVmax, median (range)	3.7 (1.6-28.6)	13.3 (2.3-70.8)	<.001
Liver SUV ratio, median (range)	1.4 (0.6-18.1)	6.2 (0.9-30.0)	<.001
PET-CT positive based on liver SUV ratio >2.5 (%)	7/70 (10%)	40/47 (85%)	<.001
Blood pool SUV ratio, median (range)	2.0 (1.2-21.2)	7.4 (1.2-39.1)	<.001
Blood pool SUV ratio >3.4 (%)	7/70 (10%)	39/47 (83%)	<.001

Liver SUV ratio, adrenal lesion SUVmax to liver SUVmean ratio. Blood pool ratio, adrenal lesion SUVmax to blood pool SUVmean ratio

Figure 3. Dot plot of adrenal lesion SUVmax to liver SUVmean ratio.

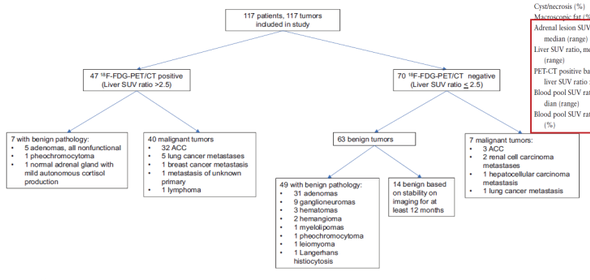

Figure 4. ^{18}F-FDG-PET/CT results and tumor diagnoses.

Table 4. Imaging characteristics of adrenocortical adenomas versus adrenocortical carcinomas and metastases

Imaging characteristic	Adrenocortical adenoma (n = 36)	Adrenocortical carcinoma (n = 35)	*P* value	Adrenal metastases (n = 12)	*P* value
Largest dimension (cm)	4.6 (0.7- 9.7)	1.5 (2.2-19.3)	<.001	4.6 (3.6-11.1)	.156
Well-defined margins (%)	36/36 (100%)	25/35 (71%)	<.001	10/12 (83%)	.059
Homogeneous (%)	5/36 (14%)	4/35 (11%)	1.000	2/12 (17%)	1.000
CT washout >60% (%)	1/3 (33%)	3/3 (100%)	.400	0/2 (0%)	1.000
Calcifications (%)	11/36 (31%)	12/35 (34%)	.934	0/12 (0%)	.044
Cyst/necrosis (%)	14/36 (39%)	27/35 (77%)	.003	8/12 (67%)	.111
Macroscopic fat (%)	10/36 (28%)	1/35 (3%)	.006	1/12 (8%)	.348
Adrenal lesion SUVmax, median (range)	4.0 (1.6-28.6)	13 (3.9-7.9)	<.001	13.2 (2.3-51.5)	.021
Liver SUV ratio, median (range)	1.4 (1.0-18.1)	6.1 (1.3-3.1)	<.001	6.7 (.9-2.3)	.007
PET-CT positive based on liver SUV ratio >2.5 (%)	10/36 (14%)	32/35 (91%)	<.001	8/12 (67%)	.001
Blood pool SUV ratio, median (range)	2.2 (1.2-21.2)	7.3 (1.5-39.1)	<.001	7.7 (1.2-27.4)	.013
Blood pool SUV ratio >3.4 (%)	5/36 (14%)	31/35 (89%)	<.001	8/12 (67%)	.001

Limitations

- ✓ Retrospective design

Strengths:

- ✓ Larger number of pts, with definitive diagnosis and higher proportion of uncommon masses

Conclusion When **used in conjunction with other** clinical assessments, 18F-FDG-PET/CT valuable tool in evaluating adrenal masses in noncancer pts

Endocrine-Related Cancer | S Faillot *et al.* | Genomics of benign adrenocortical lesions | 28:1 | 79–95

RESEARCH

Genomic classification of benign adrenocortical lesions

Simon Faillot[1], Thomas Foulonneau[1], Mario Néou[1], Stéphanie Espiard[1], Simon Garinet[1], Anna Vaczlavik[1], Anne Jouinot[1], Windy Rondof[1], Amandine Septier[1], Ludivine Drougat[1], Karine Hécale-Perlemoine[1], Bruno Ragazzon[1], Marthe Rizk-Rabin[1], Mathilde Sibony[1,2], Fidéline Bonnet-Serrano[1,3,4], Jean Guibourdenche[1,4], Rosella Libé[1,3], Lionel Groussin[1,3], Bertrand Dousset[5], Aurélien de Reyniès[6], Jérôme Bertherat[1,3] and Guillaume Assié[1,3]

Benign adrenal tumors cover a spectrum of lesions with distinct morphology and steroid secretion. Current classification is empirical. Beyond a few driver mutations pathophysiology is not well understood.

Aim Provide first unbiased molecular classification, using series of pangenomic characterization including transcriptome, miRNome, methylome, mutations, chromosomal alterations in cohort including all types of benign adrenocortical tumors

- ❑ Benign adrenocortical tumors (146) analyzed by transcriptome, methylome, miRNome, chromosomal alterations, mutational status, using expression arrays, methylation arrays, miRNA sequencing, SNP arrays, exome or targeted next-generation sequencing respectively. Pathological and hormonal data collected
- ❑ By combining omics approaches, specific subclasses identified, each related to specific **molecular signature**, reflecting **specific pathophysiological alterations**

Results females (81%); median age 46 (11-78); median adrenocortical adenoma (ACA) size 3.4 cm (1.1 - 8)

- ✓ Pangenomic analysis → 4 distinct molecular categories: 1) tumors responsible for overt CS, gathering distinct tumor types, sharing a common cAMP/PKA pathway activation by distinct mechanisms; 2) MACS and NFAT, associated with β-catenin mutations; 3) primary macronodular hyperplasia with *ARMC5* mutations (ovarian expression signature); 4) aldosterone-producing ACA, apart from other benign tumors
- ✓ Epigenetic alterations and steroidogenesis seem associated, including CpG island hypomethylation in tumors with no or mild cortisol secretion, miRNA patterns defining specific molecular groups, direct regulation of steroidogenic enzyme expression by methylation
- ✓ Chromosomal alterations and somatic mutations are subclonal, found in less than 2/3 of cells
- ✓ New pathophysiological insights (distinct molecular signatures) → difference between MAC and overt CS; *ARMC5* implication into the adreno-gonadal differentiation faith; subclonal nature of driver alterations in benign tumors: future research

Limitations

- ✓ Molecular exploration of aldosterone-producing ACA is limited
- ✓ Steroid profiling is limited to immunologic assays
- ✓ Secretion data available not fully available for all pts
- ✓ Genomic classification of samples not performed with the 5 techniques -transcriptome, mirNome, methylome, SNP array and DNA sequencing for all samples, mainly due to limited availability of good quality DNA or RNA
- ✓ Genomic explorations at the bulk tumor level, not precisely addressing tissue heterogeneity

This 1st genomic classification provides a large amount of data as a starting point

Journal of Personalized Medicine
MDPI

Article

What Is the Optimal Duration of Adjuvant Mitotane Therapy in Adrenocortical Carcinoma? An Unanswered Question

Vittoria Basile [1,†], Soraya Puglisi [1,*,†], Barbara Altieri [2], Letizia Canu [3], Rossella Libè [4], Filippo Ceccato [5], Felix Beuschlein [6,7], Marcus Quinkler [8], Anna Calabrese [1], Paola Perotti [1], Paola Berchialla [9], Ulrich Dischinger [2], Felix Megerle [2], Eric Baudin [10], Isabelle Bourdeau [11], André Lacroix [11], Paola Loli [12], Alfredo Berruti [13], Darko Kastelan [14], Harm R. Haak [15,16], Martin Fassnacht [2,17,‡] and Massimo Terzolo [1,‡]

Relevant issue on the treatment of ACC: optimal duration of adjuvant mitotane (M) treatment

Question whether a correlation exists between the duration of adjuvant mitotane treatment and recurrence-free survival (RFS) of patients with ACC

Methods A multicenter retrospective analysis; 154 ACC pts treated for 12 months with adjuvant M after radical surgery and free of disease at the M stop

Results Median follow-up 38 months, 19 pts (12.3%) experienced recurrence

- We calculated Recurrence-free survival (RFS) after M (RFSAM), from the landmark time-point of M discontinuation, to overcome immortal time bias
- Wide variability duration adjuvant M treatment among different centers and among pts cared for at the same center⟶ heterogeneous practice
- No survival advantage in pts treated for longer than 24 months
- Relationship between treatment duration and frequency of ACC recurrence not linear after stratifying our pts in tertiles of length of adjuvant treatment
- Duration adjuvant M only statistically significant factor associated with RFS (HR 0.549, 95% CI 0.306–0.983; p=0.044): hazard ratio (HR) calculated on 18 months in duration of therapy ⟶ 18 months increase of adjuvant M therapy duration ~ 45% ↓ hazard RFS

Table 4. Univariate analysis of predictive factors for recurrence-free survival (RFS).

Univariate Analysis	Diff	HR	95% CI		p
Duration of mitotane therapy +		1.302	0.509	3.334	0.58
§ R status		0.722	0.208	2.503	0.61
‡ * Hormone secretion		1.441	0.571	3.640	0.44
* ° Stage		0.917	0.272	2.526	0.87
* Tumor size	7.925	0.942	0.514	1.727	0.85
* Weiss	2.000	1.589	0.861	2.932	0.14
* Ki67%	15.000	0.805	0.426	1.521	0.50

* at diagnosis; Reference categories: + patients treated with mitotane ≤27 months, ‡ Secreting tumors, ° Stage III, § RX.

Table 5. Univariate analysis of predictive factors for recurrence free survival after adjuvant mitotane discontinuation (RFSAM).

Univariate Analysis	Diff	HR	95% CI		p
Duration of mitotane therapy +		0.894	0.354	2.257	0.812
§ R status		0.843	0.243	2.924	0.788
‡ * Hormone secretion		1.357	0.543	3.391	0.513
* ° Stage		1.118	0.342	2.993	0.838
* Tumor size	7.925	0.977	0.532	1.792	0.939
* Weiss	2.000	1.766	0.957	3.260	0.069
* Ki67%	15.000	0.820	0.442	1.521	0.529

* at diagnosis; Reference categories: + patients treated with mitotane ≤27 months, ‡ Secreting tumors, ° Stage III, § RX.

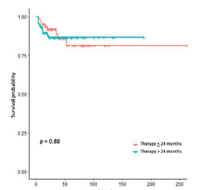

Figure 3. Kaplan–Meier estimates of recurrence free survival after adjuvant mitotane discontinuation (RFSAM) in patients treated <24 months vs. patients treated >24 months.

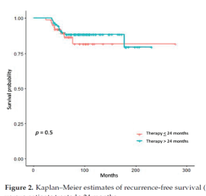

Figure 2. Kaplan–Meier estimates of recurrence-free survival (RFS) in patients treated <24 months versus patients treated >24 months.

Limitations Retrospective study

Conclusion Present findings no support: extending adjuvant M treatment >2 yrs beneficial for ACC pts with low to moderate risk of recurrence

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Clinical Research Article
ENDOCRINE SOCIETY
OXFORD

Clinical Research Article

Combination of Mitotane and Locoregional Treatments in Low-Volume Metastatic Adrenocortical Carcinoma

Alice Boilève,[1,*] Elise Mathy,[1,*] Charles Roux,[2] Matthieu Faron,[3] Julien Hadoux,[1] Lambros Tselikas,[2] Abir Al Ghuzlan,[4] Ségolène Hescot,[5] Sophie Leboulleux,[1] Thierry de Baere,[2] Livia Lamartina,[1] Frédéric Deschamps,[2] and Eric Baudin[1]

Context European/ French guidelines ENSAT stage IV low tumor burden or indolent ACC → combination M + locoregional treatments (LRT) as first-line treatment
Benefit LRT + M never evaluated in this selected group of pts

Objective evaluate therapeutic strategy LRT + M pts with low tumor burden stage IVA ACC.

Methods Retrospective chart review 2003-2018 pts stage IV ACC (= 2 or < tumoral organs) received M **Primary end point** Delay between M initiation and 1st systemic chemotherapy. **Secondary end points** Progression-free survival (PFS) and overall survival (OS) from M initiation. Adjusted analyses performed on the main prognostic factors

Results 79 pts; 48 (61%) female; median age at stage IVA diagnosis 49.8 yrs (IQR, 38.8-60.0) Metastatic sites lungs (76%); liver (48%)

- 58 (73%) pts received LRT including adrenal bed **radiotherapy** (14 pts, 18%), **surgery** (37 pts, 47%), and/or **interventional radiology** (35 pts, 44%)
- Surgery: locoregional relapse (23, 29%), hepatic (6, 8%), pulmonary (8, 10%), rarely, bone or nodes metastatic sites (3)
- Interventional radiology treatments: transcatheter arterial chemoembolization (20, 25%), radiofrequency ablation (18, 23%), cryoablation (7, 9%), microwave ablation (5, 6%).
- Treated sites: liver (22, 28%), lung (15, 19%), bone (2, 3%), other (2, 3%)

Type of treatment						
Mitotane only	19	24%	19	100%	–	
Mitotane + LRT	60	76%	–		60	100%
Lodge radiotherapy	14	18%	–		14	23%
Second surgery	34	43%	–		34	57%
Locoregional	25	32%	–		25	42%
Hepatic	9	11%	–		9	15%
Pulmonary	8	10%	–		8	13%
Other	3	4%	–		3	5%
Variables (n,%)	**All patients (n = 79)**		**Mitotane only (n = 19)**		**LRT + mitotane (n = 60)**	
Interventional radiology	35	44%	–		35	58%
Cryotherapy	7	9%	–		7	12%
Chemoembolization	20	25%	–		20	33%
Radiofrequency	18	23%	–		18	30%
Microwaves	5	6%	–		5	8%

Results Median time between M initiation and 1st chemotherapy 9 months (IQR, 4-18 months): M (6 months; IQR, 2-10 months) vs M+LRT (11 months; IQR, 4-30 months) (P = .02)

Variable	All patients (n = 79)		Mitotane only (n = 19)		LRT + mitotane (n = 60)	
Mitotanemia > 14 mg/L	46	58%	10	53%	36	60%
Chemotherapy	53	67%	18	95%[a]	35	68%[a]
< 3 mo after stage IVA diagnosis	4	5%	2	11%	2	3%
< 6 mo after stage IVA diagnosis	18	23%	10	53%[a]	7	12%[a]
Complete remission	10	13%	0	0%	10	17%
Death	49	62%	17	89%[a]	32	53%[a]
Median follow-up, mo	108	83-165	83	83-NR	108	82-172

- Median PFS1 (1st tumor-progression) 6.0 months (95% CI, 4.5-8.6): M+LRT (6.8 months; 95% CI, 5.0-13) vs M (3.3 months; 95%CI, 2.2-8.0) (HR = 0.39; 95%CI, 0.22-0.68), P = .001)
- Median PFS2 (2nd progression) 19 months (95% CI, 15-23): M+LRT (21 months; 95%CI,
- 18-37) vs M (10 months; 95%CI, 6.8-22) (HR = 0.35; 95%CI, 0.20-0.63)
- Median OS 46 months(95%CI, 41-68): M (22 months; 95%CI, 14-41) vs M+LRT (68 months; 95% CI, 46-153) with HR = 0.27; 95%CI, 0.14-0.50) (P < .001)
- 1-year, 2-year, 5-year survival probabilities 90% (95%CI, 83%-97%), 72% (95%CI, 62%-83%), 38% (95%CI, 28%-53%) respectively.
- PFS1, PFS2, OS longer M+LRT vs M (HR = 0.39; 95%CI, 0.22-0.68; HR = 0.35; 95% CI, 0.20-0.63; HR = 0.27; 95% CI, 0.14-0.50, respectively).
- The later chemotherapy introduced, the better OS, HR 0.95 (95%CI, 0.93-0-97, P <.001)

10 pts (13%) achieved a complete response (CR) with a median number of 2.8 curative procedures, all M+ LRT

Table 3. Characteristics of patients in complete remission (n = 10)

Variable		
Age at stage IVA diagnosis (median, range), y	39.4	22.2-68.7
Tumor ENSAT stage at initial ACC diagnosis (n,%)		
II	6	60%
III	3	30%
IV	1	10%
Hormonal secretions (n, %)	8	80%
Weiss ≥ 6 (n, %)	4	40%
Age ≥ 50 (n, %), y	2	20%
No. of metastatic sites (n, %)		
1	6	60%
2	4	40%
Metastatic sites (n, %)		
Liver	8	80%
Lung	3	30%
Local relapse	3	30%
Nodes	1	10%
Type of LRT (n = 10)		
Lodge radiotherapy	1	10%
Interventional radiology	7	70%
Cryotherapy	1	10%
Chemoembolization	6	60%
Radiofrequency	4	40%
Microwaves	2	20%
Second surgery	7	70%
Locoregional	4	40%
Hepatic	3	30%
Pulmonary	2	20%
Other	1	10%
No. of locoregional gestures (mean, range)	2.8	1-9
Mitotanemia > 14 mg/dL	7	70%
Chemotherapy	2	20%
< 6 mo after stage IVA diagnosis	0	0%

Table 4. Supplementary adjusted analyses on prognostic factors for overall survival (n = 79)

Variables	Categories	Multivariate HR (95 CI%)	Multivariate *P*
Model 1			
Group	Mitotane (ref) Mitotane + LRT	0.18 (0.08-0.43)	< .001
Tumor grade	Weiss ≤ 6 and Ki67 % < 20 (ref) Weiss > 6 and/or Ki67 % ≥ 20	2.0 (0.91-4.41)	.085
Resection status	R0 (ref) R1, R2, Rx	0.86 (0.46-1.49)	.6
Age, y	< 50 (ref) ≥ 50	0.6 (0.32-1.12)	.11
Secreting tumor	No (ref) Yes	0.38 (0.39-0.77)	.007
No. of metastases	<5 (ref) ≥5	1.12 (0.57-2.21)	.8
Model 2			
Group	Mitotane (ref) Mitotane + LRT	0.18 (0.08-0.40)	< .001
Tumor grade	Weiss ≤ 6 and Ki67 % < 20 (ref) Weiss > 6 and/or Ki67 % ≥ 20	2.02 (0.90-4.52)	.089
Resection status	R0 (ref) R1, R2, Rx	0.85 (0.46-1.56)	.6
Age, y	< 50 (ref) ≥ 50	0.59 (0.31-1.10)	.1
Secreting tumor	No (ref) Yes	0.39 (0.19-0.78)	.008
No. of metastatic organs	1 (ref) 2	1.08 (0.55-2.11)	.8

Limitations:

- ✓ Monocentric and retrospective study
- ✓ Pts heterogeneous regarding clinical characteristics fewer patients in the M

Strengths:

- ✓ Largest cohort reported to date and have adjusted our analysis for all known prognostic factors
- ✓ Well-characterized LTB stage IVA pts → clear definition of the population under study

Conclusion

Our results endorse European and French guidelines for stage IV ACC with 2 or fewer tumor organs and favor the combination of M and LRT as 1st-line treatment

For the first time, a significant number of CRs observed

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Clinical Research Article

Clinical Research Article

Adrenal Venous Sampling in Young Patients with Primary Aldosteronism. Extravagance or Irreplaceable?

Eleftheria Gkaniatsa,[1,2] Augustinas Sakinis,[3] Magnus Palmér,[3] Andreas Muth,[4] Penelope Trimpou,[1,2] and Oskar Ragnarsson[1,2]

Context Current clinical guidelines suggest that adrenal venous sampling (AVS) may not be mandatory in young patients with primary aldosteronism (PA) and a solitary adrenal adenoma on imaging

Objective Elucidate whether conventional imaging alone is sufficient to distinguish unilateral from bilateral PA among patients aged 40 yrs or younger

Methods Retrospective study; 45 pts with PA, aged between 26 and 40 yrs, successful AVS between 2005 – 2019.

- Results concerning laterality on imaging studies and AVS recorded
- Outcome in surgically treated pts assessed according to the Primary Aldosteronism Surgical Outcomes criteria

Table 2. Summary of patients with discordant lateralization results on imaging, AVS patients with inconclusive lateralization on imaging, and patients with concordant results

NO	Age/ Gender	Potassium supplementation (g/day)	LI/Side	CI	Radiological finding/ side/size (mm)	Treatment	Biochemical success	Clinical success	Histopathology
Patients with unilateral discase on imaging and bilateral disease according to AVS (false-positive unilateral aldosteronism)									
0	36/F	2,3			1/L Adenoma/L/8	MRA			
23	40/M	18.8			2.9/R Adenoma/R/10	ADX/R	Absent	Partial	Adenoma
7	33/F	0			2.1/R Adenoma/R/19	MRA			
13	37/F	6			2.5/L Adenoma/L/14	MRA			
28	40/M	30			3.9/L 1.4 Adenoma/L/12	ADX/L	Partial	Partial	Diffuse AH
Patients with bilateral discase on imaging and unilateral disease according to AVS (false-negative unilateral aldosteronism)									
15	38/M	15		50/R	<1 Adenoma/Bil/22, 17	ADX/R	NA	Complete	Adenoma
18	39/F	3		3.2/R	<1 Normal	MRA			
32	34/F	0		6/R	1 Normal	ADX/L	Complete	Complete	Multinodular AH
45	40/F	0		9/L	<1 Adenoma/Bil/10, 7	ADX/L	Complete	Complete	Adenoma
Patients with inconclusive lateralization on imaging									
43	37/M	0		1.6/R	Enlarged/R	MRA			
21	39/M	1.5		2.3/L	Enlarged/Bil	MRA			
19	39/F	6		2.5/R	Small nodules/Bil/5, 7	MRA			
14	38/F	6		17/L	<1 Small nodule/L/7	ADX/L	Complete	Partial	Adenoma
Patients with bilateral disease according to imaging and AVS									
29	40/M	0		1.2/R	Normal	MRA			
41	39/F	0		1.2/R	Normal	MRA			
5	31/F	0		1.2/R	Normal	MRA			
36	33/F	0		1.3/L	Normal	MRA			
26	40/F	6		1.3/L	Normal	MRA			
42	38/F	0		1.3/L	Normal	MRA			
39	36/F	0		1.6/R	Normal	MRA			
31	31/F	0		1.6/R	Normal	MRA			
22	39/F	0		1.8/R	Normal	MRA			
44	40/F	0		2.3/L	Normal	MRA			
1	26/F	0		2.7/L	Normal	MRA			
12	36/M	0		2.9/L	Normal	MRA			
Patients with unilateral disease according to imaging and AVS									
6	32/F	18		4	<1 Adenoma/L/17	ADX/L	Complete	Complete	Adenoma
20	39/F	1.5		10/L	<1 Adenoma/L/10	ADX/L	Complete	Complete	Adenoma
37	38/F	0		12/R	<1 Adenoma/ R/23	ADX/R	Complete	Complete	Adenoma
8	34/F	6		13/R	<1 Adenoma/R/15	ADX/R	Complete	Complete	Multinodular AH
25	40/F	9		14/R	<1 Adenoma/R/29	ADX/R	Complete	Partial	Adenoma
17	39/M	4.5		14/L	<1 Adenoma/R/22	ADX/R	Complete	Partial	Adenoma
9	35/F	3		15/R	<1 Adenoma/R/26	ADX/R	NA	Partial	Adenoma
16	38/F	18.8		15/L	<1 Adenoma/L/15	ADX/L	Complete	Partial	Adenoma
11	35/F	4.5		19/R	<1 Adenoma/R/10	ADX/R	NA	Complete	NA
10	35/M	7.5		21/L	<1 Adenoma/L/15	ADX/L	Complete	Partial	Adenoma
2	28/F	6		28/L	<1 Adenoma/L/14	ADX/L	Complete	Complete	Adenoma
3	29/F	6		28/L	<1 MRA	MRA			
24	40/F	2,3		32/R	<1 Adenoma/R/15	ADX/R	Complete	Complete	Adenoma
34	36/F	0 despite hypokalemia		40/L	<1 Adenoma/L/11	ADX/L	Complete	Complete	Adenoma
4	30/F	9		40/L	<1 Adenoma/L/10	ADX/L	Complete	Complete	Adenoma
27	40/F	6		43/L	<1 Adenoma/L/22	ADX/L	NA	Partial	Adenoma
40	38/F	13.5		61/R	<1 Adenoma/R/25	ADX/R	Complete	Complete	Adenoma
38	36/M	15.8		72/L	<1 Adenoma/L /10	ADX/L	Complete	Complete	Adenoma
33	34/M	4.2		80/R	<1 Adenoma/R/11	ADX/R	Complete	Partial	Adenoma
30	30/F	3		127/L	<1 Adenoma/L/12	ADX/L	Complete	Complete	Adenoma

Abbreviations: ADX, adrenalectomy; AH, adrenal hyperplasia; AVS, adrenal vein sampling; bil, bilateral; CI, contralateral index; F, female; L, left; LI, lateralization index; M, male; MRA, Mineralocorticoid receptor antagonist; NA, not assessed; R, right.

Results 45 pts (34 women) 26-40 yrs; 16/45 pts were 35 yrs or younger

- ✓ According to AVS, **25 pts** unilateral PA; **4/25 pts** unilateral aldosterone production according to AVS, **CT inaccurately suggested bilateral disease**. Following unilateral adrenalectomy: **showed complete clinical success**.
- ✓ **5/20** pts with **bilateral aldosterone production according to AVS** solitary adrenal nodule (8-19 mm) on imaging; **2 pts** with **normal adrenal glands** and **AVS-verified unilateral** aldosterone production; **2 pts with bilateral** adenoma and **AVS-verified unilateral** aldosterone production
- ✓ **2/5 pts** treated with **unilateral adrenalectomy**, **bilateral aldosterone production AVS** neither complete biochemical and/or clinical success postop
- ✓ **2/16 pts** <35 yrs discordant results, 1 unilateral and 1 bilateral aldosterone production, according to AVS

Limitations

- ✓ Retrospective design
- ✓ Pts heterogeneous regarding clinical characteristics fewer pts in the M

Strengths

- ✓ The 1st study evaluated inter-reader agreement of imaging studies in pts with PA

Table 3. Summary of discordant cases comparing lateralization according to AVS and different reading performance

No	Age/ Gender	Laterality according to AVS	Radiological finding/side/ size (mm) original report	Radiological finding/side/ size (mm) re-evaluation #1	Radiological finding/side/ size (mm) re-evaluation #2
Patients with discordant AVS and imaging results from all 3 radiological reports					
0	36/F	Bilateral	Adenoma/L/8	Adenoma/L/9	Adenoma/L/9
7	33/F	Bilateral	Adenoma/R/19	Adenoma/R/17	Adenoma/R/17
13	37/F	Bilateral	Adenoma/L/14	Adenoma/L/13	Adenoma/L/13
28	40/M	Bilateral	Adenoma/L/12	Adenoma/L/15	Adenoma/L/18
45	40/F	Unilateral/L	Adenoma/Bil/10, 7	Adenoma/Bil/13, 11	Adenoma/Bil/9, 8
Patients with discordant AVS and imaging results from at least 1 radiological report					
34	36/F	Unilateral/L	Adenoma/L/11	Adenoma/L/11	Normal
32	34/F	Unilateral/L	Normal	Adenoma/L/9	Normal
18	39/F	Unilateral/R	Normal	Adenoma/R/9	Normal
15	38/M	Unilateral/R	Adenoma/Bil/ 22, 17	Adenoma/R/20	Adenoma/Bil/ 22, 17
23	40/M	Bilateral	Adenoma/R/10	Adenoma/R/9	Enlarged/Bil
43	37/M	Bilateral	Enlarged/R	Small nodule/R/7	Small nodule/R/7
21	39/M	Bilateral	Enlarged/Bil	Normal	Normal
19	39/F	Bilateral	Small nodules/Bil/5, 7	Small nodule/R/5	Enlarged/R

Conclusion Imaging studies inaccurately predicted laterality in young pts with PA. In contrast to current clinical guidelines, our results support AVS for subtype evaluation in young adults with PA, including pts 35 yrs or younger

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Clinical Research Article

Clinical Research Article

Identification of Surgically Curable Primary Aldosteronism by Imaging in a Large, Multiethnic International Study

Gian Paolo Rossi,[1] Filippo Crimi,[2] Giacomo Rossitto,[1] Laurence Amar,[3,4] Michel Azizi,[3,4] Anna Riester,[5] Martin Reincke,[5] Christoph Degenhart,[5] Jiri Widimsky,[6] Mitsuhide Naruse,[7] Jaap Deinum,[8] Leo Schultze Kool,[9] Tomaz Kocjan,[10,11] Aurelio Negro,[12] Ermanno Rossi,[12] Gregory Kline,[13] Akiyo Tanabe,[14] Fumitoshi Satoh,[15] Lars Christian Rump,[16] Oliver Vonend,[16] Holger S. Willenberg,[17] Peter J. Fuller,[18,19] Jun Yang,[18,19,20] Nicholas Yong Nian Chee,[18] Steven B. Magill,[21] Zulfiya Shafigullina,[22] Marcus Quinkler,[23] Anna Oliveras,[24] Vin Cent Wu,[25] Zuzana Kratka,[6] Giulio Barbiero,[2] Teresa Maria Seccia,[1] and Michele Battistel[2]

Context Adrenal gland imaging is recommended by the current guidelines for the workup of PA. Diagnostic performance not been established in large, multiethnic cohorts: AVS + adrenalectomy.

Objective: Assess diagnostic accuracy of cross-sectional adrenal imaging

Methods: AVS International Study (AVIS-2). International multicenter study; tertiary referral centers (19: North America, Europe, Asia, Australia). 1625 PA pts seeking surgical cure. 1311 (81%) imaging data; 369 (23%), received final diagnosis of surgically cured unilateral PA. Pts underwent AVS and imaging by CT and/or MRI. Accuracy of detection of unilateral PA at imaging estimated by the AUC ROC using cure (biochemical and/or full clinical success) as the reference at follow-up after unilateral adrenalectomy; 558 prospectively 2013→2015; 1067 retrospectively 2012 → 2000

Results 1311 pts with imaging data available; 1142 pts (87%) underwent only CT, 101 (8%) only MR, 68 (5%) both CT/MR

- ❑ 34% and 7% showed no detectable or bilateral nodules, respectively
- ❑ Imaging did not detect the culprit adrenal in 28% of surgically cured unilateral PA pts

Table 2. Concordance between imaging findings and final diagnosis of unilateral primary aldosteronism (PA)

Cross-sectional imaging diagnosis, No., %	Final diagnosis, No. (%)		
	Right unilateral PA	Left unilateral PA	Total
Right nodule	83 (22.5%)	6 (1.6%)	89 (24.1%)
Left nodule	15 (4.1%)	183 (49.6%)	198 (53.7%)
Bilateral nodules	8 (2.2%)	7 (1.9%)	15 (4.1%)
No nodules	26 (7.1%)	41 (11.1%)	67 (18.2%)
Total	132 (35.8%)	237 (64.2%)	369 (100.0%)

- ❑ Nodule size ~ highest diagnostic accuracy 16 mm (95%CI, 12.0-21.0 mm), specificity 82% (95%CI, 64%-93%); low sensitivity 43% (95%CI, 37%-48%)
- ❑ 2% no improvement BP control with unilateral adrenalectomy; 39% cured of arterial hypertension; 44% marked; 14% mild improvement
- ❑ Clinical outcome not differ between the imaging-positive and imaging-negative pts

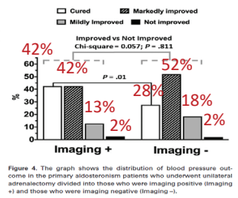

Figure 4. The graph shows the distribution of blood pressure outcome in the primary aldosteronism patients who underwent unilateral adrenalectomy divided into those who were imaging positive (imaging +) and those who were imaging negative (imaging –).

Limitations

✓ Selected cohort of PA pts comprising the most florid PA phenotypes

Strengths

✓ Snapshot of real-world clinical practice on imaging in PA

✓ Large dataset of PA pts carefully subtyped by AVS and evaluated after surgery

✓ Use of a conclusive diagnosis of unilateral disease as a gold-standard reference

Conclusion

Cross-sectional imaging did not identify a lateralized cause of disease in 40% of PA pts and failed to identify the culprit adrenal in more than ¼ pts with unilateral PA

Clinical Study | I Hacini and others | Somatic mutations in non cured PA patients | 185:3 | 405–412

Somatic mutations in adrenals from patients with primary aldosteronism not cured after adrenalectomy suggest common pathogenic mechanisms between unilateral and bilateral disease

Inès Hacini[1], Kelly De Sousa[1], Sheerazed Boulkroun[1], Tchao Meatchi[1,2], Laurence Amar[1,3], Maria-Christina Zennaro[1,4,*] and Fabio L Fernandes-Rosa[1,*]

European Journal of Endocrinology (2021) 185, 405–412

PA: most common form of secondary and curable hypertension. Different germline and somatic mutations found in aldosterone-producing adenoma (APA) and familial forms; causes of bilateral adrenal hyperplasia (BAH) remain largely unknown. Adrenalectomy = recommended treatment for pts with APA; 6% of pts not cured⟶ after surgery suggesting BAH

Objective Analyze clinical data pts with APA without biochemical success after adrenalectomy as well as the histological and genetic characteristics of their adrenal glands

Design and methods Clinical data 12 pts partial and absent biochemical cure compared to 39 PA pts with hormonal cure after surgery. Histological, morphological, genetic characterization of adrenals carried out by CYP11B2 and CYP11B1 immunostaining and by CYP11B2-guided NGS

Results

- ➢ Pts with absent hormonal cure longer duration of arterial hypertension pre-op and lower lateralization index of aldosterone production
- ➢ 10 pts, APAs expressing CYP11B2
- ➢ No difference in histological and morphological characteristics between pts with or without a hormonal cure
- ➢ Somatic mutations in APA driver genes identified in all CYP11B2 positive APAs
- ➢ *CACNA1D* mutations = most frequent genetic abnormality (60%) without vs KCNJ5 mutations (38.4%) with hormonal cure

Table 3 Genetic analysis of CYP11B2 positive APAs from PA patients without biochemical success after adrenalectomy.

APA	Gene mutated Sanger sequencing	Gene mutated NGS	Read depth	VAF	Nucleotide	Protein
1	*KCNJ5*	–	–	–	c.451G>C	p.Gly151Arg
2	*CACNA1D*	–	–	–	c.2968C>G	p.Arg990Gly
3	*CACNA1D*	–	–	–	c.1207G>C	p.Gly403Arg
4	–	*KCNJ5*	1044	28%	c.451G>C	p.Gly151Arg
5	*CACNA1D*	–	–	–	c.4117G>A	p.Val1373Asp
8	–	*CACNA1D*	2384	15%	c.1207G>C	p.Gly403Arg
9	–	*KCNJ5*	1044	28%	c.451G>C	p.Gly151Arg
10	–	*ATP1A1*	625	17%	c.311T>G	p.Leu104Arg
11	–	*CACNA1D*	1871	33%	c.3458T>A	p.Val1153Asn
12	–	*CACNA1D*	646	27%	c.2968C>G	p.Arg990Gly

NGS, next generation sequencing; VAF, variant allele frequency. *KCNJ5* (NM_000890), *ATP1A1* (NM_000701), *CACNA1D* (NM_001128839.2 and NM_000720).

Table 2 Histological characteristics of adrenals from non-cured PA patients.

Patient	CYP11B2+ adenoma size (mm)	APCC (*n*)	ZG hyperplasia	CYP11B2 expression (% of positive cells)‡	CYP11B1 expression (% of positive cells)‡
1	25	0	Y	1	2
2	7	0	Y	3	1
3	8	0	Y	3	1
4	11	3	Y	1	1
5	5	0	Y	1	2
6*	No	3	Y	–	–
7**	No	2	N	–	–
8	10	3	N	2	1
9	14	2	N	3	1
10	10	4	N	2	1
11	15	1	Y	3	1
12	11	4	N	3	1

*Micronodular hyperplasia not expressing CYP11B2; **Nodule 12 mm not expressing CYP11B2; ‡1: 1–33%; 2: 34–66%; 3: 67–100%.
APCC, aldosterone-producing cell clusters; N, no; Y, yes; ZG, zona glomerulosa.

Limitations

✓ Small number studied

Conclusions Pts partial and absent biochemical cure diagnosed later and lower lateralization index of aldosterone production, suggesting **asymmetric aldosterone production** BAH. Somatic mutations in adrenal glands ⟶ common mechanisms underlying BAH and APA

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ORIGINAL ARTICLE

Development and validation of a novel diagnostic nomogram model to predict primary aldosteronism in patients with hypertension

Meng-hui Wang[1] · Nan-fang Li[1] · Qin Luo[1] · Guo-liang Wang[1] · Mulalibieke Heizhati[1] · Ling Wang[1] · Lei Wang[1] Wei-wei Zhang[1]

PA: under-diagnosed disease

Purpose Develop and validate novel clinical nomogram to predict PA based on routine biochemical variables including new ones, calcium phosphorus product.

Methods 806 pts with hypertension randomly divided into 70% (564) as the training set and 30% (242) as the validation set. Predictors for PA extracted to construct a nomogram model based on regression analysis of the training set. An internal validation was performed to assess the nomogram model's discrimination and consistency using the AUC for ROC and calibration plots. The diagnostic accuracy compared between nomogram and other known prediction models, using ROC and decision curve analyses (DCA)

Results Female gender, serum potassium, serum calcium-phosphorus product, urine pH adopted as predictors in the nomogram.

Clinical characteristics pts with PA vs non-PA: higher SBP (p=0.007), lower serum UA (p=0.004), lower serum K (p<0.001), lower serum Ca(p=0.009), P (p=0.002), lower Ca-P product (p<0.001), higher urinary pH level (p<0.001), more frequent hypokalemia (40.2 vs. 14.0%, p<0.001), more hyperglycemia (14.0 vs. 7.9%, p=0.046)

Predictors and construction of nomogram model 8 → 5→ 4: formula for calculate score (Intercept = 3.06540): − 0.13817× gender (male = 0) −0.00065 × serum UA (mmol/L) − 1.26281 × serum K (mmol/L) − 0.24111× serum Ca-P product (mmol/L)2 + 0.19022 × urinary PH

Table 3 Multivariate logistic regression analysis of stepAIC selection to construct a nomogram model in the training set

	Multivariate logistic analysis					
	β	OR (95% CI)	*P* value	*β*	OR (95% CI)	*P* value
Gender [female = 1 male = 0]	0.5	1.6 (0.9–2.8)	0.090	0.6	1.9 (1.2–3.0)	0.006
Serum uric acid [umol/L]	−0.0	1.0 (1.0–1.0)	0.317	–		
Serum potassium [mmol/L]	−1.6	0.2 (0.1–0.4)	<0.001	−1.6	0.2 (0.1–0.4)	<0.001
Serum Ca-P product [(mmol/L)^2]	−0.6	0.5 (0.3–0.9)	0.020	−0.6	0.5 (0.3–0.9)	0.014
Urinary PH	0.4	1.5 (1.0–2.1)	0.026	0.4	1.5 (1.1–2.1)	0.017
Intercept	4.2	68.3 (1.6–2997.3)	0.029	3.5	33.9 (1.0–1138.7)	0.049

Probability (PA) = 1/(1 + exp(−(3.52464 + 0.63720 × gender (female = 1, male = 0) −1.63888 × serum potassium (mmol/L) −0.64348 × serum Ca-P product (mmol/L)^2 + 0.41799 × urinary PH)))

Ca-P product calcium-phosphorus product, *CI* confidence interval, *OR* odds ratio, *PA* primary aldosteronism

Table 4 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for the PA probability calculator in the combined set

PA Probability	Sen	Spe	Yorden index	Accuracy	PPV	NPV
≥10%	**0.90**	**0.30**	**0.20**	**0.41**	**0.24**	**0.92**
≥14%	0.80	0.48	0.27	0.54	0.27	0.91
≥18%	0.70	0.60	0.30	0.62	0.30	0.89
≥21%	**0.60**	**0.71**	**0.31**	**0.69**	**0.33**	**0.88**
≥27%	0.50	0.83	0.33	0.77	0.42	0.87
≥30%	0.40	0.87	0.27	0.78	0.43	0.86
≥34%	0.30	0.91	0.21	0.79	0.45	0.84
≥42%	0.20	0.97	0.17	0.82	0.60	0.83
≥49%	0.10	0.99	0.08	0.81	0.63	0.82

Bold entries indicate that themodel's diagnostic PA reaches 90% and 60% of the model's probability cut value, respectively

NPV negative predictive value, *PPV* positive predictive value, Sen sensitivity, Spe specificity

Table 5 Comparison of the diagnostic efficacy between nomogram model and other prediction models in the combined set

Test	Hypokalemia alone	Nomogram model	PFK score
AUC	0.63	0.72	0.68
95% CI lower	0.59	0.67	0.61
95% CI upper	0.67	0.76	0.72
The cut-off value	Serum K < 3.5 mmol/L	≥21% PA probability	≥1 point
Sensitivity	0.40	0.60	0.71
Specificity	0.85	0.71	0.52
Yorden index	0.25	0.31	0.23
Accuracy	0.77	0.69	0.56
Positive predictive value	0.42	0.33	0.26
Negative predictive value	0.85	0.88	0.88
Positive log-likelihood ratio	2.76	2.96	1.48
Negative log-likelihood ratio	0.70	0.60	0.55
Diagnose odds ratio	3.96	4.89	2.71
P value	<0.001		–
	–	0.064	

The nomogram resulted in AUC 0.73 (95%CI: 0.68–0.78) in the training set and an AUC 0.68 (0.59–0.75) in the validation set

Predicted probability and actual probability matched well in the nomogram (p > 0.05)

Based on ROC and DCA, 21–70% threshold to predict PA in the nomogram model clinically useful

Limitations:

- ✓ "High risk of bias" due to the deletion of cases with incomplete data (166/1107 ≈ 15%)
- ✓ Absence of external validation
- ✓ Single-center study with data from a tertiary hospital
- ✓ Retrospective study
- ✓ External validation absence

Conclusions

- ✓ Developed a novel nomogram to predict PA in hypertensive individuals based on routine biochemical variables
- ✓ External validation is needed to further demonstrate its predictive ability in primary care settings

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Clinical Research Article

Clinical Research Article

Increased Mortality Risk in Patients With Primary and Secondary Adrenal Insufficiency

Kanchana Ngaosuwan,[1,2] Desmond G. Johnston,[1] Ian F. Godsland,[1] Jeremy Cox,[3] Azeem Majeed,[4] Jennifer K. Quint,[5] Nick Oliver,[1] and Stephen Robinson[3]

Background

- ✓ Historically considered ↑ mortality for AI but vs. unmatched national data
- ✓ pts with primary and secondary AI (PAI, SAI) ≡ or ≠
- ✓ adrenal crisis (AC) role?

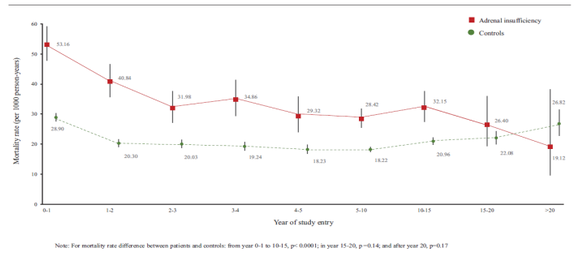
Objective Compare mortality risk and causes of death in AI with individually matched reference population.

Methods: Retrospective cohort study - UK general practitioner database (CPRD). **6821** AI (**PAI 2052**; **SAI 3948**) vs 67564 **individually-matched** controls (PAI, 20366; SAI, 39134) [1987-2017]; 3547 pts (**1015 PAI**& **2136 SAI**) vs. 34944 matched controls (10025 for PAI; 20991 for SAI) cause of death/ hospital admission [1997-2017]. Main outcomes, all-cause/ cause-specific mortality, hospital admission from AC. Exclusion: Acromegaly, Cushing disease, CS, congenital adrenal hyperplasia (CAH), malignancy of the adrenal or pituitary glands

Results: With follow-up of 40799 and 406899 person-years for pts and controls respectively, HR [95% CI] for all-cause mortality 1.68 [1.58-1.77]. HRs greater in PAI (1.83 [1.66-2.02]) than SAI (1.52 [1.40-1.64]) vs controls and PAI vs SAI (1.16 [1.03-1.30])

PAI: HR ↑both in pts taking GCs + mineralocorticoid (MCs) (HR 1.66 [1.47-1.88]) vs. GCs alone (HR 2.37 [1.99-2.82])

The highest all-cause mortality rate in pts during the 1st year follow-up (AI, 53.2 [95% CI, 47.8-59.2]; for PAI, 58.3 [48.4-70.3]; for SAI, 44.0 [37.7-51.3] / 1000 person-years, respectively) significantly higher vs controls. Mortality rates declined over time; similar to controls after 15 yrs



Note: For mortality rate difference between patients and controls: from year 0-1 to 10-15, p< 0.0001; in year 15-20, p =0.14; and after year 20, p=0.17

Figure 2. All-cause mortality rates of patients with adrenal insufficiency of any cause and matched controls, according to years of follow-up.

Results: 632 pts (207 PAI; 340 SAI): leading cause of death cardiovascular disease (CVD) (HR 1.54 [1.32-1.80]), malignant neoplasms, respiratory disease. Deaths from infection were high (HR 4.00 [2.15-7.46]) PAI/SAI.

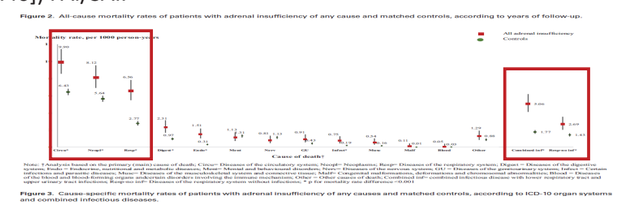


Figure 3. Cause-specific mortality rates of patients with adrenal insufficiency of any causes and matched controls, according to ICD-10 organ systems and combined infectious diseases.

AC contributed to 10% of all deaths [66 pts (61 PAI; 3 SAI)]. In the first year following diagnosis, pts hospitalization from AC higher than in later yrs (PAI>SAI).

Table 3. Hospital admissions from adrenal crisis after the diagnosis of adrenal insufficiency in patients with adrenal insufficiency of any cause, primary, and secondary adrenal insufficiency

	All adrenal insufficiency				Primary adrenal insufficiency				Secondary adrenal insufficiency			
Time from diagnosis	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)
0-1 years	3547	58[a]	3257	17.8 (13.8-23.0)	1015	36	927	38.9 (28.0-53.9)[b]	2136	11	1988	5.5 (3.1-10.0)[b]
After 1 year	2957	159	18 625	8.5 (7.3-10.0)	845	113	5370	21.0 (17.5-25.3)[b]	1821	26	11 529	2.3 (1.5-3.3)[b]
All including recurrent episodes	3547	364	22 768	16.0 (14.4-17.7)	1015	265	6911	38.3 (34.0-43.3)[b]	2136	47	13 661	3.4 (2.6-4.6)[b]

[a]Six events from 6 patients (1 primary; 5 unspecified adrenal insufficiency) were excluded from the analysis since adrenal crisis occurred on the date of diagnosis.
[b]P for incidence rate difference between primary and secondary adrenal insufficiency <.0001.

Strengths and Limitations

✓ Up to 10 controls selected for each pt in order to enhance statistical power
✓ 25% of PAI no MC prescription (similarly to Swedish Addison Registry) (not the sole explanation for mortality)

Conclusion

- Mortality ↑ in AI, especially PAI, even with individual matching, early in the disease course
- CVD major cause **but** greatest risk relative to controls infectious disease
- AC common contributor, especially in those with comorbid CVD
- Peak mortality early, PAI>
- Early education for prompt treatment of infections and avoidance of AC hold potential to ↓ mortality

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Clinical Research Article

Clinical Research Article

Mortality Risk in Patients With Adrenal Insufficiency Using Prednisolone or Hydrocortisone: A Retrospective Cohort Study

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Background:

✓ Longer duration of action of prednisolone concerns ~ adverse effects (AEs) on the cardiometabolic system/ bone
✓ Small European study → adverse lipid profile AI(prednisolone,P) vs. AI(HC)
✓ Small tertiary care study→ AI(P) vs. AI(HC) similar blood glucose, lipid profile, BMI, greater satisfaction P.
✓ AI(P) similar incidence AC to AI(HC)

Objective To determine mortality rates

Methods Observational study, data from UK primary care database (Clinical Practice Research Datalink): patients with PAI/ SAI, treated with either P or HC, and control individuals matched for age, sex, period, place of follow-up.

Results: 6821 pts (4228, 62% (PAI 68%, SAI 62%) on HC; 1250, 18% (PAI 7%, SAI 23%) on P) and **54,314** controls (41,934 and 12,380, respectively). Adjusted HR for mortality similar (P, 1.76 [95% CI, 1.54-2.01] vs HC 1.69 [1.57-1.82]; *P*= 0.65). Similarly for SAI. **PAI**: 1405 (HC) vs 137 (P); 13965 and 1347 controls, respectively. After adjustment, HR for P-treated pts higher than taking HC (2.92 [2.19-3.91] vs 1.90 [1.66-2.16]; *P* = 0.0020).

Table 2. All-cause mortality relative to controls, categorized by type of glucocorticoid replacement

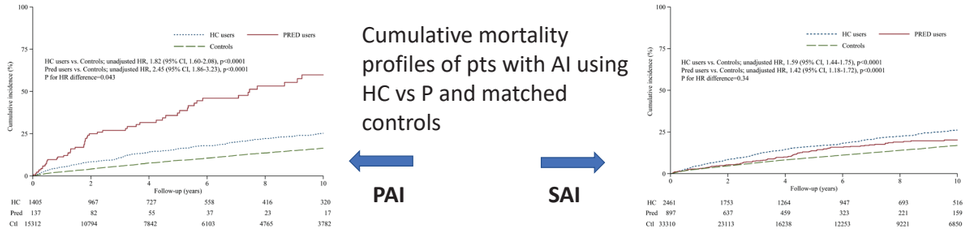
	Study patients				Controls				Unadjusted HR			Adjusted HR†		
	No. at risk	No. death	Person-years	Mortality rate (per 1000 person-years)	No. at risk	No. death	Person-years	Mortality rate (per 1000 person-years)	HR (95% CI)	*P*	*P* for risk difference	HR (95% CI)	*P*	*P* for risk difference
Adrenal insufficiency of any type														
Hydrocortisone	4228	828	24 574	33.7 (31.5-36.1)	41 934	5009	256 815	19.5 (19.0-20.1)	1.73 (1.61-1.86)	<0.0001	Ref	1.69 (1.57-1.82)	<0.0001	Ref
Prednisolone	1250	267	6725	39.7 (35.2-44.8)	12 380	1580	66 430	23.8 (22.6-25.0)	1.67 (1.47-1.90)	<0.0001	0-69	1.76 (1.54-2.01)	<0.0001	0.65
Primary adrenal insufficiency														
Hydrocortisone	1405	266	8618	30.9 (27.4-34.8)	13 965	1529	90 449	16.9 (16.1-17.8)	1.82 (1.60-2.08)	<0.0001	Ref	1.90 (1.66-2.16)	<0.0001	Ref
Prednisolone	137	61	597	102.2 (79.5-131.3)	1347	307	7618	40.3 (36.0-45.1)	2.45 (1.86-3.23)	<0.0001	0.043	2.92 (2.19-3.91)	<0.0001	0.0020
Secondary adrenal insufficiency														
Hydrocortisone	2461	479	14 392	33.3 (30.4-36.4)	24 401	3127	148 431	21.1 (20.3-21.8)	1.59 (1.44-1.75)	<0.0001	Ref	1.51 (1.37-1.66)	<0.0001	Ref
Prednisolone	897	121	4958	24.4 (20.4-29.2)	8909	791	45 698	17.3 (16.1-18.6)	1.42 (1.18-1.72)	<0.0001	0.34	1.44 (1.18-1.74)	<0.0001	0.67

†Adjustment for concomitant autoimmune disease and malignancy.

Table 3. Mortality of patients with adrenal insufficiency using prednisolone compared with those using hydrocortisone (internal comparison)

Type of adrenal insufficiency	No. death/ Total No. (%)		*P*-chi	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)†	*P*
	Hydrocortisone	Prednisolone					
Any type	828/ 4228 (19.6%)	267/ 1250 (21.4%)	0.17	1.16 (1.01-1.33)	0.035	1.14 (0.98-1.33)	0.082
Primary	266/ 1405 (18.9%)	61/ 137 (44.5%)	<0.0001	3.08 (2.33-4.07)	<0.0001	1.62 (1.17-2.23)	0.0030
Secondary	479/ 2461 (19.5%)	121/ 897 (13.5%)	<0.0001	0.73 (0.60-0.89)	0.0020	0.88 (0.71-1.09)	0.24

Note: †Adjustment for age at diagnosis, sex, date of start of follow-up, fludrocortisone use, concomitant autoimmune disease, and malignancy.



Cumulative mortality profiles of pts with AI using HC vs P and matched controls

PAI **SAI**

Limitations:

✓ PAI: only 34% of P users but 82% of HC users had taken fludrocortisone (FC)
✓ Proportion with coexistent autoimmune disease was higher in the pts, especially in P-treated groups: older, more likely to have another autoimmune disease and malignancy, and less likely to have MC replacement
✓ No causes of death reported
✓ No GCs doses reported

Conclusion: In PAI but not in SAI, mortality was higher with P. The number of P-treated pts was small, they had greater risk factors. The ↑ mortality associated with P persisted despite statistical adjustment.

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Clinical Research Article

Clinical Research Article

Improved Urinary Cortisol Metabolome in Addison Disease: A Prospective Trial of Dual-Release Hydrocortisone

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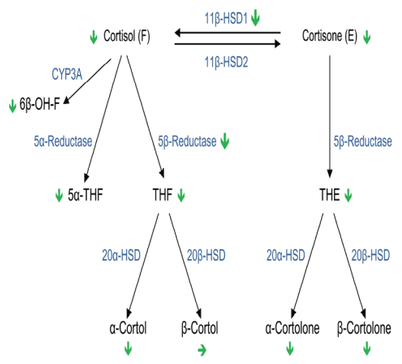
Context Oral once-daily dual-release HC (DR-HC) replacement therapy: improved metabolic profile compared to conventional 3-times-daily (TID-HC) therapy among patients with PAI ~ more physiological cortisol profile + modified pattern of cortisol metabolism

Objective Study cortisol metabolism during DR-HC and TID-HC

Design Randomized, open, controlled, randomized, 2-armed, 2-period, 12-wk, crossover, multicenter trial **Intervention and Participants** DC-HC and same daily dose of TID-HC administered to pts with PAI (50) vs healthy individuals (124) **Main Outcome Measures** Urinary corticosteroid metabolites measured by gas chromatography/ mass spectrometry at 24-hour urinary collections



Main metabolites of cortisol (F): 6β-hydroxy-cortisol (6β-OH-F), cortisone (E), tetrahydrocortisol (THF), 5α-tetrahydrocortisol (5α-THF), tetrahydrocortisone (THE), α-cortol, β-cortol, α-cortolone, and β-cortolone.
Summation of urinary cortisol and its main metabolites (THF, 5α-THF, α-cortol, β-cortol, E, THE, α-cortolone, and β-cortolone) = 24-hour total cortisol metabolites (TCMs) → **marker daily cortisol excretion rate**
Activity of enzymes involved in cortisol metabolism evaluated by calculation of ratios between products and substrates.
(THF + 5α-THF)/THE → **marker of 11β-HSD1 activity**
urinary free E/urinary free F (UFE/UFF) → **marker of 11β-HSD2 activity**
absolute value of 5α-THF urine → **marker of 5α-reductase activity** absolute value of THF urine → **marker of 5β-reductase activity**
ratio THF/5α-THF → **marker of** the balance between the 2 enzymes
ratio α- and β-cortols/THF → **marker of** activity of 20β-hydroxydehydrogenase (20β-HSD) ratio α- and β-cortolones/THE→ **marker of** activity of 20α-hydroxydehydrogenase (20α-HSD)

Results

- Total cortisol metabolites ↓ during DR-HC vs TID-HC and reached control values
- During DR-HC, 11β-HSD1 activity ↓vs TID-HC, but ↑ vs controls
- 11β-HSD2 activity ↓with TID-HC vs controls but normalized with DR-HC
- 5α- and 5β-reduced metabolites ↓ with DR-HC vs TID-HC
- ↑5β-reductase activity both treatments

❑ 24-hour urinary cortisol metabolome profiling → PAI treated with conventional TID-HC replacement therapy had higher cortisol exposure compared to healthy individuals with alterations in tissue-specific metabolism of GCs [↑ 11β-HSD1 activity]

❑ Treatment with DR-HC ↓ cortisol exposure and shifted the cortisol urinary metabolome profile toward normal

❑ Replacement therapy with DR-HC ↓ both daily and evening/night time cortisol exposure compared to conventional TID-HC ↓ $AUC_{0\text{-}10h}$ and $AUC_{10\text{-}24h}$

❑ ↑ 11β-HSD2 activity with DR-HC a role in the ↓BP observed in pts

❑ not correlation between cortisol metabolome profile and change in body weight, BMI, BP

Limitations

✓ cannot be excluded differences in tissue-specific regulation of cortisol metabolism: urinary ratio evaluates only global 11β-HSD1 activity; in obese pts, 11β-HSD1 expression in adipose tissue has been ~ (+)ve with BMI vs liver (-)ve correlated BMI → "global" 11β-HSD1 activity

Conclusions

✓ The urinary cortisol metabolome shows striking abnormalities in pts receiving conventional TID-HC replacement therapy, with ↑ 11β-HSD1 activity → unfavorable metabolic phenotype in PAI

✓ Its change toward normalization with DR-HC may mediate beneficial metabolic effects

✓ The urinary cortisol metabolome may serve as tool to assess optimal cortisol replacement therapy

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Clinical Research Article

Clinical Research Article

Adrenal Insufficiency at the Time of COVID-19: A Retrospective Study in Patients Referring to a Tertiary Center

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Context COVID-19: global health emergency; infected pts with chronic diseases often present with a severe impairment
AI ~with ↑infection risk and immunological alterations→ AC

Objective Evaluate the incidence of COVID-19 symptoms and complications in AI pts

Design and Setting Retrospective case-control study. Pts on active follow-up **dedicated tertiary endocrinological center→ highly instructed on possible risks related to infections complications and on how to manage replacement therapy;** lived in Lombardy, one of most affected areas **Pts** 279 with PAI/SAI and 112 controls (benign pituitary lesions without hormonal alterations) **Intervention** Standardized questionnaire by phone, data on COVID-19 suggestive symptoms and consequences

Results

❑ February → April 2020, prevalence of symptomatic (= complaining at least 1 symptom of viral infection) pts ≡ between the 2 groups (**24%** in AI and **22%** in controls, *P*=0.79)

❑ Highly suggestive COVID-19 symptoms (at least 2 including fever and/or cough) equally in AI and controls (12.5% in both groups)

Table 1. Clinical Features and Collected Data of AI Patients and Controls

	PAI (n = 60)	SAI (n = 219)	P^1	AI (n = 279)	Controls (n = 112)	P^2
Age, y	56.8 ± 15.7 (20-86)	57.5 ± 15.6 (21-94)	0.75	57.3 ± 15.6 (20-94)	57.5 ± 14.3 (27-89)	0.96
Females, n (%)	41 (68.3)	98 (44.7)	0.001[a]	139 (49.8)	59 (52.7)	0.65
AI etiology, n (%)						
Addison disease	47 (78.3)		-	-	-	-
Adrenal surgery	13 (21.6)					
Pituitary neoplasms		182 (83.1)				
Other		49 (22.4)				
Replacement therapy						
CO, n (%)	34 (56.7)	187 (85.4)	<0.001[a]	221 (79)	-	-
HC, n (%)	13 (21.6)	19 (8.7)	0.01[a]	32 (11.5)		
m-HC, n (%)	13 (21.6)	13 (5.9)	0.0007[a]	26 (9.5)		
Smoking habit, n (%)	5 (8.3)	38 (17.3)	0.10	43 (15.4)	21 (18.8)	0.45
Flu shot, n (%)	20 (33.3)	79 (36.1)	0.76	99 (35.6)	28 (25)	0.04[a]
Symptomatic patients, n (%)	15 (25)	52 (23.7)	0.87	67 (24)	25 (22.3)	0.79
Symptoms duration, d	8.5 (3-19)	7 (3-15)	0.42	5 (3-15)	7 (3-15)	0.65
HS symptoms, n (%)	4 (6.7)	31 (14.2)	0.19	35 (12.5)	14 (12.5)	1.00
HS symptoms duration, d	14 (7-33)	7 (3-15)	0.14	7 (3-15)	15 (7-30)	0.04[a]
Active workers, n (%)	10 (16.7)	21 (9.6)	0.05[a]	31 (11.1)	13 (11.6)	0.86
High-risk profession, n (%)	5 (8.3)	6 (2.7)	0.06	11 (3.9)	4 (3.6)	0.13
Contacts, n (%)	3 (5)	14 (6.4)	>0.999	17 (6.1)	6 (5.4)	1.00

Age is expressed as mean and range while symptoms duration as median and IQR (interquartile range).
Abbreviations: AI, adrenal insufficiency; CO, cortisone acetate; contacts, direct contacts with infected people; HC, hydrocortisone; HS, highly suggestive symptoms of COVID-19 (at least 2 including fever or cough); m-HC, modified release hydrocortisone; P^1, *P* value PAI vs SAI; P^2, *P* value AI vs controls; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; symptomatic patients, patients presenting at least 1 suggestive symptom of viral infection.

Results

31.3% symptomatic AI pts, replacement therapy dose ↑ [PAI: 47.4%; SAI: 25%, *P*=0.001). ↑1.5-fold regular dose in 42.9% and 2-fold in the others; 1 AD pt practiced intramuscular HC injections. Symptomatic pts not ↑ replacement therapy: only mild and rapidly improving symptoms. Most pts not considered symptoms as related to COVID-19 at the time of their occurrence. Antibiotics prescribed by GP in 16.7% symptomatic AI pts and 20.8% controls (*P* = 0.76).

❑ **No pt required hospitalization and no AC reported**

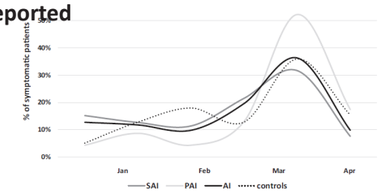

Figure 1. Distribution of symptomatic patients over time, from January to April 2020. We expressed, as a percentage, the ratio between patients who complained symptoms in a specific period and the total of symptomatic patients, in each group. Most patients, both in AI and controls, complained their suggestive symptoms during COVID-19 outbreak, especially on March 2020. AI, patients with adrenal insufficiency; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

Conclusions AI pts adequately treated and trained seem to display the same incidence of COVID-19-suggestive symptoms and disease severity as controls

Clinical Study | M Quinkler and others | Frequent adrenal crisis | 184:6 | 761–771
European Journal of Endocrinology (2021) **184**, 761–771

Characterization of patients with adrenal insufficiency and frequent adrenal crises

Marcus Quinkler[1], Robert D Murray[2], Pinggao Zhang[3], Claudio Marelli[4], Robert Petermann[5], Andrea M Isidori[6] and Bertil Ekman[7] on behalf of the EU-AIR Investigators

Objective characterize clinical and biochemical features of pts with PAI and SAI who developed ACs **to identify potential risk factors during a prospective observational period** and estimate the incidence of ACs in these pts

Design Retrospective case-control analysis of the European Adrenal Insufficiency Registry (EU-AIR; NCT01661387) of pts with PAI, SAI, CAH long-term treatment modified-release HC or other GCs replacement therapies
Methods 2694 with AI (**1054 PAI**; 1640 SAI) - August 2012→ February 2019. Pts who developed ≥ 1 AC matched 1:3 with pts without ACs for age, sex, AI type. Data collected at baseline and follow-up (mean ± s.d.: PAI 3.2 ± 1.7 yrs; SAI 2.9 ± 1.7 yrs)

Results

- ✓ 168 ACs in 1054 PAI (2572 patient-years) incidence **6.53 ACs per 100 patient-years**; 113 ACs in 1640 SAI (3547 patient-years): incidence 3.17 ACs per 100 patient-years.
- ✓ **≥1 AC** in 148 pts (vs 252): **84 PAI**: 60% ≥ 1 AC low incidence <0.5 ACs/year; 40% ≥1 AC every 2nd yr; **16% had ≥ 1 AC** /yr. 64 SAI (vs 192): 65% <0.5 ACs/yr; 9.4% ≥1 /yr
- ✓ Pts with PAI with ACs had a significantly shorter mean ± s.d. duration of disease (11.9 ± 11.3 vs 15.8 ± 12.9 yrs; P = 0.013) than pts without ACs
- ✓ No differences in BMI, HbA1c, BP and frequencies of diabetes mellitus or hypertension between subgroups (PAI and SAI, with and without ACs)
- ✓ At baseline, PAI pts with AC had higher serum K (4.3 ± 0.5 vs 4.2 ± 0.4 mmol/L; *P* = 0.03) and lower Na (138.5 ± 3.4 vs 139.7 ± 2.9 mmol/L; *P* = 0.004) than pts without AC
- ✓ At last observation, SAI pts with AC had higher HC doses than pts without AC (11 .9 ± 5.1 vs 10.1 ± 2.9 mg/m2; *P*<0.001).

Results

- ✓ The incidence of AEs, infectious intercurrent illnesses and infectious serious AEs were higher in pts with ACs than without ACs

Table 5 Incidence rate of important events based on patient-years. Patients with PAI and SAI who experienced ≥ 1 AC during the study period until the data cut-off point of February 5, 2019 were categorized as '≥ 1 AC' (*n* = 84, *n* = 64, respectively). Those two groups were matched 1:3 for age, sex and AI type with patients with AI and no ACs, labelled 'no AC' (*n* = 252, *n* = 192, respectively).

	PAI				SAI			
	≥1 AC (*n* = 84)	No AC (*n* = 252)	IRR (95% CI)	*P* value	≥1 AC (*n* = 64)	No AC (*n* = 192)	IRR (95% CI)	*P* value
Any adverse event	5.2	2.9	1.8 (1.5–2.1)	<0.001	3.4	1.5	2.3 (1.9-2.8)	<0.001
Adrenal crisis	0.7	0	–	–	0.6	0	–	–
Infectious intercurrent illness	1.4	1.1	1.3 (1.1–1.5)	0.006	1.0	0.5	2.0 (1.5–2.5)	<0.001
Infectious serious adverse event	0.1	0.04	2.5 (1.4–4.2)	0.001	0.3	0.03	8.9 (4.7–17.0)	<0.001
Death	0	0.01	0*	–	0.01	0.01	1.4 (0.3–6.2)*	0.702
n (%)	0 (0)	6(2.4)	–	–	3 (4.7)	4 (2.1)	–	–

Incidence rate ratio (IRR) = number of reports per recorded patient-year; 95% CI is Exact Fisher 95% CI, *P* value from Fisher Exact Test; *For death the odds ratio with 95% CI based on patient-years is given.
AC, adrenal crisis; AI, adrenal insufficiency; PAI, primary AI; SAI, secondary AI.

Limitations

- ✓ Lower incidence of ACs explained by the fact that centres involved in EU-AIR specialized tertiary endocrine centers: frequent teaching; AC emergency kits and steroid cards

Strengths

- ✓ Real-world data
- ✓ Disease specific controls- pts matched with ACs for age and sex (1:3)
- ✓ Prospective nature of the registry, large size of the cohorts

Conclusions

- ❑ Vast majority of pts (94.5%) did not experience any ACs over the duration of the registry
- ❑ Concomitant diseases and cardiovascular risk factors do not feature in the risk profile of AC
- ❑ Pts with AC had a higher incidence of infectious events; impaired immune system

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Clinical Research Article

Clinical Research Article

Reproductive and Perinatal Outcomes in Women with Congenital Adrenal Hyperplasia: A Population-based Cohort Study

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Context

- ↓ fertility reported for women with CAH, especially for salt-losing form
- Data are sparse on reproductive and perinatal outcomes in these women

Objective Investigate reproductive and perinatal outcomes in women with CAH

Design and Setting Population-based and nationwide study using the National CAH Register, the Total Population Register, the Medical Birth Register of Sweden
Participants 272 women with CAH due to 21-hydroxylase deficiency (21OHD) and 27200 controls matched by sex, age, place of birth; median age 31 yrs
Main outcome measures Proportion of CAH women that have given birth, reproductive and perinatal outcomes

Results 272 women with CAH [99 women had SW CAH, 67 women SV CAH, 49 women NCCAH]
- ➢ 69 gave birth to at least 1 child (25.4%) → lower frequency than controls (45.8%) (*P*<0.001).
- ➢ Women with CAH fewer children than controls (1.8 vs 2.1) and slightly older at birth of their first child [SW>SV+NCCAH].
- ➢ More women with CAH diagnosed with gestational diabetes than controls, 4.9% vs 1.4% (*P*<0.05)
- ➢ More women with CAH were delivered through cesarean section, 51.4% vs 12.3% (*P*<0.05) [SW+SV>NCCAH)
- ➢ No difference in Apgar score or frequency of small-for-gestational age between children born to mothers with CAH and controls

Table 2. Pregnancy and singleton births outcomes in women with congenital adrenal hyperplasia and controls based on data from the MBR

Outcome	Controls n = 4237	CAH n = 61	SW n = 8	SV n = 26	NC n = 16
Total number of births, n	8681	108	12	44	30
Births per woman, n	2.0 ± 0.9	1.8 ± 0.7[a,c]	1.5 ± 0.5	1.7 ± 0.61	1.9 ± 0.8
Age at first birth, years	26.7 ± 4.9	28.1 ± 4.9[a,c]	30.2 ± 4.1	28.6 ± 4.4	27.4 ± 5.8
BMI at first visit to maternity care, kg/m^2	23.6 ± 4.0	23.3 ± 3.5	23.8 ± 2.9	22.6 ± 3.5	24.5 ± 4.0
Weight gain during pregnancy, kg	13.9 ± 5.2	14.1 ± 5.1	12.8 ± 3.6	16.11 ± 5.5	14.9 ± 3.4
Preeclampsia, %	8.0	4.9	0	0	12.5
Gestational diabetes, %	1.4	4.9 [a,c]	0	3.8	12.5
Instrumental vaginal delivery, %	6.6	2.8	0	4.6	3.3
Cesarean section, %	12.3	51.4[a,c,**]	90.9[b,c,**]	63.9[c,**]	33.3
Planned, %	51.6	55.8	90.0	43.5	50.0
Emergency, %	48.4	44.2	10.0	56.5	50.0

Data are given as median and interquartile range, mean ± SD, or percentage.
Abbreviations: BMI, body mass index; CAH, congenital adrenal hyperplasia; NC, non-classical CAH; SV, simple virilizing; SW, salt wasting.
[a]Comparisons between controls and all women with CAH.
[b]Comparisons between SW and NC.
[c]Comparisons between SV and NC.
*P < .05, **P < .01, ***P < .001

Table 3. Perinatal outcome in women with congenital adrenal hyperplasia and controls based on data from the MBR

Outcome	Controls n = 4237	CAH n = 61	SW n = 8	SV n = 26	NC n = 16
Total number of children, n	8733	108	12	44	30
Gestational age, weeks	39.4 ± 1.9	39.3 ± 1.9	39.3 ± 1.4	39.6 ± 1.4	38.9 ± 3.0
Preterm, %	5.7	3.7	0	2.3	10
Term, %	87.6	92.6	100	88.6	90
Post term, %	6.6	3.7	0	9.1	0
Apgar score <7 at 5 minutes, %	1.1	1.0	0	2.8	0
Stillbirth, %	0.4	0.0	0	0	0
Birth weight, g	3508 ± 578	3489 ± 515	3336 ± 452	3429 ± 452	3634 ± 621
SGA	3.4	4.7	0	9.3[c,*]	0
AGA	93.3	90.6	100	90.7	89.7
LGA	3.3	4.7	0	0	10.3
Birth length, cm	50.3 ± 2.6	50.0 ± 2.4	49.7 ± 1.8	50.1 ± 2.4	50.5 ± 2.7
Head circumference, cm	34.7 ± 1.7	34.6 ± 1.5	34.5 ± 1.0	34.5 ± 1.3	34.9 ± 1.9

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; MBR, medical birth register; CAH, congenital adrenal hyperplasia; NC, non-classical CAH; SV, simple virilizing; SGA, small for gestational age; SW, salt wasting.
[c]Comparisons between SW and NC.
*P < .05.

Limitations

- ✓ Lack of information on assisted reproductive techniques used, hormone treatment, relatively small number in the CAH severity groups

Strengths

- ✓ Reproductive and perinatal outcomes of the largest cohort of women with CAH presented so far

Conclusions The largest cohort designed to investigate reproductive and perinatal outcomes in women with CAH. The birth rate lower in women with CAH; gestational diabetes and cesarean section were more common, but perinatal outcomes were comparable with controls.

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Clinical Research Article

Clinical Research Article

Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia

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Context Standard GC therapy in CAH regularly fails to control androgen excess, causing GC overexposure and poor health outcomes

Objective Whether modified-release hydrocortisone (MR-HC), which mimics physiologic cortisol secretion: could improve disease control

Methods 6-month, **randomized, phase 3 study** conducted of MR-HC [1/3 daily dose taken at 07:00h and 2/3 daily dose taken at 23:00h] vs standard GC, followed by a single-arm MR-HC extension study. Primary outcomes were change in 24-hour SD score (SDS) of androgen precursor 17-hydroxyprogesterone (17OHP) for phase 3, and efficacy, safety and tolerability of MR-HC for the extension study. 2/ 2016 → 1/ 2018; **good disease control at 24 weeks (09:00h 17OHP < 1200ng/dL)**

Results 138 pts screened, 122 randomly assigned, 117 completed

- Study failed primary outcome at 6 months: both groups better hormonal control 24 wks vs baseline →negative change 17OHP SDS 24-hour profile; better biochemical control MR-HC, lower 17OHP SDS at 4,12 wks, between 07:00h to 15:00h at 6 months
- Good disease control 52% baseline, 6 months 91% for MR-HC vs 71% standard therapy; 17OHP variability (amplitude) over 24 hours ↓ MR-HC group vs standard group
- Extension study, pts good disease control 80% at 18 months vs 52% baseline; A4 96% vs 45% at baseline
- Median daily HC dose 25 mg baseline; 6 months 31 mg for standard therapy, 30 mg for MR-HC; 18 months 20 mg MR-HC
- 3 AC occurred in phase 3; 0 on MR-HC; 4 in extension study

MR-HC pt-benefit: menses restoration in 8 pts (1 standard therapy), 3 pts and 4 partner pregnancies (0 standard therapy).

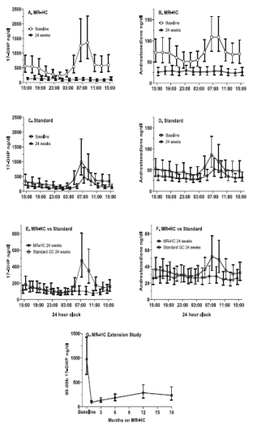

Figure 2. Twenty-four-hour endocrine profiles for 17-hydroxyprogesterone (17OHP) and androstenedione at week 24 vs baseline (geometric mean ± 95% CIs, patients meeting the criteria for the efficacy analysis) and 09:00hrs 17OHP during the extension study. A, At week 24, the 17OHP 24-hour profile for patients receiving modified-release hydrocortisone (MR-HC) was flat, and the morning rise in 17OHP observed at baseline was no longer present. B, Similar results were observed for androstenedione. Patients in the standard glucocorticoid group had improvement in hormonal control with glucocorticoid dose adjustments according to the protocol, but the pattern of hormone secretion did not change. C, 17OHP and D, androstenedione, profiles continued to display a morning increase. At week 24, the MR-HC vs standard groups differed during the morning hours but not throughout the 24 hours for E, 17OHP, and F, androstenedione. G, During the extension study, the geometric mean 09:00h 17OHP fell from baseline into the optimal range and remained there despite a reduction in MR-HC daily dose.

Limitations

- ✓ Open-label design and complexity protocol and statistical analysis.
- ✓ Intensive monitoring + more aggressive dose uptitration than usually performed in clinical practice may explain the improved control in standard group

Strengths

- ✓ International, multicenter, randomized design

Table 3. Study outcomes and disease-relevant clinical events[a]

	MR-HC group	Standard group	Comparison between groups
Biochemical outcomes from phase 3	N = 53	N = 52	Treatment effect[b] (95% CI), *P*[c]
Baseline natural log 17OHP SDS profile	1.25 ± 0.73	1.03 ± 0.82	
Change from baseline in natural log 17OHP SDS profile			
24-h profile at 4 wks	−0.37 ± 0.63	−0.07 ± 0.42	−0.26 (−0.46 to −0.07), *P* = .007
24-h profile at 12 wks	−0.52 ± 0.85	−0.10 ± 0.67	−0.30 (−0.54 to −0.05), *P* = .019
Primary end point: 24-h profile at 24 wks	−0.40 ± 0.83	−0.17 ± 0.78	−0.07 (−0.30 to 0.16), *P* = .55
07:00h-15:00h profile at 24 wks	−0.69 ± 0.96	−0.21 ± 0.79	−0.29 (−0.56 to −0.01), *P* = .044
Baseline natural log 17OHP 24-h AUC	65.2 ± 38.5	54.0 ± 39.2	
Change from baseline in natural log 17OHP 24-h AUC			
24-h profile at 4 wks	−23.9 ± 27.7	−6.1 ± 19.3	−16.6 (−25.5 to −7.8), *P* < .001
24-h profile at 12 wks	−35.5 ± 35.3	−13.5 ± 28.5	−17.8 (−29.0 to −6.6), *P* = .002
24-h profile at 24 wks	−37.7 ± 42.6	−17.8 ± 29.0	−13.8 (−25.8 to −1.8), *P* = .025
Amplitude ratio of 17OHP[d], median (95% nonparametric CI))	0.36 [0.24, 0.65]	0.92 [0.77, 1.37]	0.38 (0.24, 0.61), *P* < .001
Baseline natural log androstenedione 24-h AUC	21.4 ± 10.4	13.9 ± 12.2	
Change from baseline in natural log androstenedione 24-h AUC			
24-h profile at 4 wks	−12.5 ± 22.2	−3.1 ± 11.3	−8.9 (−15.6 to −2.1), *P* = .011
24-h profile at 12 wks	−20.6 ± 23.8	−8.0 ± 15.1	−10.9 (−18.3 to −3.5), *P* = .004
24-h profile at 24 wks	−22.9 ± 26.9	−9.3 ± 20.4	−10.5 (−18.7 to −2.3), *P* = .013
Disease-relevant clinical events phase 3 study	N = 61	N = 61	
Adrenal crises, No. of patients (%)	0 (0)	3 (5.8)	NA
Stress dosing, No. of patients (%)	26 (49.1)	36 (69.2)	NA
Restoration of menses, No. of patients (%)	4 (7.5)	1 (1.9)	NA
Partner pregnancy (%)	2 (3.8)	0 (0)	NA
Biochemical outcomes from extension study	(N = 50)		
Good disease controle (17OHP) at 18 mos, No. of patients (%)	40 (80.0)	–	NA
17OHP suppressed, No. of patients (%)‡	2 (4.0)	–	NA
Disease-relevant clinical events phase 3 study	(N = 91)		
Adrenal crises, No. of patients (%)	4 (4.4)	–	NA
Stress dosing, No. of patients (%)	72 (79.1)	–	NA
Restoration of menses, No. of patients	4 (4.4)	–	NA
Patient pregnancy	3 (3.3)	–	NA
Partner pregnancy	2 (2.2)	–	NA

‡Suppressed 17OHP defined as undetectable.
Abbreviations: 17OHP, 17-hydroxyprogesterone; AUC, area under the curve; GC, glucocorticoid; MR-HC, modified-release hydrocortisone; NA, not available; SDS, SD score.
[a]Plus-minus values are means ± SD.
[b]Treatment effect is defined as least-squares mean difference (MR-HC − standard GC) for SDS profiles and 24-hour AUC adjusted for baseline value and prebaseline therapy, as the ratio MR-HC to standard GC for amplitude ratio, and as the odds ratio MR-HC vs standard GC for good disease control adjusted for baseline disease control status.
[c]*CIs* and *P* values were obtained from an analysis of covariance model for SDS profiles and 24-hour AUC, by the Hodges-Lehmann, and Wilcoxon methods, respectively, for amplitude ratio, and from a logistic model for good disease control.
[d]Amplitude is defined as the maximum divided by the minimum over the 24-hour assessment period. The ratio is the amplitude at 24 weeks divided by the amplitude at baseline.
[e]Good disease control defined as 09:00h 17OHP less than 1200 ng/dL.

Conclusion

MR-HC improved biochemical disease control in adults with reduction in steroid dose over time and pt-reported benefit

Dosing at bedtime and waking, and hormonal measurements at 0900h to judge the nighttime dose and around midday to judge the morning dose

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Clinical Research Article

Clinical Research Article

Tildacerfont in Adults With Classic Congenital Adrenal Hyperplasia: Results from Two Phase 2 Studies

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Context CAH due to 21OHD typically treated with lifelong supraphysiologic doses of GCs Tildacerfont, potent, selective, nonsteroidal, oral, 2nd-generation corticotropin-releasing factor type-1 receptor antagonist: ↓excess androgen production, allowing for GC dose ↓

Objective Assess tildacerfont safety and efficacy

Design and Setting 2 Phase 2 open-label studies. 12-week, phase 2a, multicenter, open-label, multiple-dose, dose-escalation study and 12-week, Phase 2, multicenter, open label study evaluating oral tildacerfont 400 mg QD **Pts** Adults with 21OHD **Intervention** Oral tildacerfont 200 to 1000 mg once daily (QD) (n = 10) or 100 to 200 mg twice daily (n = 9 and 7) for 2 wks (Study 1), and 400 mg QD (n = 11) for 12 wks (Study 2) **Main Outcome Measure** Efficacy evaluated by changes from baseline at 8 am in ACTH, 17OHP, A4 according to baseline A4 ≤ 2× ULN or A4 > 2× ULN. Safety was evaluated using AEs and laboratory assessments.

Results

- Study 1; 24 pts; 16 no dexamethasone: evaluable participants with baseline A4 > 2× ULN (11; 19-67 years, 55% female) ↓from baseline in ACTH (−59.4% to −28.4%), 17OHP (−38.3% to 0.3%); A4 (−24.2% to −18.1%), with no clear dose response.
- Study 2; 11 pts; 8 no dexamethasone: participants with baseline A4 > 2× ULN (5; 26-63 years, 40% female) had ~80% maximum mean ↓ biomarker levels. ACTH and A4 normalized 60% and 40%, respectively.
- Both studies: participants with baseline A4 ≤ 2× ULN maintained biomarker levels
- AEs (in 53.6% of pts overall) included headache (7.1%) and upper respiratory tract infection (7.1%).
- Testicular adrenal rest tumors (TARTs) improvement in males

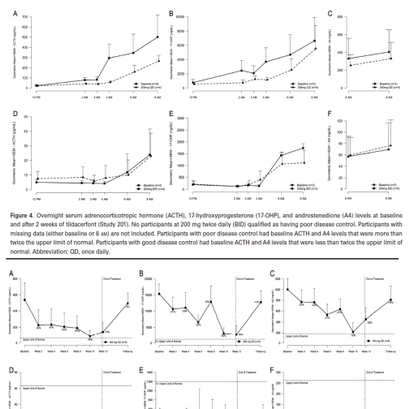

Figure 4. Overnight serum adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), and androstenedione (A4) levels at baseline and after 2 weeks of tildacerfont (Study 201). No participants at 200 mg twice daily (BID) qualified as having poor disease control. Participants with missing data (either baseline or 8 *AM*) are not included. Participants with poor disease control had baseline ACTH and A4 levels that were more than twice the upper limit of normal. Participants with good disease control had baseline ACTH and A4 levels that were less than twice the upper limit of normal. Abbreviation: QD, once daily.

Figure 5. Changes from baseline in adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), and androstenedione (A4) levels at 8 *AM* during 12 weeks of tildacerfont treatment by baseline disease control status (Study 202). Participants were required to be on a stable regimen of glucocorticoid replacement for a minimum of 30 days before baseline that was expected to remain stable throughout the study. Assessments were taken at approximately 8 *AM* prior to morning glucocorticoid dose. Geometric means are presented with percentage reduction derived from the geometric mean ratios. Axes are different between poor and good disease control to enable presentation of good disease control participants with mean values below the target levels. Abbreviation: QD, once daily.

Limitations

- ✓ Small and heterogeneous population
- ✓ Drug-drug interaction with dexamethasone

Conclusions For pts with 21OHD, up to 12 wks of oral tildacerfont ↓ or maintained key hormone biomarkers toward normal. Proof of concept through the achievement of receptor engagement, indicated via ↓ACTH; 17OHP and A4

ΜΕΤΑΒΟΛΙΣΜΟΣ ΟΣΤΩΝ

ΑΘΑΝΑΣΙΟΣ ΑΝΑΣΤΑΣΙΛΑΚΗΣ

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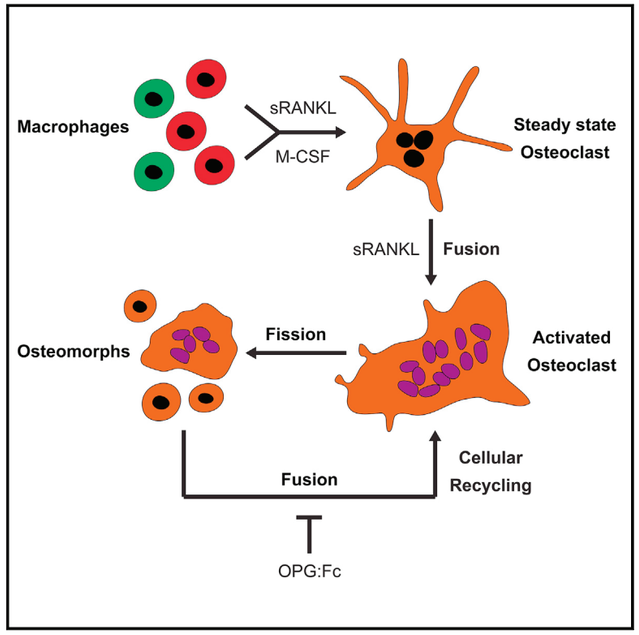
Cell

Article

Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption

Graphical abstract



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In Brief

Tracking osteoclasts during cycles of fission and fusion reveals a transcriptionally distinct "osteomorph" population that are fusion competent, motile, and capable of forming osteoclasts that resorb bone.

Highlights

- Osteoclasts fission into daughter cells called osteomorphs
- Osteomorphs fuse and recycle back into osteoclasts
- Osteomorph upregulated genes control bone structure and function in mice
- Osteomorph upregulated genes are implicated in rare and common bone diseases in humans

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Article

Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption

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SUMMARY

Osteoclasts are large multinucleated bone-resorbing cells formed by the fusion of monocyte/macrophage-derived precursors that are thought to undergo apoptosis once resorption is complete. Here, by intravital imaging, we reveal that RANKL-stimulated osteoclasts have an alternative cell fate in which they fission into daughter cells called osteomorphs. Inhibiting RANKL blocked this cellular recycling and resulted in osteomorph accumulation. Single-cell RNA sequencing showed that osteomorphs are transcriptionally distinct from osteoclasts and macrophages and express a number of non-canonical osteoclast genes that are associated with structural and functional bone phenotypes when deleted in mice. Furthermore, genetic variation in human orthologs of osteomorph genes causes monogenic skeletal disorders and associates with bone mineral density, a polygenetic skeletal trait. Thus, osteoclasts recycle via osteomorphs, a cell type involved in the regulation of bone resorption that may be targeted for the treatment of skeletal diseases.

INTRODUCTION

The skeleton provides the scaffold to support body weight, enable body movement, protect vital organs, and control mineral homeostasis while also providing the location for hematopoiesis. Accordingly, it is a dynamic organ that is continuously remodeled throughout life in response to diverse environmental stimuli. At the microscopic level, remodeling is achieved by the coordinated action of osteoclasts that resorb old bone and osteoblasts that form new bone, activities that are coupled in both time and space (Hattner et al., 1965). Osteoclasts are specialized cells formed by the fusion of committed monocyte/macrophage hematopoietic lineage precursor cells (Boyle et al., 2003; Ikeda and Takeshita, 2016). The importance of osteoclasts in bone homeostasis and human health is evidenced by the diseases in which osteoclast formation and function is dysregulated, such

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Clinical Research Article

Clinical Research Article

The Duration of Denosumab Treatment and the Efficacy of Zoledronate to Preserve Bone Mineral Density After Its Discontinuation

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Abbreviations: BMD, bone mineral density; BMI, body mass index; BTM, bone turnover marker; CTX, C-terminal telopeptide of type 1 collagen; CV, coefficient of variation; Dmab, denosumab; DXA, dual-energy x-ray absorptiometry; ECTS, European Calcified Tissue Society; FN, femoral neck; LS, lumbar spine; P1NP, procollagen type 1 N-terminal propeptide; ZOL, zoledronate.

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Abstract

Context: Zoledronate is used to prevent bone loss following denosumab discontinuation but its efficacy differs among studies.
Objective: To test if the duration of denosumab treatment affects the efficacy of subsequent zoledronate infusion.
Methods: This multicenter, prospective cohort study, conducted at 2 Greek and 1 Dutch bone centers, included 47 postmenopausal women (n = 47) who received a single zoledronate infusion 6 months after the last denosumab injection and then were followed for 1 year. Twenty-seven women received ≤ 6 denosumab injections (≤ 6 Group) and 20 received > 6 denosumab injections (> 6 Group). The main outcome measure was changes in lumbar spine (LS) bone mineral density (BMD).

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Results: At 12 months LS-BMD values were maintained in the ≤ 6 Group (0.98 ± 0.10 to 0.99 ± 0.9 g/cm^2, $P = 0.409$) but decreased significantly in the > 6 Group (1.0 ± 0.11 to 0.93 ± 0.12 g/cm^2, $P < 0.001$). The percent change of LS-BMD of the ≤ 6 Group (+1.0%) was significantly different ($P < 0.001$) from the change of the > 6 Group (–7.0%). In the whole cohort, the duration of denosumab treatment was negatively correlated with the percentage change of LS-BMD ($r_s = –0.669$, $P < 0.001$) but not with the change of femoral neck (FN)-BMD. Bone turnover markers increased in all patients 6 months following zoledronate administration with no difference between the 2 groups.
Conclusion: The duration of denosumab treatment significantly affects the efficacy of subsequent zoledronate infusion to maintain BMD gains. Frequent follow-up of patients treated with denosumab longer than 3 years is advisable as additional therapeutic interventions may be needed.

Key Words: bone mineral density, bone turnover markers, denosumab, postmenopausal osteoporosis, zoledronate

In patients with osteoporosis who are discontinuing denosumab (Dmab) therapy, an increase in bone turnover above pretreatment values, resulting in rapid decrease of bone mineral density (BMD), is typically observed (1, 2). To prevent this "rebound phenomenon," it is currently recommended that patients who are stopping Dmab should be treated with bisphosphonates (3) and intravenous zoledronate (ZOL) is the most widely studied in randomized controlled trials and observational studies (4-11). There are, however, differences in reported efficacy of ZOL to maintain denosumab-induced gains in BMD, with some studies showing preservation of BMD after 1 year in the majority of treated patients (4, 5, 12), while in other studies the effect was only partial (6, 7, 10). These results raise questions about potential patient-related and/or treatment-related determinants of the response to ZOL. Two clinically important determinants are the timing of the ZOL infusion and the period of Dmab administration before its discontinuation. While a 6-month interval between the Dmab injection and the ZOL infusion is currently accepted as optimal timing independently of the levels of bone turnover markers (3), the effect of duration of Dmab therapy and its relation to the changes of bone turnover and BMD remain to be fully elucidated.

We addressed these questions in treatment-naïve women with postmenopausal osteoporosis who were treated with denosumab for 1.0 to 5.5 years and received a single ZOL infusion 6 months after the last Dmab injection.

Patients and Methods

AfterDmab (Zoledronic Acid to Maintain Bone Mass After Denosumab Discontinuation) was a 2-year parallel assignment, open label, multicenter, randomized, efficacy study (NCT02499237) (4). According to the study protocol, treatment-naïve postmenopausal women with osteoporosis received Dmab until reaching osteopenic BMD values at the hip or spine, and then 1 of the 2 arms of the study received an intravenous infusion of ZOL 5 mg 6 months after the last Dmab injection (ZOL arm) and was followed for 2 years. A total of 27 patients were initially included in the ZOL arm of the study and both the initial results as well as the results of a third-year follow-up of the study extension have been recently published (4, 5).

Twenty-five additional patients fulfilling the AfterDmab study inclusion and exclusion criteria were administered a single ZOL infusion 6 months following the last Dmab injection. Five out of the 25 additional patients were lost to follow-up (2 died, 1 developed breast cancer and did not follow the protocol's visits, and 2 retracted their consent); the 20 remaining patients were prospectively followed according to the AfterDmab study protocol in the Endocrinology outpatient clinics of: the 424 General Military Hospital, Thessaloniki, Greece; the 251 Hellenic Air Force & VA General Hospital, Athens, Greece; and the Leiden University Medical Center, Leiden, The Netherlands.

The total cohort of 47 patients, including the 27 patients of the AfterDmab ZOL arm and the 20 prospectively followed additional patients, was retrospectively divided into 2 groups according to the median number (6.0) of Dmab injections: the ≤ 6 Group (≤ 6 Dmab injections or ≤ 3 years of Dmab treatment) and the > 6 Group (7 or more Dmab injections or > 3 years of Dmab treatment), and were analyzed accordingly. All patients had received cholecalciferol 800 IU/day and calcium carbonate 500 mg twice daily and had normal serum 25-hydroxyvitamin D and calcium concentrations both at the time of ZOL administration and throughout the 12 months of follow-up. No patient received a second ZOL infusion. The protocol for treatment and follow-up was approved by the Medical Ethical Committees of all 3 hospitals; all AfterDmab patients signed an informed

consent according to institutional requirements. The additional patients were originally part of an opting-out protocol which changed to opting in and patients still under care have signed informed consent according to institutional requirements.

At baseline and 12 months areal BMD was measured by dual energy x-ray absorptiometry (DXA) at the lumbar spine (LS; L1-L4) and femoral neck (FN) (Lunar Corporation, Madison, WI, USA) and radiographs of the spine were performed at the same time points. Morning fasting blood samples were obtained from all participants right before and at 6 and 12 months following ZOL infusion for the measurement of serum procollagen type 1 N-terminal propeptide (P1NP), and C-terminal telopeptide of type 1 collagen (CTX), as previously described (4). Specifically, the samples of the 27 patients from the AfterDmab study were measured in a single batch by electrochemiluminescence immunoassay (ECLIA) on a Cobase 411 analyzer (Roche Diagnostics, Mannheim, Germany) (P1NP intraassay coefficient of variation [CV] ≤ 2.3%, interassay CV ≤ 3.0%; CTX intraassay CV ≤ 2.5%, interassay CV ≤ 4.6%); the samples from the additional 20 patients were not measured in a single batch but on a daily basis using the same assay and either the Cobase 411 analyzer or the E-170 system (Roche BV, Woerden, The Netherlands; assay variation for CTX 2.5% and for P1NP 3%).

Treatment Outcomes

We aimed to compare the 1-year effect of ZOL infusion given 6 months following the last Dmab injection among patients with a history of either ≤ 3 years of Dmab treatment (the ≤ 6 Group) or > 3 years of Dmab treatment (the > 6 Group).

The primary endpoint of this analysis was the difference in LS-BMD changes between the 2 groups from baseline to 12 months. Secondary endpoints included: the difference in FN-BMD changes between the 2 groups from baseline to 12 months; the relationship between the duration of Dmab treatment and BMD changes at the LS and FN; and the differences in serum bone turnover marker levels between the 2 groups throughout the 12 months of follow-up. The incidence of new vertebral fractures (clinical and morphometric) and other fragility fractures were exploratory endpoints.

Statistical Analysis

Data of baseline characteristics are summarized by mean ± SD unless stated otherwise. The Shapiro-Wilk test was used to test the normality of distribution of continuous variables. The Levene's test was used to assess the homogeneity of variance. To compare continuous variables (absolute values) between 2 independent groups, independent sample T-test or Mann-Whitney test were performed, depending on the normal or nonnormal distribution of data, respectively. In case of more than 2 repeated measures, repeated measures analysis of variance (ANOVA) or Friedman test was used. In case of statistically significant trend, multiple pairwise comparisons were performed with Bonferroni post hoc correction. Spearman's (r_s) coefficient of correlation was used for bivariate correlations between continuous variables. Analysis was intention-to-treat. A 2-sided P value of < 0.05 was considered statistically significant in all tests. Statistical analysis was performed with IBM SPSS Statistics, version 25.

Results

Forty-seven postmenopausal women (mean age 65.7 ± 9.2 years) were included in the present analysis: 27 patients in the ≤ 6 Group and 20 patients in the > 6 Group. Eleven patients had received exactly 6 Dmab injections and were all included in the ≤ 6 Group. The patients in the > 6 Group had lower body mass index (BMI) and more prevalent fractures at Dmab discontinuation, while no other statistical differences between the 2 groups were observed at baseline (Table 1).

Changes in LS-BMD and FN-BMD in both groups 1 year after the ZOL infusion are shown in Fig. 1 and Table 2. Compared with baseline, LS-BMD did not change at 12 months in the ≤ 6 Group. However, in the > 6 Group LS-BMD significantly decreased. Regarding the primary endpoint of the study, the percentage change of LS-BMD of the ≤ 6 Group (+1.0%) was significantly different (P < 0.001) compared with the relevant change of the > 6 Group (−7.0%), although the absolute BMD values did not differ between groups either at baseline or 12 months (Table 2). FN-BMD did not change in the ≤ 6 Group but decreased significantly in the > 6 Group. Similar to LS-BMD, the absolute FN-BMD values did not differ between groups at baseline and 12 months, and this was also the case with the changes as the 1.26% increase of the ≤ 6 Group was not different (P = 0.079) than the 2.56% decrease of the > 6 Group. The duration of Dmab treatment was negatively and significantly correlated with the percentage change of LS-BMD (r_s = −0.669, P < 0.001) but not with that of FN-BMD (r_s = −0.187, P = 0.241) (Fig. 2).

At 12 months, 2 patients were classified as having osteoporosis both at the LS and FN in the ≤ 6 Group and 2 in the > 6 Group.

Bone Turnover Markers

At study entry (6 months after the last Dmab injection) serum P1NP levels were above the upper limit of the postmenopausal reference range (76 ng/mL) in 2 patients, 1 in the ≤ 6 Group and 1 in the > 6 Group, while in 1 patient from the ≤ 6 Group these were above the premenopausal values (56 ng/mL); 1 patient of the ≤ 6 Group had serum CTX values above the premenopausal reference range (0.573 ng/mL) (Fig. 3). The ZOL infusion was followed by a significant increasing trend in serum CTX and P1NP values during the 12 months following ZOL infusion in both groups (Table 2 and Fig. 3).

In the ≤ 6 Group serum CTX levels rose significantly at 12 months; however, in only 3 patients values were above the premenopausal range at that time point (Fig. 3). The change between baseline and 6 months was not significant in contrast with the change between 6 months and 12 months (Table 2). In the > 6 Group the CTX changes were not significant either at 6 or 12 months, respectively (Table 2), while CTX levels were above the upper limit of the premenopausal range at 12 months in only 1 patient (Fig. 3).

In both groups, serum P1NP levels significantly increased at 12 months. However, changes in either group occurred after 6 months from ZOL administration (Table 2). In the ≤ 6 Group 2 patients had values above the premenopausal range at 6 months; at 12 months, 1 patient had values above the upper limit of the premenopausal range and 4 above the postmenopausal range (Fig. 3). In the > 6 Group, 1 patient had values above the premenopausal range at 6 months, while at 12 months, 3 patients had values above the upper premenopausal threshold and 3 above the postmenopausal range (Fig. 3).

No patient had values above the upper limit of the postmenopausal range for both P1NP and CTX after 12 months post-ZOL infusion.

Between groups, the percentage change of P1NP after 12 months in the ≤ 6 Group (77.3%) did not significantly differ (P = 0.322) from the relevant increase (100.4%) in the > 6 Group. This was also the case with the percentage increase in CTX in the ≤ 6 Group (72.2%) which did not differ (P = 0.82) from the increase in the > 6 Group (24%).

With the exception of a positive correlation (r_s = 0.374, P = 0.01) between P1NP values at 6 months

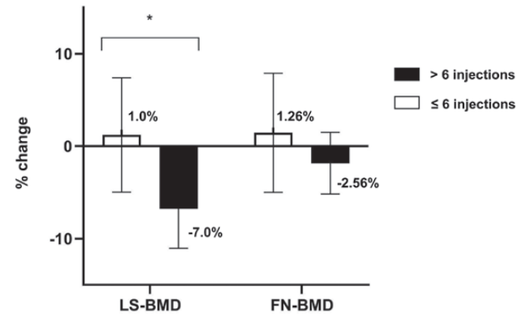

Figure 1. Percentage changes in bone mineral density after 12 months. Abbreviations: LS-BMD: bone mineral density lumbar spine, FN-BMD: bone mineral density femoral neck. *P < 0.001

Table 1. Baseline characteristics for treatment groups

Characteristics	≤ 6 injections (n = 27)	> 6 injections (n = 20)	P value
Age (years)	66.3 ± 9.13	64.80 ± 9.44	0.587
BMI (kg/m^2)	28.9 ± 3.85	24.00 ± 5.11	**<0.001**
BMD LS (g/cm^2)	0.98 ± 0.1	1.0 ± 0.11	0.6
BMD LS T-score	-1.70 ± 0.71	-1.5 ± 0.96	0.093
BMD FN (g/cm^2)	0.8 ± 0.08	0.78 ± 0.06	0.386
BMD FN T-score	-1.65 ± 0.65	-1.91 ± 0.54	0.351
P1NP (ng/mL)	25.10 ± 23.70	26.47 ± 29.36	0.858
CTX (ng/mL)	0.18 ± 0.12	0.25 ± 0.14	0.124
Vitamin D (nmol/L)	75.13 ± 30.90	92.67 ± 29.90	0.061
Calcium (mmol/L)	2.31 ± 0.11	2.36 ± 0.07	0.080
Phosphate (inorganic) (mmol/L)	1.15 ± 0.20	1.19 ± 0.21	0.520
Baseline fractures (nr of Fx)	0.48 ± 0.75	1.35 ± 1.5	**0.012**
Pts with Vertebral fractures	6	7	
Number of Dmab injections (median)	4	8	
Number of Dmab injections (mean)	4.4 ± 1.5	8.3 ± 1.2	**<0.001**
Years on Dmab treatment	2.2 ± 0.79	4.2 ± 0.6	**<0.001**

The time of zoledronate administration is considered as the "Baseline" time point. Years on Dmab treatment corresponds also with years with diagnosed osteoporosis as all patients were treatment-naïve before Dmab treatment.
Abbreviations: BMI, body mass index; BMD LS, bone mineral density of the lumbar spine; BMD FN, bone density measurement of the femoral neck; nr of Fx, number of fractures per patient; Pts, patients.

Table 2. Comparison (absolute values) of bone mineral density and bone turnover markers within and between groups

Variable	≤6 injections	>6 injections	Comparison between groups (*P* value)
BMD LS (g/cm^2)			
BL	0.98 ± 0.10	1.0 ± 0.11	0.6
12 months	0.99 ± 0.9	0.93 ± 0.12	0.052
Comparison within group	*P* = 0.409	***P* < 0.001**	
BMD FN (g/cm^2)			
BL	0.79 ± 0.09	0.78 ± 0.07	0.386
12 months	0.80 ± 0.07	0.76 ± 0.08	0.05
Comparison within group	*P* = 0.394	***P* = 0.034**	
P1NP (ng/mL)			
BL	25.10 ± 23.7	26.5 ± 29.4	0.858
6 months	30.7 ± 13.8	35.8 ± 12.7	0.196
12 months	44.5 ± 18.3[a,d]	53.1 ± 23.3[b,e]	0.232
Comparison within group	***P* = 0.001**[f]	***P* = 0.006**[f]	
CTx (ng/mL)			
BL	0.18 ± 0.15	0.25 ± 0.14	0.124
6 months	0.22 ± 0.11	0.25 ± 0.08	0.464
12 months	0.31 ± 0.16[c,d]	0.31 ± 0.14	0.966
Comparison within group	***P* < 0.001**	*P* = 0.275	

Abbreviations: BMD, bone mineral density; CTX, C-terminal telopeptide of type 1 collagen; FN, femoral neck; LS, lumbar spine; P1NP, procollagen type 1 N-terminal propeptide.
[a]*P* = 0.001 *vs* Baseline,
[b]*P* = 0.007 *vs* baseline,
[c]*P* < 0.001 *vs* baseline,
[d]*P* < 0.001 *vs* 6 months,
[e]*P* = 0.01 *vs* 6 months,
[f]Greenhouse-Geisser correction

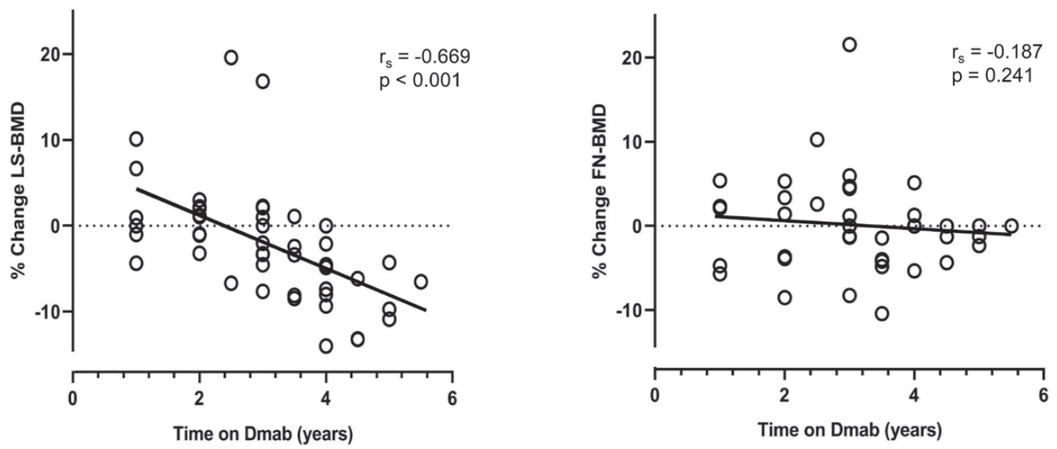

Figure 2. Correlation of time on Dmab treatment with changes in lumbar spine (LS) and femoral neck (FN) BMD.

and the years on Dmab treatment in the total cohort, no other correlations were found between bone turnover markers (BTMs) and the rest continuous variables of the study.

Fractures

During the study, 1 patient of the > 6 Group sustained a clinical vertebral fracture 12 months after ZOL. No other fractures were observed.

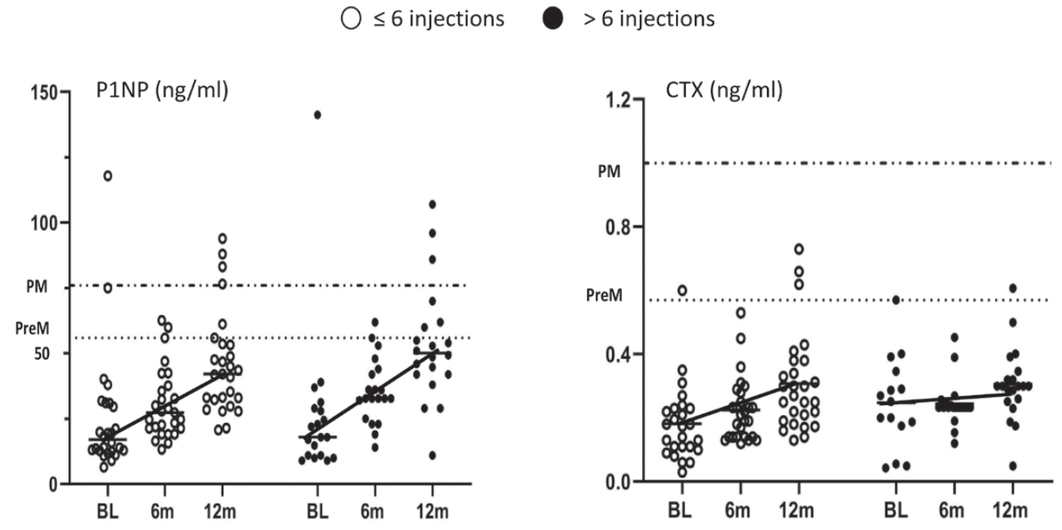

Figure 3. Distribution of bone turnover markers in both groups throughout the study. Solid lines = mean values, also joined for every group of patients. Abbreviations: PM, upper limit of postmenopausal range; P1NP 76 ng/mL, CTX 1.0 ng/mL; PreM, upper limit of premenopausal range; P1NP 56 ng/mL, CTX 0.57 ng/mL. BL, Baseline; m, months.

Adverse Events

Twenty-three (49%) of the 47 patients developed symptoms compatible with a transient acute phase reaction that was symptomatically treated with paracetamol. No other adverse events were recorded. No cases of osteonecrosis of the jaw or atypical femoral fracture were observed.

Discussion

In women with postmenopausal osteoporosis who became osteopenic with Dmab therapy for up to 3 years, a single ZOL 5 mg infusion given 6 months after the last Dmab injection, maintained the BMD gains at the spine and the hip for 1 year. In contrast, women treated for periods longer than 3 years with Dmab experienced significant BMD losses at both skeletal sites (7% and 2.6%, respectively). Duration of Dmab treatment is, therefore, an important determinant of the response to ZOL as further demonstrated by the significant negative correlation between length of Dmab treatment and changes in LS-BMD. Our results confirm and extend recent observations and recommendations by Sølling et al (7) and European Calcified Tissue Society (ECTS) experts (3), respectively, by providing evidence of the efficacy of ZOL over a broad time interval of Dmab use. Sølling et al reported that 20 patients with osteoporosis who were treated with Dmab for a mean of 5.2 years and received ZOL 6 months after the last Dmab injection lost 4.8% LS-BMD and 3.0% FN-BMD after 1 year (7), results very similar to ours. Furthermore, our data provide full support to the recommendation of ECTS experts for different management strategies of patients treated with Dmab for less than 2.5 years compared with those treated for longer periods (3). Notably, in the study of Sølling et al (7) 90% of the patients had received bisphosphonates before starting Dmab. It appears, therefore, that earlier bisphosphonate treatment does not affect the response, as also suggested in a larger observational study (8).

The obvious question is whether the difference in response to ZOL between the 2 groups in our study is related to differences in BTM changes following Dmab discontinuation. It has been previously suggested that the magnitude of the rebound phenomenon is related to the duration of Dmab treatment, possibly due to longer-term inhibition of osteoclast differentiation, which leads to a larger pool of osteoclast precursors that could differentiate synchronously upon Dmab withdrawal (8). It may, therefore, be that the ZOL 5 mg infusion may not be adequate to control a postulated greater stimulation of bone resorption caused by the longer duration of Dmab therapy. While this suggestion is pathophysiologically attractive, it is not supported by our data. Neither baseline nor follow-up levels of bone turnover markers differed between the 2 groups of patients. Although serum P1NP values at 6 months were positively correlated with treatment duration, in both groups of studied women significant changes in BTMs of similar magnitude occurred between 6 and 12 months after the ZOL infusion and in no patient in either group an increase in both serum P1NP and CTX values above the upper limit of the postmenopausal range was observed. Differences,

therefore, in bone turnover that may explain differences in BMD responses in our study are unlikely. The possibility of a transient, early difference in bone marker kinetics between the groups cannot be excluded but in published studies of BTM measurements after cessation of Dmab treatment, peak levels were observed between 6 and 12 months independently of ZOL use (1, 4). Furthermore, based on the findings of our study, the only one at present to include exclusively treatment-naïve patients, we could not identify a value of either serum CTX or P1NP that might help in the early identification of patients at risk for higher bone loss requiring adjustment of the management. The ECTS group recommended to monitor BTM at 3 and 6 months after ZOL and in case of increased BTMs above the mean of age- and sex-matched cohorts to consider a new infusion of ZOL. Although the recommendation is rational, our results cannot support this notion as no significant changes were observed in the 6-month BTMs.

Our 2 studied groups of women not only had different duration of exposure to denosumab but also differed significantly in 2 major independent risk factors of bone fragility, namely, BMI and number of prevalent fractures. Women with longer Dmab exposure had lower BMI values and higher number of prevalent fractures, suggesting that this group had more severe osteoporosis, this being the reason they received Dmab for longer periods to increase BMD to T-score values higher than −2.5. This speculation is also supported by the findings of the Sølling et al study (7). It may, therefore, be that the state of the disease is an important determinant of the response to Dmab treatment and its discontinuation. More severe disease requires longer treatment, which when stopped leads to greater BMD losses toward the original values. In our patients, the period since the recognition of the disease is clear because all patients were started on Dmab, whereas in most reports the majority of studied patients had already received bisphosphonates, the specific pharmacological properties of which may complicate the analysis of the responses. Whether there is an intrinsic mechanism that defines BMD levels at a given time for each untreated individual is currently unknown. However, if this is the case, and the skeleton of each individual tends to return to its pretreatment status, previously described as mechanostatic reset to a lower bone mass (13), it may explain the cause of a BTM-independent failure of ZOL to maintain the Dmab-induced BMD gains among patients with more severe disease. Unfortunately, BMD values before initiating Dmab therapy were, by design, not included in our study and we cannot, therefore, test this hypothesis, which warrants further investigation. An alternative, not mutually exclusive, mechanism may be related to the pharmacodynamic properties of Dmab in osteoporosis. In a bone biopsy study of osteoporotic women treated with Dmab for 10 years the degree of bone matrix mineralization increased in patients who received Dmab for 2 or 3 years vs placebo. With continuing treatment, matrix mineralization increased further significantly from years 2 or 3 to year 5 but not thereafter (14). Thus, during treatment with Dmab for 5 years more mineral was added to bone compared with 2 or 3 years for a similar reduction of bone remodeling (14). Accordingly, more mineral should have been added to bone in the > 6 Group of women in our study compared with that added to the bone of the women of the ≤ 6 Group. After discontinuation of Dmab, a ZOL 5 mg infusion—which induced similar changes in BTMs in the 2 groups—while sufficient to prevent the loss of the added mineral in the women of the ≤ 6 Group was insufficient to fully prevent the loss of the higher load of added mineral in the women of the > 6 Group. The result was maintenance of BMD in the former group and decrease in the latter. This hypothesis is compatible with the demonstrated relationship with the length of Dmab treatment as well as with the findings of all 3 prospective studies of the efficacy of bisphosphonates in patients discontinuing Dmab (4, 7, 15). Independently of the mechanism underlying the response, it is notable that in 91.5% of our patients BMD values remained osteopenic 1 year after ZOL administration. This finding in combination with the low rate (2.1%) of vertebral fractures justifies the selection of ZOL in a therapeutic strategy of patients with osteoporosis according to a "treat-to-target" approach targeting a total hip T-score between −1.5 and −2.0 (16).

The main limitation of our study is the lack of randomization due to the design of the analysis. Consequently, the 2 groups are not equal in size although they had been treated and followed prospectively according to the same protocol. However, the study allowed the systematic comparison of BMD and BTM changes among patients with a different duration of Dmab treatment who received ZOL 6 months following its discontinuation; the lack of early blood sampling may be considered an additional limitation.

In conclusion, the duration of Dmab treatment is a significant determinant of the overall BMD response after a single ZOL infusion among patients discontinuing Dmab treatment. A pragmatic approach would be to follow closely patients with longer than 3-year history of Dmab therapy as these may need additional therapeutic interventions in order to consolidate the BMD gains of previous treatment.

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Affirmation of Originality: All authors affirm that the work submitted for publication is original and has not been published other than as an abstract or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration.

Additional Information

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Data Availability: All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Clinical Research Article

Clinical Research Article

Investigation of Mechanical, Material, and Compositional Determinants of Human Trabecular Bone Quality in Type 2 Diabetes

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Abbreviations: μ-CT, microcomputed tomography; aBMD, areal bone mineral density; AGE, advanced glycation end-product; ANCOVA, analysis of covariance; BV/TV, bone volume fraction; DA, degree of anisotropy; E-xLR, enzymatic crosslink ratio; fAGE, fluorescent advanced glycation end-product; FTIR, Fourier transform infrared spectroscopy; HbA1c, glycosylated hemoglobin A1c; NE-xLR, nonenzymatic crosslink ratio; SMI, structure model index; T2D, type 2 diabetes; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; TGA, thermogravimetric analysis; XRD, X-ray diffraction.

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Abstract

Context: Increased bone fragility and reduced energy absorption to fracture associated with type 2 diabetes (T2D) cannot be explained by bone mineral density alone. This study, for the first time, reports on alterations in bone tissue's material properties obtained from individuals with diabetes and known fragility fracture status.

Objective: To investigate the role of T2D in altering biomechanical, microstructural, and compositional properties of bone in individuals with fragility fracture.

Methods: Femoral head bone tissue specimens were collected from patients who underwent replacement surgery for fragility hip fracture. Trabecular bone quality parameters were compared in samples of 2 groups, nondiabetic (n = 40) and diabetic (n = 30), with a mean duration of disease 7.5 ± 2.8 years.

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Results: No significant difference was observed in aBMD between the groups. Bone volume fraction (BV/TV) was lower in the diabetic group due to fewer and thinner trabeculae. The apparent-level toughness and postyield energy were lower in those with diabetes. Tissue-level (nanoindentation) modulus and hardness were lower in this group. Compositional differences in the diabetic group included lower mineral:matrix, wider mineral crystals, and bone collagen modifications—higher total fluorescent advanced glycation end-products (fAGEs), higher nonenzymatic cross-link ratio (NE-xLR), and altered secondary structure (amide bands). There was a strong inverse correlation between NE-xLR and postyield strain, fAGEs and postyield energy, and fAGEs and toughness.

Conclusion: The current study is novel in examining bone tissue in T2D following first hip fragility fracture. Our findings provide evidence of hyperglycemia's detrimental effects on trabecular bone quality at multiple scales leading to lower energy absorption and toughness indicative of increased propensity to bone fragility.

Key Words: diabetes, bone quality, AGEs, trabecular bone, fragility fracture, bone toughness

Type 2 diabetes (T2D) affects bone homeostasis leading up to 3-fold increased hip fracture risk compared with those without diabetes (1-3). This high fragility fracture risk is observed despite adequate areal bone mineral density (aBMD) in T2D (4-9). Thus, aBMD underestimates fracture risk in T2D, making the clinical identification of those at risk for fractures difficult. Beyond aBMD, the key factors contributing to bone strength are the parameters of bone quality—microstructure, bone material properties, bone mineral content and mean crystal size, bone protein (Amide I and II) quantity and its secondary structure, and bone cell activity and dynamics (Fig. 1A). These determinants have been examined individually in few studies and material properties are often listed as the cause of poor bone quality in diabetes (10-13). Only animal studies (14-19) and 3 recent studies of human tissue have attempted to address this question comprehensively (10, 11, 13). A limitation of the previous human studies is that bone tissue was collected at the time of arthroplasty and may therefore have confounding effects associated with arthritis (including increased trabecular bone density) (10, 11, 13). Furthermore, no prior studies of bone tissue material properties in humans have been conducted with known diabetic status and known fragility fracture status. The current study is novel in examining human bone tissue following first hip fragility fracture.

The mechanisms underlying this poor bone quality and high fracture risk in diabetes are not well understood. Prolonged hyperglycemia leads to an increase in the nonenzymatic reactions (Maillard reactions) and the formation of advanced glycation end-products (AGEs) through post-translation modification (20). AGEs then accumulate in the bone tissue and react irreversibly with amino acid residues of peptides or proteins to form protein adducts or protein crosslinks (21). This phenomenon, widely recognized as nonenzymatic crosslinking (NE-xL), is the underlying mechanism for multiple complications of diabetes, as it alters normal cellular functioning and tissue quality (22, 23). AGE accumulation may also alter mineralization through hyperglycemia affecting bone strength (15).

In the present ex vivo study, we aimed for multiscale characterization of bone tissue from individuals with and without diabetes, following hip fracture. This study includes investigation of the structural parameters at voxel size consistent with use of microcomputed tomography (μ-CT) and corresponding apparent level mechanical properties measured through the uniaxial compression test. We also examine bone material properties (nanoindentation) as well as bone composition (thermogravimetric analysis [TGA]), mineral crystal size (X-ray diffraction [XRD]), alterations in protein content, enzymatic crosslink ratio (E-xLR), nonenzymatic crosslink ratio (NE-xLR) (Fourier transform infrared spectroscopy [FTIR]), and fluorescent (f)AGE content in the human diabetic bone tissue.

Material and Methods

Study Participants

Bone samples were taken from 2 groups of patients who underwent bipolar hemiarthroplasty or total hip replacement following fragility fracture of hip—patients without diabetes (n = 40) and with diabetes (n = 30). Replacement surgery was the recommended treatment as these hip fractures were unsuitable for management with cannulated cancellous screw or proximal femoral nail. Patients' age also favored replacement surgery for better outcome. T2D was diagnosed according to the American Diabetes Association criteria (24). None of the patients had history of hip fracture prior to the fracture reported

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Reports and Recommendations

Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS

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Abstract

Context: Antiresorptive therapy significantly reduces fracture risk in patients with benign bone disease and skeletal-related events (SREs) in patients with bone metastases (BM). Osteonecrosis of the jaw (ONJ) is a rare but severe condition manifested as necrotic bone lesion or lesions of the jaws. ONJ has been linked to the use of potent antiresorptive agents, termed *medication-related ONJ* (MRONJ).

Objective: We aimed to identify the differences various aspects of MRONJ among distinct patient categories and provide recommendations on how to mitigate the risk and optimally manage MRONJ in each of them.

Methods: A working group of the European Calcified Tissue Society (ECTS) and 2 experts performed an updated detailed review of existing literature on MRONJ incidence, characteristics, and treatment applied in bone diseases with variable severity of skeletal insult, ranging from osteoporosis to prevention of cancer treatment–induced bone loss and SREs in cancer patients with BM.

Results: The risk for MRONJ is much higher in patients with advanced malignancies compared to those with benign bone diseases because of the higher doses and more frequent administration of antiresorptive agents in individuals with compromised general health, along with coadministration of other medications that predispose to MRONJ. The overall risk for MRONJ is considerably lower than the benefits in all categories of patients.

Conclusion: The risk for MRONJ largely depends on the underlying bone disease and the relevant antiresorptive regimen applied. Physicians and dentists should keep in mind that the benefits of antiresorptive therapy far outweigh the risk for MRONJ development.

Key Words: bisphosphonates, bone metastases, denosumab, osteonecrosis of the jaw, osteoporosis

Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; AI, aromatase inhibitor; ALN, alendronate; ARONJ, antiresorptive agent–related osteonecrosis of the jaw; BM, bone metastases; BMA, bone-modifying agent; BP, bisphosphonate; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CLO, clodronate; CTIBL, cancer treatment–induced bone loss; Dmab, denosumab; DRONJ, denosumab-related osteonecrosis of the jaw; ECTS, European Calcified Tissue Society; IBN, ibandronate; IV, intravenous; MM, multiple myeloma; MRONJ, medication-related osteonecrosis of the jaw; ONJ, osteonecrosis of the jaw; OP, osteoporosis; OPG, orthopantomography; PAM, pamidronate; QoL, quality of life; RIS, risedronate; RLX, raloxifene; SRE, skeletal-related event; TKI, tyrosine kinase inhibitor; TPTD, teriparatide; VEGF, vascular endothelial growth factor; ZOL, zoledronate.

An imbalance of bone turnover, with relatively increased osteoclast-mediated bone resorption rate, characterizes a broad spectrum of bone diseases, ranging from osteoporosis (OP) and other benign bone diseases to cancer treatment–induced bone loss (CTIBL; aromatase inhibitor (AI)-induced bone loss, and androgen deprivation–induced bone loss) and bone metastases (BM) in advanced malignancies. In all these conditions, targeting the osteoclast with antiresorptive agents is currently the cornerstone of treatment of the respective bone disease. Among them, bisphosphonates (BPs), and denosumab (Dmab) are the more potent and more frequently used agents in everyday clinical practice.

BPs are divided into oral, including alendronate (ALN), risedronate (RIS), clodronate (CLO), and ibandronate (IBN), and intravenous (IV) agents, including IBN, pamidronate (PAM), and zoledronate (ZOL). In general, oral BPs are preferred in OP and other benign bone diseases, whereas for prevention of CTIBL and the management of BM, IV BPs are mostly used (Table 1). Dmab binds the receptor activator of nuclear factor κ-B ligand (RANKL), thus inhibiting osteoclast differentiation, function, and survival (1). BPs and Dmab

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ΜΕΤΑΒΟΛΙΣΜΟΣ ΟΣΤΩΝ | ΑΘΑΝΑΣΙΟΣ ΑΝΑΣΤΑΣΙΛΑΚΗΣ

Table 2. Nonantiresorptive medications associated with osteonecrosis of the jaw development

Class	Representatives
Glucocorticoids	
VEGF inhibitors	Bevacizumab, aflibercept
TKIs	Sunitinib, imatinib, cabozantinib, sorafenib, regorafenib, axitinib, pazopanib, dasatinib
mTORi	Everolimus, temsirolimus
BRAF inhibitors	Dabrafenib, trametinib
Monoclonal Abs against CD20	Rituximab
Immune checkpoint inhibitors	Nivolumab, monoclonal Abs against CTLA-4 (ipilimumab)
Lenalidomide	
Chemotherapy regimens	Cytarabine, idarubicin, and daunorubicin; gemcitabine, vinorelbine, and doxorubicin; doxorubicin and cyclophosphamide; 5-azacitidine
Leflunomide	
Anti-TNF agents	Adalimumab

Abbreviations: Abs, antibodies; BRAF, B-Raf; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; TKIs, tyrosine kinase inhibitors; mTORi, inhibitors of mammalian target of rapamycin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Table 3. Staging according to the American Association of Oral and Maxillofacial Surgeons and the alleged nonexposed variant

Stage	Description
At risk	Patients treated with bone-modifying agents but without apparent necrotic bone (eg, all asymptomatic patients treated with antiresorptives)
Stage 0	No clinical evidence of necrotic bone but nonspecific symptoms or clinical/radiographic findings
Stage 1	Exposed and necrotic bone, or fistulae that probe to bone, that are asymptomatic with no evidence of significant adjacent or regional soft-tissue inflammation or infection
Stage 2	Exposed and necrotic bone, or fistulae that probe to bone, associated with infection, evident by pain and adjacent or regional soft-tissue inflammatory swelling, with or without purulent drainage
Stage 3	Exposed and necrotic bone, or fistulae that probe to bone, associated with pain and infection, and at least one of the following: (1) pathologic fracture, (2) extra-oral fistula, (3) oral-antral fistula, or (4) radiographic evidence of osteolysis extending to the inferior border of the mandible or floor of the maxillary sinus
Nonexposed variant (not widely adopted)	Presence of otherwise unexplained pain in the jaws, fistula, swelling, mobile teeth, or mandibular fracture diagnosed after excluding common diseases of the jaw known to cause similar manifestations

may also contribute. Additionally, jaw osteoclasts may absorb higher amounts of BPs than long bone osteoclasts (18). Indirect evidence of the pivotal role of bone turnover suppression in MRONJ development derives from the facts that MRONJ has almost exclusively been attributed to the most potent antiresorptives and is far more common among BM or MM patients, for whom higher doses are administered in more frequent intervals, compared to OP. Additional, indirect, evidence comes from the improved extraction socket healing and resolution of ONJ when parathyroid hormone was administered in animals (19-21) and humans (22, 23).

Local inflammation and infections

Periodontal or periapical disease was common in initially reported cases (24). Subsequently, animal models proved that inflammation or bacterial infection combined with antiresorptives can induce ONJ (25, 26). A complex biofilm, composed of bacteria, especially *Actinomyces* species (10, 27), along with fungi and viruses (28), has been identified in biopsies of necrotic bone from ONJ lesions. Increased local infections and impaired oral mucosa healing with BPs suggested a synergistic role of antiresorptives with inflammation and infection (29, 30). BP administration has been associated with proliferation and adhesion to hydroxyapatite of oral bacteria (31). Furthermore, BPs may impair the immune response to infection through activation of γ δ T cells and altered production of proinflammatory cytokines (32).

Angiogenesis inhibition

Angiogenesis requires binding of signaling molecules, such as vascular endothelial growth factor (VEGF), to their receptors on endothelial cells, and is considered vital for tumor growth and metastases. VEGF inhibitors are used by oncologists to deter tumor growth. Osteonecrosis, which is an avascular necrosis, entails interruption of the blood supply in the lesion. Administration of antiangiogenic agents, for example, antibodies targeting VEGF and TKIs, has been linked with ONJ occurrence (11). Additionally, glucocorticoids, especially in the high doses used in the oncology setting, exert antiangiogenic effects (33). High doses of potent BPs, especially ZOL, have been consistently associated with decreased angiogenesis according to in vitro studies (34, 35) and decreased VEGF levels in human studies (36, 37). On the contrary, there is no evidence that Dmab exerts antiangiogenic effects (35).

Immune system dysfunction

Accumulated indirect evidence suggests that dysregulation of the immunological response may contribute to MRONJ development. The higher MRONJ occurrence when glucocorticoids are coadministered with BPs both in animals (38, 39) and

for treatment of BM. Several local risk factors predispose to ONJ development (Fig. 1), the most common being tooth extraction. In cancer patients, tooth extraction not only after but also before initiation of BMA has been associated with MRONJ development (88). However, some studies suggest that preexisting dental disease, rather than tooth extraction, is the risk factor (88-93). In a recent systematic review, a 10% risk of MRONJ was noted in patients with periodontal disease treated with BPs (6). As expected, coexistence of local infection (periodontal/periapical inflammation) and tooth extraction further increases the risk of MRONJ (94). Systemic risk factors such as type of disease and concomitant therapies (eg, chemotherapy, glucocorticoids, antiangiogenic agents) also increase MRONJ risk (93, 95-110) (see Fig. 1). Among them, glucocorticoids, especially in the high doses used in oncology, alone or in combination with other medications, represent a prominent risk factor. Smoking (111-113), age (88, 97, 114), sex (74, 114), diabetes mellitus (112, 115), and obesity (111) have also been associated with ONJ risk, especially in oncology.

Despite the initial enthusiasm regarding the role of markers of bone resorption in the prediction of MRONJ risk, a systematic review suggested that no marker is useful in this setting (116).

Recently, a decline in the incidence of BRONJ has been reported, probably due to prevention of clinical risk factors. A 9-year (2009-2018) survey showed that the number of new MRONJ cases was stable from 2009 to 2015, with a mean of 51.3 cases per year declining during the years 2016 to 2018 to 33.3 cases per year (117). Increased clinician awareness as well as the reluctance of dental practitioners to perform dental procedures in patients on antiresorptives may have contributed to this decline in the incidence of ONJ.

Medication-related Osteonecrosis of the Jaw Associated With Denosumab Use

Similarly to BPs, the incidence in OP patients is considerably lower than in cancer patients and risk factors appear identical (63, 118-129). A systematic review of randomized controlled trials that directly compared Dmab with BPs in postmenopausal women with OP identified no reports of MRONJ (126), whereas in the FREEDOM and FREEDOM extension study the incidence of MRONJ was 5.2 per 10 000 patient-years (130). According to the FAERS database, Dmab-treated OP patients had an odds ratio of 0.63 (95% CI, 0.56-0.70; $P < .001$) to develop MRONJ compared to untreated OP patients, whereas in contrast the odds ratio was 4.9 (95% CI, 4.4-5.4; $P < .001$) for cancer patients treated with Dmab for prevention of SREs compared to untreated cancer patients (131). Similarly, according to the Multinational Association of Supportive Care in Cancer report, in cancer patients treated with Dmab, MRONJ frequency ranged from 0.7% to 6.9% for BM, whereas in the setting of CTIBL it was 0% (78).

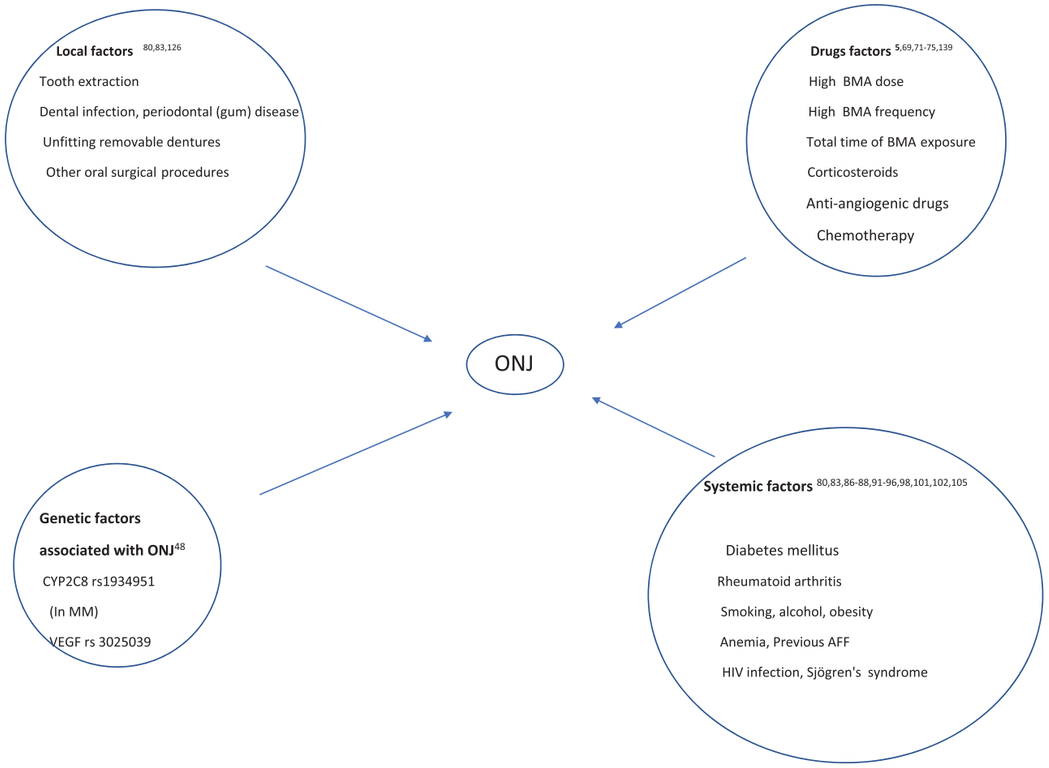

Figure 1. Risk factors for antiresorptive agent-related osteonecrosis of the jaw. AFF, atypical femoral fracture; BMA, bone-modifying agents; MM, multiple myeloma; ONJ, osteonecrosis of the jaw; VEGF, vascular endothelial growth factor.

needed and achieves long-term symptom relief (94, 206, 207). Cure rates with conservative management are higher for OP than for cancer patients (207). Management includes the following:

- maintenance of optimal oral hygiene, including self and regular professional care;
- treatment of any dental and periodontal disease;
- antiseptic mouth rinses; and

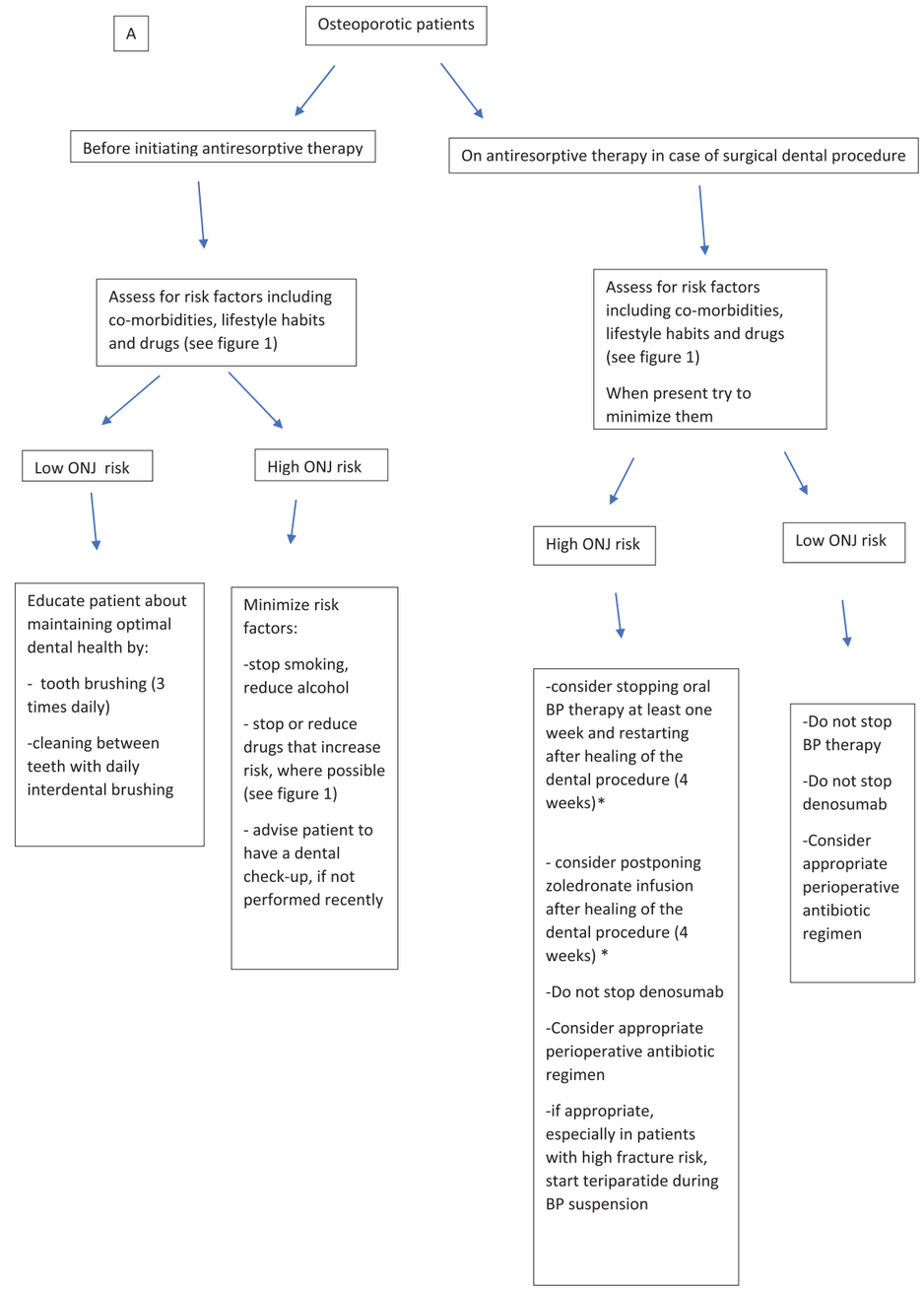

Figure 2. Recommendations for prevention of antiresorptive agent-related osteonecrosis of the jaw in patients taking bone-modifying agents (BMA) due to A, osteoporosis, and B, cancer. ONJ, osteonecrosis of the jaw; RCT, randomized controlled trial. *In the absence of RCT.

- systemic antibiotic therapy, if indicated. Dosages and duration of therapy varies depending on the stage of ONJ and the general condition of the patient.

Conservative management is mainly applied in the earlier stages of ONJ (see Fig. 3):

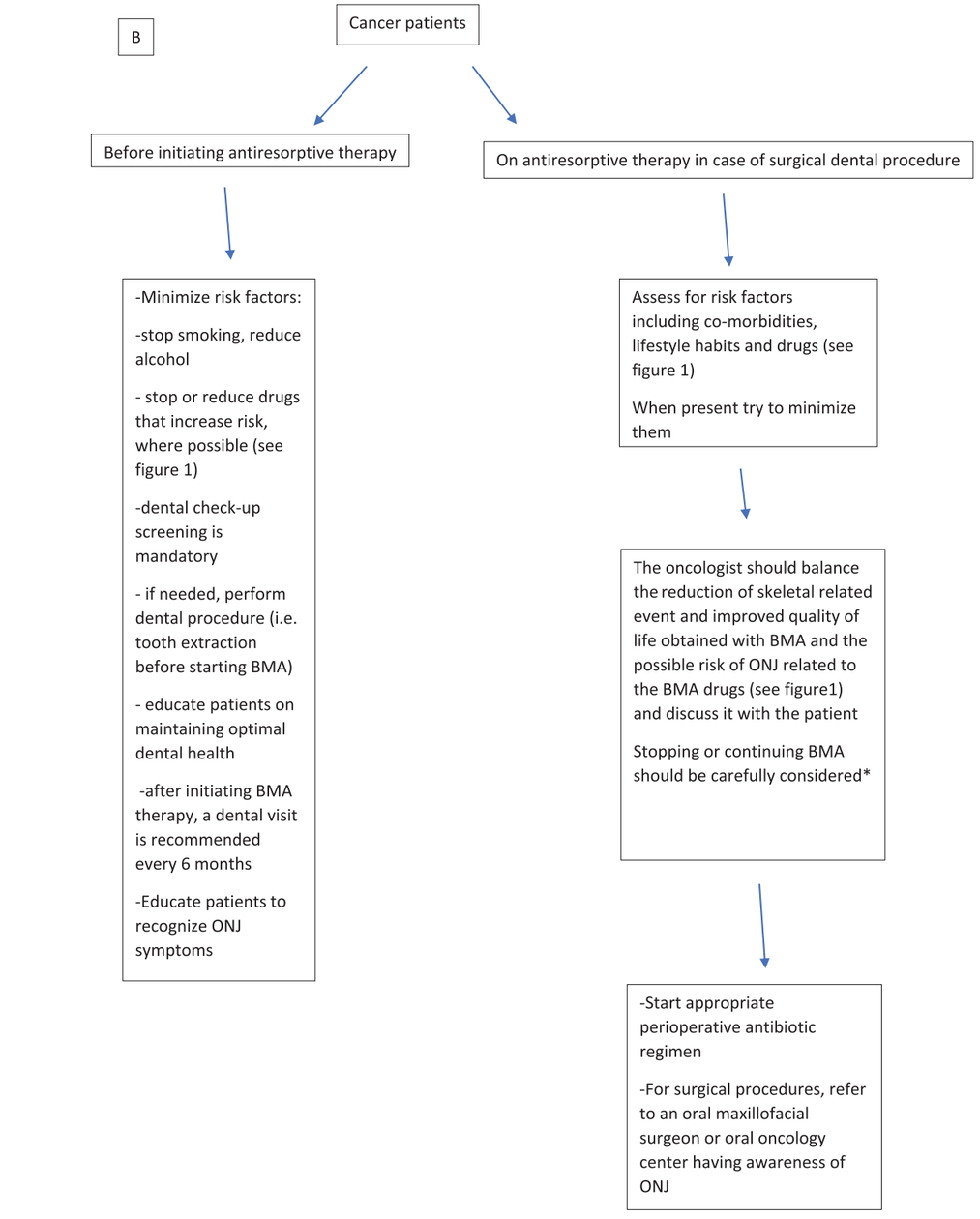

Figure 2. Continued.

- At-risk patients: Close clinical and radiographic monitoring is advised but there is no need for intervention. Nevertheless, patients must be informed about the possibility of bone exposure and necrosis and be able to early identify signs and symptoms
- Stage 0: Since symptoms are not specific, the objective is to symptomatically control pain and infections, and closely monitor for signs of progression

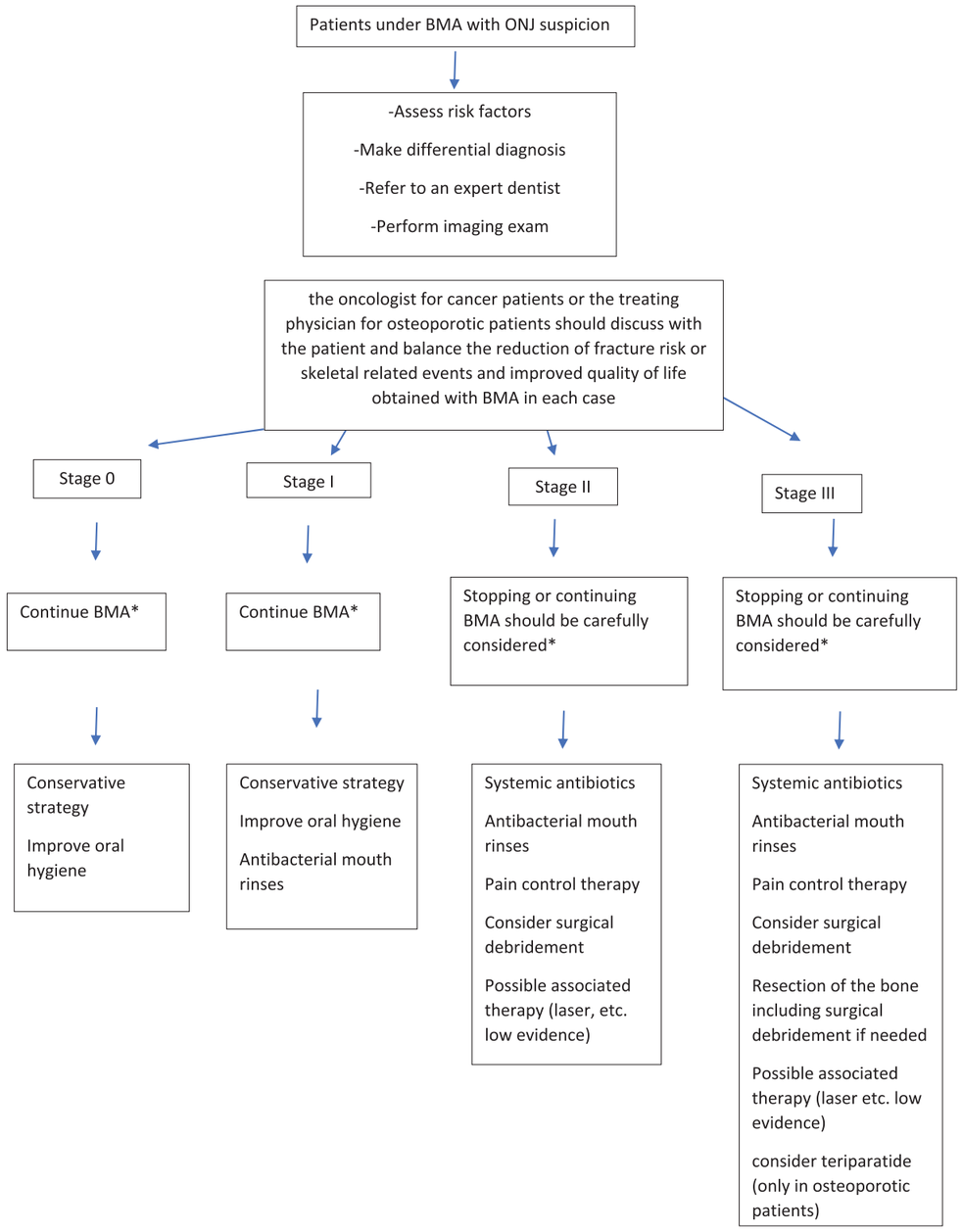

Figure 3. Recommendations for management of antiresorptive agent-related osteonecrosis of the jaw in patients taking bone-modifying agents (BMA). Staging of antiresorptive agent-related osteonecrosis of the jaw according to the American Association of Oral and Maxillofacial Surgeons (2014). ONJ, osteonecrosis of the jaw; RCT, randomized controlled trial. *In the absence of RCT.

- Stage 1: Management with chlorhexidine mouthwash and regular follow-up. Neither antibiotic nor surgical intervention is required
- Stage 2: Owing to necrosis and associated infection, an antibiotic regimen with an antimicrobial mouthwash and oral antibiotics is the treatment of choice

Teriparatide (TPTD) was helpful in ONJ management in several case reports (22, 23, 208-215). In a recent study in patients with established MRONJ, TPTD treatment for 8 weeks resulted in a significantly higher number of lesions healed and reduced bone defects by 52 weeks compared with placebo (216). Once-weekly TPTD was also effective (217). At

present, TPTD treatment is contraindicated in patients with active malignancies or a history of BM or skeletal radiation. However, given the rapid turnover of TPTD, a brief exposure (eg, 8 weeks) will most likely not affect the "alleged" risk of osteosarcoma, reported in rats but never demonstrated in humans (218), or activate quiescent malignant cells.

Weak evidence suggests other experimental conservative treatments may be helpful (Table 4).

Conservative therapy should be preferred over surgical management unless obvious progression of disease is observed or the pain is not controlled by conservative means.

Surgical management

Surgical treatment should be performed by experienced dentists or surgeons. Surgical management is applied in the latter stages of ONJ (see Fig. 3):

- Stage 2: Besides the antibiotic regimen reported earlier, debridement is often needed (232-238)
- Stage 3: Surgical management is indicated along with an antibiotic regimen. The surgical approach varies (232-238), ranging from limited debridement to complete resection with possible immediate reconstruction with plates or obturators (232, 239). A more conservative treatment should initially be considered, limiting operative therapy for cases not solved by this approach (238, 240, 241). However, the limited available data do not allow conclusive indications on surgical intervention. According to previous guidelines, removal of the necrotic bone with tension-free closure should be preferred, as it is considered to provide the most positive results.

Surgical success rates have been reported higher in OP and MM patients in comparison to patients with solid tumors (242).

Adjuvant treatments have also been proposed (243), although scientific evidence has often been controversial because of the lack of randomized controlled trials (Table 4).

Special Considerations

Table 5 presents the suggested approaches in i) dental procedures in low- and high-risk patients receiving antiresorptive treatment, and ii) patients receiving antiresorptives who develop ONJ.

A balanced evaluation of the risk-to-benefit ratio of continuing or stopping antiresorptives should always be performed in such patients. A detailed medical history should be obtained, evaluating the duration and type of antiresorptives (current or past), concurrent pharmacological treatments, the presence of other risk factors for ONJ, and the risk of fracture or SRE. Clinical decision should also be made in relation to the invasiveness of the procedure.

Discontinuation of antiresorptive treatment in patients requiring dental procedures is particularly controversial because of low evidence to support strong recommendations. The following are the most accepted guidelines:

- American Dental Association Guidelines in 2011 recognized the lower risk in OP patients and stated that discontinuation of oral BPs is not necessary before dental procedures (200)
- The AAOMS, admitting the lack of scientific evidence, suggested in 2014 a drug holiday in patients who have been on BPs or Dmab for at least 4 years (6)
- The US Food and Drug Administration stated there are "no substantial data available to guide decisions regarding the initiation or duration of a drug holiday" (258)
- An ONJ International Task Force in 2015 recommended stopping antiresorptive treatment in patients needing extensive invasive surgery or presenting with significant ONJ risk factors (64) until soft-tissue healing has occurred.

Our recommendations on the subject, along with our concerns, are summarized in Table 5. Discontinuation until the surgical site heals could be considered in case of BPs, especially if the fracture risk is low and the MRONJ risk is high. Theoretically, since the uptake of BPs is comparatively increased at sites of local bone injury with high bone turnover, withholding BP treatment may reduce their local deposition in the jawbone. It has been proposed that BPs may be discontinued 1 week before the procedure and resumed when healing of oral mucosa is completed (84, 245), usually 2 to 4 weeks after the dental treatment (9, 74). However, the optimal duration of the off-treatment period is unknown and, furthermore, the efficacy of such an approach is questionable given the residual effect of BPs due to their long-term skeletal retention and the fact that no study results to date have confirmed that drug holidays are effective in preventing MRONJ. Recent evidence from a study in OP patients (249) suggests that tooth extraction can be safely performed without BP discontinuation while suspension of BP treatment in animals (250) and humans (251, 252) who developed MRONJ did not provide any significant benefit. Lower doses of antiresorptive therapy have also been proposed (74), but without supporting evidence. Especially in cancer patients, in whom the vast majority of MRONJ incidents occur, although it has been recommended to withhold

Table 4. Adjuvant therapies applied in management of osteonecrosis of the jaw

During conservative management	During surgical management
• Bone marrow stem cell intralesional transplantation (219)	• Laser-assisted surgical debridement (220, 221)
• Leukocyte and platelet rich fibrin membrane placement (183, 222, 223)	• Preoperative antibiotic treatment followed by laser and wound local treatment with platelet-rich plasma applications (224)
• Ozone (225)	• Surgical debridement in combination with platelet-derived growth factor (183)
• Pentoxifylline (226)	• Intraoperative fluorescence guidance (227, 228)
• Vitamin E (226)	• Longer-term preoperative antibiotics (229)
• Hyperbaric oxygen therapy	• Adjunctive therapy with hyperbaric oxygen combined with surgery (230, 231)

Table 5. Recommendations for dental management in specific conditions

A.Dental procedures during antiresorptive therapy
Patients at low risk of ONJ
Conservative treatments (restorative treatment, non-surgical endodontic treatment, prosthodontic/orthodontic therapy) are safe[a]
Elective dentoalveolar surgery, simple extractions, and procedures that do not involve osteotomy are considered to be of low risk (9)
Placement of dental implants entails small risk
Antimicrobial mouthwash before/after procedure is advised. Systemic antibiotics are also advised in nonconservative treatments (180)
Antiresorptive treatment management
Osteoporotic patients
Do not discontinue bisphosphonates[b]
Do not discontinue denosumab—perform procedure preferably 5-6 mo following the last injection
Lower doses of antiresorptives (74)? No supporting evidence
Cancer patients
Do not discontinue bisphosphonates[b,c]
Do not discontinue denosumab
Patients at high risk of ONJ
Mild conservative treatments (restorative treatment, removal of dental caries) are usually safe
Nonsurgical endodontic treatment has a small risk—could be an alternative to extraction (244)[d]
Root canal treatment and/or decoronation preferred over extraction (244)
Antimicrobial mouthwash, systemic antibiotics before/after the procedure, avoidance of anesthetic agents that contain vasoconstrictor, avoidance of gingival tissue damage
Denture wearing not prohibited (avoid exerting excessive pressure or friction) (79)
Antiresorptive treatment management
Osteoporotic patients
Bisphosphonates could be discontinued (at least 1 wk before and until surgical site healing) (84, 245)[e]
Do not discontinue denosumab—perform procedure preferably 5-6 months following last injection (245, 246)[f]—perform next denosumab injection 4-6 wk after the procedure but not > 4 wk later than it should be done
Consider replacing antiresorptives with teriparatide[g]
No data on romosozumab
Cancer patients
Personalized decision in agreement with treating oncologist, weighing risk of ONJ against risks of SREs
Bisphosphonates could be discontinued
Short-term denosumab discontinuation (eg, 3 wk before and 4-6 wk after dental procedure has been advised) (247)—no clear benefit[h]
B.Antiresorptive treatment management in patients who develop ONJ
Consider discontinuing antiresorptives until complete soft-tissue closure after carefully weighing risk of ongoing ONJ with risk of fractures or SREs[i]
Consider teriparatide until complete soft-tissue closure (22) (in osteoporotic but probably not in cancer patients—individualized approach)[j]

Abbreviations: ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.
[a]A few, not well-documented cases of ONJ reported after nonsurgical endodontic procedures (248).
[b]Residual effect of bisphosphonates questions the effect of discontinuation on ONJ; in osteoporotic patients tooth extraction safely performed without bisphosphonate discontinuation (249); suspension of bisphosphonates not beneficial in animals (250) and humans (251, 252) who developed ONJ.
[c]Reduction in SRE risk is greater and the risk of ONJ lower in first years of bisphosphonate therapy (247).
[d]Soft-tissue damage during endodontic treatment has also been associated with initiation of ONJ process (253).
[e]Unknown optimal duration of off-treatment period.
[f]Based on denosumab pharmacokinetics, its effect on bone turnover is almost depleted around 6 months following the last injection (245, 246).
[g]Concerns: limited duration of teriparatide treatment (23); temporary decrease at least of hip bone mineral density (254); uncertain effect on rebound phenomenon after denosumab discontinuation (246).
[h]OPG-Fc discontinuation before tooth extraction ameliorated subsequent ONJ development in rodents (250); in contrast, in a multicenter retrospective Japanese study short-term denosumab discontinuation had no effect on ONJ risk (255).
[i]Concerns: denosumab discontinuation infers increased risk of multiple vertebral fractures (256, 257); discontinuation of either ZOL or OPG-Fc in rats with established ONJ did not lead to ONJ resolution (250).
[j]Teriparatide is theoretically contraindicated in cancer patients but a brief exposure (eg, 8 wk) should not activate quiescent malignant cells.

antiresorptive therapy following dental procedures until soft-tissue healing has occurred (64), current evidence supporting this recommendation is limited and controversial, with some studies showing a benefit (242, 259) while others have shown a neutral effect on the outcome of the dental procedure (94, 260, 261).

In Dmab-treated OP patients, discontinuation should be discouraged in light of the risk for multiple vertebral fractures (256, 257, 262). Instead, based on the pharmacokinetics of Dmab, dental procedures could be planned at around 5 to 6 months following the last injection, when the effects of Dmab on bone turnover are depleted (245, 246). In cancer patients, Dmab could be withheld but only for a short period (3 wk before to 4-6 wk after the dental procedure) (247), because of the risk both of multiple vertebral fractures and SREs. However, there is no evidence that such a strategy

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Clinical Research Article

Clinical Research Article

PaTH Forward: a Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism

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Abbreviations: AE, adverse event; CTx, C-telopeptide; FECa, fractional excretion of calcium; HPES, Hypoparathyroidism Patient Experience Scale; P1NP, procollagen type 1 N-terminal propeptide; PEG, polyethylene glycol; PTH, parathyroid hormone; rh, recombinant human; SAE, serious adverse event; SC, subcutaneous; sCa, serum Ca; SF-36, generic 36-Item Short Form Health Survey.

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Abstract

Context: Hypoparathyroidism is characterized by insufficient levels of parathyroid hormone (PTH). TransCon PTH is an investigational long-acting prodrug of PTH(1-34) for the treatment of hypoparathyroidism.

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ORIGINAL ARTICLE

JBMR®

Safety and Efficacy of Oral Human Parathyroid Hormone (1-34) in Hypoparathyroidism: An Open-Label Study

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ABSTRACT

The standard treatment of primary hypoparathyroidism (hypoPT) with oral calcium supplementation and calcitriol (or an analog), intended to control hypocalcemia and hyperphosphatemia and avoid hypercalciuria, remains challenging for both patients and clinicians. In 2015, human parathyroid hormone (hPTH) (1-84) administered as a daily subcutaneous injection was approved as an adjunctive treatment in patients who cannot be well controlled on the standard treatments alone. This open-label study aimed to assess the safety and efficacy of an oral hPTH(1-34) formulation as an adjunct to standard treatment in adult subjects with hypoparathyroidism. Oral hPTH(1-34) tablets (0.75 mg human hPTH(1-34) acetate) were administered four times daily for 16 consecutive weeks, and changes in calcium supplementation and alfacalcidol use, albumin-adjusted serum calcium (ACa), serum phosphate, urinary calcium excretion, and quality of life throughout the study were monitored. Of the 19 enrolled subjects, 15 completed the trial per protocol. A median 42% reduction from baseline in exogenous calcium dose was recorded ($p = .001$), whereas median serum ACa levels remained above the lower target ACa levels for hypoPT patients (>7.5 mg/dL) throughout the study. Median serum phosphate levels rapidly decreased (23%, $p = .0003$) 2 hours after the first dose and were maintained within the normal range for the duration of the study. A notable, but not statistically significant, median decrease (21%, $p = .07$) in 24-hour urine calcium excretion was observed between the first and last treatment days. Only four possible drug-related, non-serious adverse events were reported over the 16-week study, all by the same patient. A small but statistically significant increase from baseline quality of life (5%, $p = .03$) was reported by the end of the treatment period. Oral hPTH(1-34) treatment was generally safe and well tolerated and allowed for a reduction in exogenous calcium supplementation, while maintaining normocalcemia in adult patients with hypoparathyroidism.
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KEY WORDS: HYPOPARATHYROIDISM; ORAL PARATHYROID HORMONE; PARATHYROID-RELATED DISORDERS; CALCIUM/PHOSPHATE DISORDERS; PARATHYROID HORMONE

Introduction

Primary hypoparathyroidism (hypoPT) is a rare mineral metabolism disorder, with a prevalence of 22 per 100,000 individuals[(1)] and is biochemically characterized by low serum calcium and low or undetectable parathyroid hormone (PTH) levels. The leading cause of hypoPT in adults is iatrogenic, typically secondary to excision or injury incurred during anterior neck surgery.[(2)] Less common etiologies include autoimmune disease, congenital absence, and genetic disorders resulting in defective biosynthesis or secretion of the hormone.[(3)] The characteristic hypocalcemia in hypoPT is due to PTH levels

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Clinical Research Article

Clinical Research Article

Vertebral Fracture Assessment in Postmenopausal Women With Postsurgical Hypoparathyroidism

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Abstract

Context: Hypoparathyroidism is a rare endocrine disorder whose skeletal features include suppression of bone turnover and greater volume and width of the trabecular compartment. Few and inconsistent data are available on the prevalence of vertebral fractures (VF).

Objective: To evaluate the prevalence of VF assessed by vertebral fracture assessment (VFA) in postmenopausal women with chronic postsurgical hypoparathyroidism.

Design: Cross-sectional study

Setting: Ambulatory referral center.

Patients or Other Participants: Fifty postmenopausal women (mean age 65.4 ± 9 years) with chronic postsurgical hypoparathyroidism and 40 age-matched healthy postmenopausal women (mean age 64.2 ± 8.6).

Main outcome measures: Lumbar spine, femoral neck, and total hip bone mineral density were measured by dual X-ray absorptiometry (Hologic Inc., USA) in all subjects. Site-matched spine trabecular bone score was calculated by TBS iNsight (Medimaps, Switzerland). Assessment of VF was made by VFA (iDXA, Lunar GE, USA) using the semiquantitative method and the algorithm-based qualitative assessment.

Results: All-site BMD values were higher in the hypoparathyroid *vs* the control group. By VFA, we observed a 16% prevalence of VF in hypoparathyroid women *vs* 7.5% in control subjects. Among those with hypoparathyroidism who fractured, 5 (62.5%) had grade 1 wedge, 2 (25%) had grade 2 wedge, and 1 (12.5%) had grade 2 wedge and grade 2 biconcave VF. In the hypoparathyroid group, 57% with VFs and 32% without VFs had symptoms of hypoparathyroidism.

Conclusion: We demonstrate for the first time that in postmenopausal women with chronic postsurgical hypoparathyroidism, VFs are demonstrable by VFA despite normal BMD.

Key Words: VFA, fracture, postmenopausal women, hypoparathyroidism

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Hypoparathyroidism is a rare disorder of mineral metabolism characterized by low serum calcium levels and low or undetectable parathyroid hormone (PTH). The most common form occurs as a complication of anterior neck surgery. It is defined as chronic when insufficient parathyroid function persists for more than 6 months after surgery (1). A prevalence of postsurgical hypoparathyroidism ranging from 1.3 to 30/100 000 persons per year is reported by epidemiological studies from several different geographical areas (2-4). Reported incidences range from 0.8% to 13.4% after anterior neck surgery (4-6).

Most of the clinical manifestations and complications of hypoparathyroidism are related to its biochemical profile, namely low serum calcium and PTH levels. They involve several organs (1). Among them, the skeleton has been a focus because of potential deleterious effects of persistent exposure to low or undetectable PTH. Skeletal features of hypoparathyroidism include low bone turnover with greater volume and width of the trabecular compartment and lower cortical porosity (7). Histological findings in the hypoparathyroid skeleton comprise reduction of the mineralizing surface and reduced indices of bone turnover (7). By dual X-ray absorptiometry (DXA), these skeletal abnormalities are evident as normal or above average bone mineral density (BMD) and trabecular microarchitecture [as evaluated by trabecular bone score (TBS)], compared to healthy subjects (7,8). Assessment of bone quality by high-resolution peripheral quantitative computed tomography show higher trabecular number at tibia and reduced cortical porosity at both tibia and radius (9). To date, there are no clear data elucidating how these skeletal characteristics could potentially relate to clinically relevant reduction or increase in bone fragility in hypoparathyroidism. Indeed, there are no definitive data on the prevalence of fragility fracture in hypoparathyroidism (10). According to Underbjerg et al, discrepancy exists between the risk of upper extremities fractures in the non-surgical (higher risk) *vs* the postsurgical hypoparathyroid subjects, compared to the general population. A study in 104 patients with idiopathic hypoparathyroidism showed higher prevalence of vertebral fractures (VF) compared to healthy subjects, particularly in association with postmenopausal status and anticonvulsant therapy (11). Other studies reported inconsistent results in the prevalence of VF and non-VF in hypoparathyroid *vs* control subjects (12-14).

Vertebral fracture assessment (VFA) is an established, reliable and accurate methodology for the diagnosis of VF in patients with osteoporosis and other metabolic bone disease (15-19). As such, VFA is recommended for the evaluation of VF in adult patients and children with different metabolic bone disease by national and international consensus statements and guidelines (19-21). When analyzed by radiologists with the requisite expertise in the evaluation of vertebral morphology, VFA has significant advantages compared to the conventional X-ray (16,22). The VFA methodology is associated with lower radiation exposure, easier and faster spine image acquisition, and the lack of the parallax effect that increases vertebral distortion and therefore the rate of misdiagnosis with routine vertebral X-ray.

To our knowledge, no study has yet assessed the prevalence of VF in postmenopausal women with chronic postsurgical hypoparathyroidism. In particular, VFA has not been employed in this cohort of patients. The primary aim of the study was to assess this issue by comparing postmenopausal hypoparathyroid women with a cohort of age-matched healthy women. We also evaluated risk factors for VF in postmenopausal women with chronic hypoparathyroidism.

Materials and Methods

Participants

We studied 50 postmenopausal women with chronic postsurgical hypoparathyroidism (mean age 65.4 ± 9 years) and 40 age-matched healthy postmenopausal women (mean age 64 ± 8.5 years) as the control group. Hypoparathyroid subjects were recruited between November 2017 and December 2019 among those consecutively referred to the Unit of Internal Medicine and Metabolic Bone Disease, Sapienza University of Rome and meeting inclusion and exclusion criteria. The diagnosis of chronic postsurgical hypoparathyroidism was established by the persistent presence of serum calcium and PTH levels below normal for at least 1 year after neck surgery

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Clinical Research Article

Clinical Research Article

Use of Preoperative Imaging in Primary Hyperparathyroidism

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Abbreviations: 4D, 4-dimensional; CT, computed tomography; ICD, International, Classification of Diseases; iPTH, intact parathyroid hormone; IV, intravenous; NPV, negative predictive value; PET, positron emission tomography; PHPT, primary hyperparathyroidism; PPV, positive predictive value; SPECT, single photon emission computed tomography; US, ultrasound

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Abstract

Context: Preoperative imaging is performed routinely to guide surgical management in primary hyperparathyroidism, but the optimal imaging modalities are debated.

Objective: Our objectives were to evaluate which imaging modalities are associated with improved cure rate and higher concordance rates with intraoperative findings. A secondary aim was to determine whether additive imaging is associated with higher cure rate.

Design, Setting, and Patients: This is a retrospective cohort review of 1485 adult patients during a 14-year period (2004-2017) at an academic tertiary referral center that presented for initial parathyroidectomy for de novo primary hyperparathyroidism.

Main Outcome Measures: Surgical cure rate, concordance of imaging with operative findings, and imaging performance.

Results: The overall cure rate was 94.1% (95% confidence interval, 0.93-0.95). Cure rate was significantly improved if sestamibi/single-photon emission computed tomography (SPECT) was concordant with operative findings (95.9% vs. 92.5%, $P = 0.010$). Adding a third imaging modality did not improve cure rate (1 imaging type 91.8% vs. 2 imaging types 94.4% vs. 3 imaging types 87.2%, $P = 0.59$). Despite having a low number of cases (n = 28), 4-dimensional (4D) CT scan outperformed (higher sensitivity, specificity, positive predictive value, negative predictive value) all imaging modalities in multiglandular disease and double adenomas, and sestamibi/SPECT in single adenomas.

Conclusions: Preoperative ultrasound combined with sestamibi/SPECT were associated with the highest cure and concordance rates. If pathology was not found on ultrasound and sestamibi/SPECT, additional imaging did not improve the cure rate or concordance. 4D CT scan outperformed all imaging modalities in multiglandular disease and double adenomas, and sestamibi/SPECT in single adenomas, but these findings were underpowered.

Key Words: preoperative, imaging, primary hyperparathyroidism, cure, concordance

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Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient setting and is the third most common endocrine disorder, with prevalence differing between sex and race (1-3). Despite routine serum calcium measurements, PHPT remains underrecognized (4, 5). The estimated prevalence of PHPT in 2018 was 23 cases per 10 000 women and 8.5 per 10 000 men, with an incidence of 66 cases per 100 000 person-years in women and 25 per 100 000 person-years in men (3, 6). The attributable cause in about 70% to 80% of cases is a single parathyroid adenoma with the remainder comprising multiglandular disease, which includes both double adenomas and 4-gland hyperplasia. Parathyroid malignancy is seen in 1%, typically with a more aggressive presentation (3, 7). PHPT workup uses laboratory investigation to establish the diagnosis and imaging guide surgical planning (1, 3). Pharmacologic management involves bisphosphonate or calcimimetic therapy to reduce the deleterious effects of hypercalcemia, when surgical indications are not met. However, parathyroidectomy remains the standard of care and most cost-effective option, with established criteria helping to guide surgical referral (1, 3, 6, 8).

Although preoperative imaging is not required to establish a diagnosis, it is typically performed routinely to guide surgical management. Because of the wide variability between institutional protocols and surgeon preferences, the optimal imaging modality is debated (9). Historically, ultrasound (US) and nuclear scintigraphy (sestamibi/single-photon emission computed tomography [SPECT]) are first-line imaging modalities with comparable accuracy for preoperative localization for PHPT (6, 9, 10). However, with increasing utilization of 4-dimensional (4D)-CT, the role of these traditional modalities is being questioned (11–13).

The ability to perform a focal exploration depends on reliable preoperative localization. Despite reported cure rates of ~96% with focal exploration, limited data show that preoperative localization may not be the most accurate, with nonlocalized abnormal parathyroid glands being identified at surgical exploration. Given these discrepancies, there is a need to better define the role for preoperative imaging to optimize surgical decision-making and outcomes (14–16).

The aim of this study was to evaluate the primary imaging modalities associated with an improved cure rate based on intraoperative concordance with imaging in patients with PHPT. A secondary aim was to determine the effect of additive imaging modalities on remission rates.

Methods

The institutional review board approved this retrospective cohort study of patients undergoing initial surgery for de novo primary hyperparathyroidism from 2004–2017 at any United States-based Cleveland Clinic Health System. Consent was determined to not be necessary and was waived by the Cleveland Clinic Foundation institutional review board/independent ethics committee given the minimal risk posed to patients for this study. All patients were ≥ 18 years of age and were identified using the International Classification of Diseases 9 or 10 codes for primary hyperparathyroidism (252.0, E21.0, E21.3, E21.4, and E21.5). All charts were manually reviewed to confirm inclusion within the study.

Data collection

A manual chart review was conducted to collect variables. Demographics, including age, sex, and race, were obtained. Preoperative and postoperative laboratory values related to primary hyperparathyroidism, including calcium, intact parathyroid hormone (iPTH), and phosphorus, were reviewed. The preoperative laboratory values were the most recent in our medical record system before surgical management with a target of being within 1 month of the operative date. The postoperative laboratory values collected at 1 month postoperatively and at least 6 months after parathyroidectomy. If patients did not have preoperative laboratory values, and/or 6-month postoperative laboratory values, they were excluded from analysis. Preoperative imaging consisted of ultrasound, plain technetium sestamibi scintigraphy, sestamibi SPECT with iodine subtraction (sestamibi/SPECT), CT, or 4D CT. The CT neck images were subdivided into categories (4D CT, CT neck with and without

ΘΥΡΟΕΙΔΗΣ

ΓΕΩΡΓΙΟΣ ΣΗΜΑΙΑΚΗΣ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ – ΔΙΑΒΗΤΟΛΟΓΟΣ
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Mini-Review

Mini-Review

COVID-19 and Thyroid Diseases: A Bidirectional Impact

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Abbreviations: ACE2, angiotensin-converting enzyme 2; AITD, autoimmune thyroid disease; ARDS, acute respiratory distress syndrome; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GO, Graves ophthalmopathy; HICU, high intensity of care unit; IFN, interferon; IL-6, interleukin-6; LICU, low intensity of care unit; LT3, liothyronine; MMI, methimazole; NTI, nonthyroidal illness syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAT, subacute thyroiditis; T3, triiodothyronine; T4, thyroxine; TNF, tumor necrosis factor; TSH, thyrotropin (thyroid-stimulating hormone).

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Abstract

Context: COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has become the most lethal and rapidly moving pandemic since the Spanish influenza of 1918-1920, is associated with thyroid diseases.

Methods: References were identified through searches of PubMed and MEDLINE for articles published from Jan 1, 2019 to February 19, 2021 by use of the MeSH terms "*hypothyroidism*", "*hyperthyroidism*", "*thyroiditis*", "*thyroid cancer*", "*thyroid disease*", in combination with the terms "*coronavirus*" and "*COVID-19*". Articles resulting from these searches and references cited in those articles were reviewed.

Results: Though preexisting autoimmune thyroid disease appears unlikely to render patients more vulnerable to COVID-19, some reports have documented relapse of Graves' disease (GD) or newly diagnosed GD about 1 month following SARS-CoV-2 infection. Investigations are ongoing to investigate molecular pathways permitting the virus to trigger GD or cause subacute thyroiditis (SAT). While COVID-19 is associated with nonthyroidal illness, it is not clear whether it also increases the risk of developing autoimmune hypothyroidism. The possibility that thyroid dysfunction may also increase susceptibility for COVID-19 infection deserves further investigation. Recent data illustrate the importance of thyroid hormone in protecting the lungs from injury, including that associated with COVID-19.

Conclusion: The interaction between the thyroid gland and COVID-19 is complex and bidirectional. COVID-19 infection is associated with triggering of GD and SAT, and possibly hypothyroidism. Until more is understood regarding the impact of coronavirus on the thyroid gland, it seems advisable to monitor patients with COVID-19 for new thyroid disease or progression of preexisting thyroid disease.

Key Words: COVID-19, thyroid diseases, hyperthyroidism, subacute thyroiditis, autoimmune thyroiditis, non-thyroidal illness, hypothyroidism, thyroid cancer

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ΘΥΡΟΕΙΔΗΣ | ΓΕΩΡΓΙΟΣ ΣΗΜΑΙΑΚΗΣ

COVID-19 is an infectious disease caused by a newly identified non-segmented single-stranded ribonucleic acid (RNA)-β coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is thought to have spread from infected animal species to humans, this leading in turn to person-to-person transmission [1]. COVID-19 has proven to be the most lethal and most rapidly moving pandemic since that of 1918, having caused 2 857 866 deaths as of April 8, 2021. In humans, it affects, inter alia, the respiratory, neurological, cardiovascular, and gastrointestinal systems. The virus is highly contagious, showing in some people high morbidity and mortality mainly due to severe acute respiratory syndrome (SARS) and exaggerated immune response (cytokine storm), leading to sepsis and death [2].

Although the disease affects all ages, the worst prognosis is seen in the elderly, in individuals with chronic underlying diseases—particularly obesity and diabetes mellitus—and reduced organ reserves, and in those with a particular genetic susceptibility to the virus, allowing it an easy entrance. COVID-19 has had a dramatic impact on daily life, profoundly affecting anxiety levels, the healthcare system, human activity and behavior, and the economy; all of which is proving exceedingly difficult for societies worldwide to cope with [3].

The spike proteins covering the coronavirus bind to angiotensin-converting enzyme 2 (ACE2) receptors, regulators of the renin-angiotensin-aldosterone system (RAAS), which are present on the epithelial surface of human cells. SARS-CoV-2 recruits a serine protease, TMPRSS2, which facilitates viral protein priming and cytoplasmic entry [4]. SARS-CoV-2 cell receptor (ACE2 receptor) genes are variably expressed in human organs, with the highest expression being in the small intestine, followed by the testis, heart, thyroid, kidney, and lungs, rendering these tissues particularly susceptible to infection [5]. The widespread expression of the ACE2 receptor and its variable density may explain the variety of symptoms and spectrum of organ failure occurring in patients with COVID-19 and other underlying diseases.

The fact that there is an abundance of ACE2 receptors in the thyroid parenchyma may expose the thyroid gland to SARS-CoV-2 infection. Awareness of the potential for resulting thyroid pathology allows the identification of vulnerable patient groups in a timely fashion so that therapeutic intervention and long-term monitoring can be implemented. Additionally, a patient's thyroid status may have a direct impact on the course of COVID-19 due to the impact of thyroid hormone on multiple organs systems, including the cardiovascular and respiratory systems. In addition, given that thyroid abnormalities have been associated with disorders such as diabetes, obesity, kidney, dysfunction, and liver disease and that patients with these conditions are at increased risk for COVID-19 infection [6], it is possible that an underlying poorly controlled thyroid disorder may aggravate SARS-CoV-2 infection [7].

The aim of this mini-review is to summarize the current data regarding associations of COVID-19 with hyperthyroidism, with special focus on the potential impact of SARS-CoV-2 as a causal factor in the development of subacute thyroiditis (SAT) and as a trigger or perpetuator of Graves' disease (GD). Associations between COVID 19 and non-thyroidal illness and hypothyroidism will be explored. Moreover, the possibility will also be considered that thyroid dysfunction may be associated with worse COVID-19 outcomes. If this is the case, monitoring of thyroid status in COVID-19 patients, particularly those with preexisting thyroid disease, may be prudent.

Methods

References were identified through searches of PubMed and MEDLINE for articles published from Jan 1, 2019 to February 19, 2021 by use of the MeSH terms "*hypothyroidism*", "*hyperthyroidism*", "*thyroiditis*", "*thyroid cancer*", "*thyroid disease*", in combination with the terms "*coronavirus*" and "*COVID-19*". Articles resulting from these searches and references cited in those articles were reviewed. Relevant articles were also identified through searching authors' personal files. Preference was given to the most recent articles. A formal systematic review and grading of evidence was not undertaken. Greater emphasis was placed on high quality articles; however, given the fast pace at which knowledge regarding this topic is accruing, weight was also given to case reports and case series, due to their hypothesis-generating value.

Results

COVID-19 and the Immune System, and Subsequent Clinical Course

The immune profile of patients with COVID-19 has revealed that the disease causes severe lymphocyte

Clinical Study | I Campi and others | Thyroid dysfunctions in COVID-19 | 184:5 | 699–709

The spectrum of thyroid function tests during hospitalization for SARS COV-2 infection

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Abstract

Objective: Alterations in thyroid function tests (TFTs) have been recorded during SARS-CoV-2 infection as associated to either a destructive thyroiditis or a non-thyroidal illness.
Methods: We studied 144 consecutive COVID-19 patients admitted to a single center in intensive or subintensive care units. Those with previous thyroid dysfunctions or taking interfering drugs were excluded. Differently from previous reports, TSH, FT3, FT4, thyroglobulin (Tg), anti-Tg autoantibodies (TgAb) were measured at baseline and every 3–7 days. C-reacting protein (CRP), cortisol and IL-6 were also assayed.
Results: The majority of patients had a normal TSH at admission, usually with normal FT4 and FT3. Low TSH levels were found either at admission or during hospitalization in 39% of patients, associated with low FT3 in half of the cases. FT4 and Tg levels were normal, and TgAb-negative. TSH and FT3 were invariably restored at the time of discharge in survivors, whereas were permanently low in most deceased cases, but only FT3 levels were predictors of mortality. Cortisol, CRP and IL-6 levels were higher in patients with low TSH and FT3 levels.
Conclusions: Almost half of our COVID-19 patients without interfering drugs had normal TFTs both at admission and during follow-up. In this series, the transient finding of low TSH with normal FT4 and low FT3 levels, inversely correlated with CRP, cortisol and IL-6 and associated with normal Tg levels, is likely due to the cytokine storm induced by SARS-Cov-2 with a direct or mediated impact on TSH secretion and deiodinase activity, and likely not to a destructive thyroiditis.

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Introduction

Due to the ACE2 expression, thyroid may become a target of coronavirus infection (1, 2, 3, 4) and indeed a thyroid involvement has been demonstrated by histology during the SARS-Cov-1 (5) and SARS-Cov-2 (6) outbreaks, as thyroid follicular cells damage or lymphocytic infiltration, respectively. An alteration in thyroid function tests (TFT) mainly characterized by the reduction of TSH levels has been recorded during SARS-CoV-2 infection as associated to either a destructive thyroiditis or a non-thyroidal illness (NTI). Indeed, cases of destructive thyrotoxicosis (7, 8, 9) or subacute thyroiditis (10, 11, 12, 13, 14, 15, 16) have been reported in patients with COVID-19 infection. On the other hand, SARS-CoV-2 coronavirus can cause immune response hyperactivity leading to the release of pro-inflammatory cytokines which may cause a cytokine storm (15). In this context, changes in serum

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3 ORIGINAL ARTICLE - AUSTRALIA, JAPAN, SE ASIA

WILEY

Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity

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Funding information
None.

Abstract

Objective: Existing studies reported the potential prognostic role of non-thyroidal illness syndrome (NTIS), characterized by low triiodothyronine (T3) with normal/low thyroid-stimulating hormone (TSH), mainly in severe COVID-19. None considered the significant impact of SARS-CoV-2 viral load on adverse outcomes. We aimed to clarify the prognostic role of NTIS among predominantly mild-to-moderate COVID-19 patients.
Design: A prospective study of COVID-19 patients.
Patients and Measurements: Consecutive adults admitted to Queen Mary Hospital for confirmed COVID-19 from July to December 2020 were prospectively recruited. SARS-CoV-2 viral load was represented by cycle threshold (Ct) values from real-time reverse transcription-polymerase chain reaction of the respiratory specimen on admission. Serum TSH, free thyroxine and free T3 were measured on admission. The outcome was deterioration in clinical severity, defined as worsening in ≥1 category of clinical severity according to the Chinese National Health Commission guideline.
Results: We recruited 367 patients. At baseline, 75.2% had mild disease, and 27 patients (7.4%) had NTIS. Fifty-three patients (14.4%) had clinical deterioration. Patients with NTIS were older, had more comorbidities, worse symptomatology, higher SARS-CoV-2 viral loads and worse profiles of inflammatory and tissue injury markers. They were more likely to have clinical deterioration ($p < .001$). In multivariable stepwise logistic regression analysis, NTIS independently predicted clinical deterioration (adjusted odds ratio 3.19, $p = .017$), in addition to Ct value <25 ($p < .001$), elevated C-reactive protein ($p = .004$), age >50 years ($p = .011$) and elevated creatine kinase ($p = .017$).
Conclusions: Non-thyroidal illness syndrome was not uncommon even in mild-to-moderate COVID-19 patients. NTIS on admission could predict clinical deterioration in COVID-19, independent of SARS-CoV-2 viral load, age and markers of inflammation and tissue injury.

KEYWORDS
COVID-19, euthyroid sick syndromes, prognosis, SARS-CoV-2, thyroid function tests, thyroid gland

THYROID
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ORIGINAL STUDIES
THYROID FUNCTION AND DYSFUNCTION

Activation of Type I and Type II Interferon Signaling in SARS-CoV-2-Positive Thyroid Tissue of Patients Dying from COVID-19

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Background: Thyroid dysfunctions have been reported after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. However, the biological mechanisms behind these conditions remain unexplored. Herein, we report on changes of the immune transcriptome in autoptic thyroid tissues of people who have died from coronavirus disease 2019 (COVID-19).
Methods: Twenty-five autoptic thyroid specimens of subjects dying from COVID-19 were investigated. Eleven autoptic thyroid specimens of subjects dying from causes other than infectious conditions served as controls. RNA transcripts of 770 immune-related genes together with RNA genomes of multiple coronavirus types were measured by the nCounter system. Reverse transcription–polymerase chain reaction for two SARS-CoV-2 genes was used to assess virus positivity. Results were validated by immunohistochemistry.
Results: The SARS-CoV-2 genome and antigens were detected in 9 of 25 (36%) thyroid specimens from the COVID-19 cohort. Virus-negative thyroid tissues from COVID-19 subject did not show changes of gene transcription nor significant numbers of infiltrating immune cells. Conversely, SARS-CoV-2-positive thyroid specimens showed marked upregulation of immune genes, especially those proper of the type I and type II interferon (IFN) pathways. In infected tissues, infiltrates of innate immune cells (macrophages and polymorphonuclear neutrophils) were prevalent.
Conclusions: The thyroid gland can be directly infected by the SARS-CoV-2. Infection strongly activates IFN pathways. The direct viral insult combined with an intense immune response may trigger or worsen thyroid conditions in predisposed individuals.

Keywords: autopsy, COVID-19, interferons, SARS-CoV-2, thyroid

Introduction

At the end of 2019, cases of pneumonitis of unknown etiology were reported in Wuhan, China (1). In a few months, the coronavirus disease 2019 (COVID-19) was spreading worldwide (2). The disease typically involves the lungs, but recent findings report that COVID-19 is also a condition associated with endothelial damage (3). As a consequence, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) may affect multiple organs, including endocrine glands. Different endocrine tissues, in fact, have been shown to express the angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS2), two surface proteins acting as host cell entry factors for SARS-CoV-2 (4,5). Accordingly, endocrine dysfunctions especially of the thyroid have been reported. However, the spectrum of thyroid disorders linked to SARS-CoV-2 infection is rather broad. The first reports of altered thyroid functions were classified under three different conditions: nonthyroidal illness syndrome (NTIS), thyrotoxicosis, and subacute thyroiditis (SAT) (6–9). Although NTIS and thyrotoxicosis are not necessarily associated with the direct virus infection of thyroid cells (9), SAT is a likely consequence of virus replication within thyroid follicular cells (10). In addition, the possible thyroid tropism of SARS-CoV-2 (11–13) is suggested by the observation that COVID-19 may precede the onset of Graves' disease (GD), an immune-mediated condition linked to both genetic and

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Clinical Research Article

Clinical Research Article

Thyroid Immune-related Adverse Events Following Immune Checkpoint Inhibitor Treatment

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Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; FT4, free thyroxine; HR, hazard ratio; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; OR, odds ratio; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival; TGAb, thyroglobulin antibody; TPOab, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

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Abstract

Context: Thyroid dysfunction occurs commonly following immune checkpoint inhibition. The etiology of thyroid immune-related adverse events (irAEs) remains unclear and clinical presentation can be variable.
Objective: This study sought to define thyroid irAEs following immune checkpoint inhibitor (ICI) treatment and describe their clinical and biochemical associations.
Methods: We performed a retrospective cohort study of thyroid dysfunction in patients with melanoma undergoing cytotoxic T-lymphocyte antigen-4 (CTLA-4) and/or programmed cell death protein-1 (PD-1) based ICI treatment from November 1, 2009, to December 31, 2019. Thyroid function was measured at baseline and at regular intervals following the start of ICI treatment. Clinical and biochemical features were evaluated for associations with ICI-associated thyroid irAEs. The prevalence of thyroid autoantibodies and the effect of thyroid irAEs on survival were analyzed.

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2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction

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Keywords
Subfertility · Assisted reproductive technology · In vitro fertilization · Intracytoplasmic sperm injection · Thyroid autoimmunity · Subclinical hypothyroidism/hyperthyroidism · Thyroid cancer · Radioactive iodine

Abstract
Severe thyroid dysfunction may lead to menstrual disorders and subfertility. Fertility problems may persist even after restoring normal thyroid function, and then an assisted reproductive technology (ART) may be a solution. Prior to an ART treatment, ovarian stimulation is performed, leading to high oestradiol levels, which may lead to hypothyroidism in women with thyroid autoimmunity (TAI), necessitating levothyroxine (LT4) supplements before pregnancy. Moreover, women with the polycystic ovarian syndrome and idiopathic subfertility have a higher prevalence of TAI. Women with hypothyroidism treated with LT4 prior to ART should have a serum TSH level <2.5 mIU/L. Subfertile women with hyperthyroidism planning an ART procedure should be informed of the increased risk of maternal and foetal complications, and euthyroidism should be restored and maintained for several months prior to an ART treatment. Fertilisation rates and embryo quality may be impaired in women with TSH >4.0 mIU/L and improved with LT4 therapy. In meta-analyses that mainly included women with TSH levels >4.0 mIU/L, LT4 treatment increased live birth rates, but that was not the case in 2 recent interventional studies in euthyroid women with TAI. The importance of the increased use of intracytoplasmic sperm injection as a type of ART on pregnancy outcomes in women with TAI deserves more investigation. For all of the above reasons, women of subfertile couples should be screened routinely for the presence of thyroid disorders.

Introduction

The prevalence of thyroid disorders in women aged 20–45 years is high, and that of subfertility is increasing worldwide in part due to improved public awareness and diagnosis. Therefore, the female partner in a subfertile

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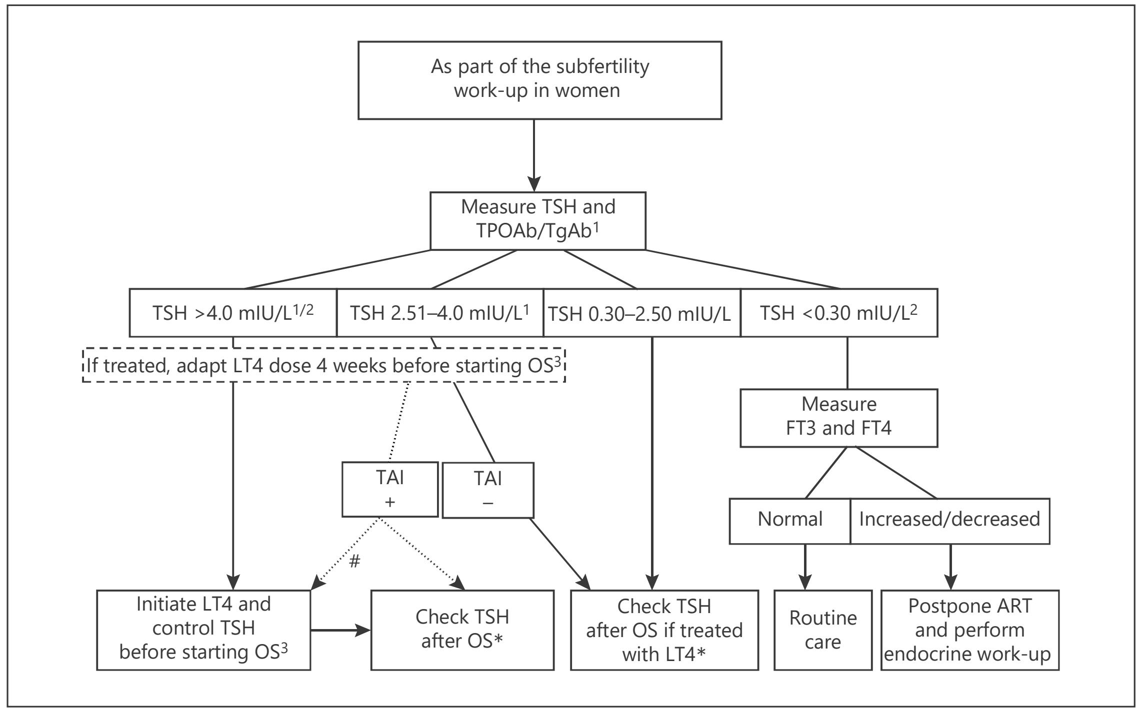

Fig. 1. Algorithm for workup and management of thyroid disorders in women of subfertile couples starting an ART procedure. [1]If not possible for local terms, then measure TgAb in case TSH >2.5 mIU/L and negative TPOAb/look for sonographic criteria of TAI if available. [2]Or above/below the reference range of the assay for non-pregnant women or institutional population-specific values. [3]LT4 dose depending on baseline TSH level and body weight; start 25 μg when TSH 2.51–4.0 mIU/L → target TSH <2.5 mIU/L. [#]Decide to treat on a case-by-case basis (cf text for details). *In case of pregnancy, the day of the second/confirmatory hCG measurement. TAI, thyroid autoimmunity; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; LT4, levothyroxine; hCG, human chorionic gonadotropin; OS, ovarian stimulation; ART, assisted reproductive technology. The figure is reproduced from Unuane and Poppe (Female infertility: do we forget the thyroid? *J Endocrinol Invest*. 2015) with permission from Springer.

more pronounced elevation of TSH might still benefit from LT4 treatment. The same Cochrane systemic review as mentioned before [88] identified 2 studies that met the inclusion criteria [13, 21], but the results of one of those studies were not used because the integrity of the data could not be verified. The other study randomized 64 women (with and without TAI) with TSH >4.5 mIU/L scheduled for IVF/ICSI to LT4 or no treatment. LT4 treatment was associated with 27–100% chance of live birth compared to 25% in the control group. The level of evidence was downgraded for imprecision from low to very low.

Chapter-Specific Recommendations/Suggestions
We suggest that LT4 treatment is initiated before OS in women with TSH levels >4.0 mIU/L/ULRR undergoing IVF/ICSI (2, ØOOO).

Screening/Management in Daily Practice

We suggest screening for thyroid dysfunction (TSH) and autoimmunity (TPOAb) in women of subfertile couples planning an ART treatment. The presence of increased TgAb levels can be verified in women with TSH levels >2.5 mIU/and no increased TPOAb levels.

According to the general principles of screening by Wilson and Jungner, the case of subfertility and ART fulfils many of the prerequisites [94]. The presence of increased TPOAb levels may identify women at risk for developing hypothyroidism after OS or during gestation and be a predictive marker for the development of postpartum thyroiditis [95]. Furthermore, women with PCOS, POI, and idiopathic subfertility have a higher prevalence of TAI and serum TSH levels compared with fertile women [6, 9, 25]. Serum TSH levels >3.5 mIU/L are associated with impaired ART outcomes, and LT4 treat-

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Thyroid Function Test Abnormalities in Twin Pregnancies

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Background: Compared with singletons, a twin pregnancy is associated with a larger thyroid hormone demand and an increased stimulation of gestational thyroid function due to higher concentrations of human chorionic gonadotropin. However, such effects have been sparsely quantified. The aim of this study was to evaluate thyroid function and thyroid function test abnormalities in twin pregnancies during early and late pregnancy compared with singletons.
Methods: We included 1208 twin pregnancies and 46,834 singleton pregnancies with thyroid function tests available. Thyroid function test abnormalities were defined using population-based reference ranges. The analyses were adjusted for potential confounders including maternal age and body mass index.
Results: Compared with singletons, a twin pregnancy was associated with a lower thyrotropin (TSH) ($\beta = -0.46$ [95% confidence interval, CI −0.49 to −0.44], $p < 0.001$) and a higher free thyroxine (fT4) ($\beta = 0.91$ [CI 0.69–1.16], $p < 0.001$) during early pregnancy. During late pregnancy, a twin pregnancy was associated with a higher TSH ($\beta = 0.35$ [CI 0.29–0.42], $p < 0.001$) while fT4 did not differ ($\beta = -0.11$ [CI −0.22 to 0.01], $p = 0.065$). During early pregnancy, a twin pregnancy was associated with a higher risk of overt hyperthyroidism (odds ratio, OR = 7.49 [CI 6.02–9.33], $p < 0.001$), subclinical hyperthyroidism (OR = 5.26 [CI 4.17–6.64], $p < 0.001$), and isolated hypothyroxinemia (OR = 1.89 [CI 1.43–2.49], $p < 0.001$), but with a lower risk of subclinical hypothyroidism (OR = 0.27 [CI 0.13–0.54], $p < 0.001$). In late pregnancy, a twin pregnancy was associated with a higher risk of subclinical hypothyroidism (OR = 4.05 [CI 3.21–5.11], $p < 0.001$), isolated hypothyroxinemia (OR = 1.48 [CI 1.04–2.10], $p = 0.028$), and subclinical hyperthyroidism (OR = 1.76 [CI 1.27–2.43], $p < 0.001$).
Conclusions: During early pregnancy, a twin pregnancy was associated with a higher thyroid function and a higher risk of (subclinical) hyperthyroidism, as well as a higher risk of isolated hypothyroxinemia. During late pregnancy, a twin pregnancy was associated with a higher TSH concentration and a higher risk of subclinical hypothyroidism, as well as a persistently higher risk of isolated hypothyroxinemia and subclinical hyperthyroidism. The study was approved by Chinese Clinical Trial Registry (registration no. ChiCTR1800014394).

Keywords: thyroid, dysfunction, TSH, fT4, twin pregnancy

Introduction

ADEQUATE THYROID HORMONE availability is crucial for the growth and development of the fetus, predominantly the fetal brain (1). During the first 18–20 weeks of pregnancy, the fetus predominantly depends on the placental transfer of maternal thyroid hormones. Some studies showed that thyroid dysfunction during pregnancy is associated with various adverse pregnancy and child outcomes such as spontaneous abortion, preterm birth, gestational hypertensive disorders, gestational diabetes, low birth weight, and suboptimal offspring neuropsychological development (2,3).

Physiological changes during pregnancy increase the demand for thyroid hormone production such as an increase in thyroxine binding proteins (mainly thyroxine binding globulin), placental type 3 deiodinase expression, and the consumption of thyroid hormone by the fetus (4,5). In parallel, thyroid hormone production is upregulated through additional stimulation of the thyroid gland by high concentrations of human chorionic gonadotropin (hCG). In a twin

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Maternal Thyroid Hormone Programs Cardiovascular Functions in the Offspring

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Background: Maternal thyroid hormone (TH) plays an essential role for fetal development, especially for the cardiovascular system and its central control. However, the precise consequences of altered TH action during the different periods in pregnancy remain poorly understood.
Methods: To address this question, we used mice heterozygous for a mutant thyroid hormone receptor α1 (TRα1) and wild-type controls that were born to wild-type mothers treated with 3,3′,5-triiodothyronine (T3) during the first or the second half of pregnancy. We then phenotyped the offspring animals as adults by *in vivo* measurements and *postmortem* tissue analyses.
Results: Maternal T3 treatment in either half of the pregnancy did not affect postnatal growth development. Serum thyroxine and hypophyseal thyrotropin subunit beta or deiodinase type II expression was also not affected in any group, only TRα1 mutant males exhibited a reduction in serum T3 levels after the treatment. Likewise, hepatic deiodinase type I was not altered, but serum selenium levels were reduced by the maternal treatment in wild-type offspring of both genders. Most interestingly, a significant increase in heart weight was found in adult wild-types born to mothers that received T3 during the first or second half of pregnancy, while TRα1 mutant males were protected from this effect. Moreover, we detected a significant increase in heart rate selectively in male mice that were exposed to elevated maternal T3 in the second half of the pregnancy.
Conclusion: Taken together, our findings demonstrate that maternal TH is of particular relevance during the second half of pregnancy for establishing cardiac properties, with specific effects depending on TRα1 or gender. The data advocate routinely monitoring TH levels during pregnancy to avoid adverse cardiac effects in the offspring.

Keywords: cardiovascular system, fetal programming, heart, pregnancy, thyroid hormone, TRα1 signaling

Introduction

THYROID HORMONE (TH) is important for development (1). As the fetal thyroid gland does not produce hormones until late pregnancy in humans, around embryonic day 15 in mice (2), the embryonal demand for the hormone needs to be met by the maternal thyroid gland (3). Consequently, defects in maternal thyroid function can severely impact the fetus, especially the developing brain (4), as well as pregnancy outcomes including miscarriage and growth retardation. Moreover, the offspring's setting of the hypothalamic/pituitary/thyroid (HPT) axis can be permanently altered (5,6).

The HPT axis regulates circulating THs via an endocrine feedback loop. Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus, stimulating the anterior pituitary to produce thyrotropin (TSH), which drives the thyroid gland to release THs. THs in turn negatively regulate TRH and TSH, thereby affecting their own production and release (7). This tightly controlled mechanism is required as TH has potent effects on many physiological functions, including energy homeostasis (8) and cardiac contractility or heart rate (9–11). The active hormone 3,3′,5-triiodothyronine (T3) acts via nuclear TH receptors (TRs), namely TRα1 and TRβ (12), which bind to target genes and lead to activation or suppression of gene expression (13).

Despite TH's major role in development, it is currently controversial whether pregnant women should be routinely screened for thyroid function, and whether to substitute in subclinical cases (14,15). As maternal thyroid dysfunction can impair cognitive and motor development in the offspring

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Paternal Subclinical Hypothyroidism Affects the Clinical Outcomes of *In Vitro* Fertilization/Intracytoplasmic Sperm Injection

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Background: Maternal subclinical hypothyroidism (SCH) is a risk factor for adverse pregnancy outcomes. However, it is still unclear whether SCH affects male fertility. The aim of this study was to determine the association between paternal SCH and clinical outcomes after *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI).
Methods: This retrospective study included 2511 couples with paternal euthyroidism ($n=2282$) or SCH ($n=229$) who visited our clinic for infertility treatment between April 1, 2017, and September 30, 2019. The primary outcomes were the fertilization rate and clinical pregnancy rate; the secondary outcomes were the good-quality embryo rate, blastocyst formation rate, implantation rate, and early miscarriage rate. These outcomes were compared between the euthyroid and the SCH groups after adjusting for various potential confounders.
Results: The mean paternal ages in the euthyroid and SCH groups were 34.5 and 36.0 years, respectively ($p=0.002$). Semen parameters and sperm DNA fragmentation index were similar between the two groups (all $p>0.05$). The adjusted fertilization (0.69 vs. 0.71, $p=0.30$), good-quality embryo (0.49 vs. 0.52, $p=0.31$), blastocyst formation (0.51 vs. 0.53, $p=0.57$), and early miscarriage (0.11 vs. 0.10, $p=0.81$) rates were also similar between the two groups. There was a significantly decreased adjusted clinical pregnancy rate [confidence interval, CI] and implantation rate [CI] in the paternal SCH group compared with the euthyroid group (0.32 [0.26–0.40] vs. 0.42 [0.40–0.45], $p=0.009$ for the clinical pregnancy rate; 0.24 [0.19–0.29] vs. 0.29 [0.27–0.31], $p=0.037$ for the implantation rate). Stratified analysis indicated that these differences were only significant in men aged ≥35 years ($p=0.009$ and 0.022, respectively) and not in men <35 years ($p=0.39$ and 0.45, respectively).
Conclusions: Paternal SCH was associated with worse clinical outcomes after IVF/ICSI, whereas this detrimental impact was only present in males ≥35 years old. Prospective studies and basic research are warranted to confirm these results and to clarify the mechanisms underlying these associations, respectively.

Keywords: subclinical hypothyroidism, thyroid function, IVF/ICSI, clinical outcomes

Introduction

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyrotropin (TSH) concentration coexisting with a normal serum thyroxine (T4) concentration. In our previous study, we identified an association between maternal SCH and decreased ovarian reserve (1). Others have also described associations between maternal SCH and adverse pregnancy outcomes, such as a decreased good-quality embryo rate or clinical pregnancy rate, or an increased risk of miscarriage (2–5). Women with SCH might therefore benefit from levothyroxine (LT4) supplementation before or during their attempt to conceive (6). However, the effect of LT4 supplementation on naturally conceived pregnancies and pregnancies achieved by assisted reproductive technology (ART) is different: LT4 supplementation significantly decreases the odds of pregnancy loss in pregnancies achieved by ART, but not in naturally conceived pregnancies, among women with SCH. By contrast, LT4 seems to reduce the risks of pregnancy loss and preterm birth in naturally conceived pregnancies, but not in pregnancies achieved by ART, among patients with thyroid autoimmunity (TAI), as indicated by our previously published study (6). These different effects suggest that SCH may influence the fertility of infertile

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ORIGINAL RESEARCH ARTICLE

Thyroid-stimulating hormone and free thyroxine fail to predict the severity and clinical course of hyperemesis gravidarum: A prospective cohort study

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Abbreviations: FT4, free thyroxine; GTT, gestational thyrotoxicosis; hCG, human chorionic gonadotropin; HG, hyperemesis gravidarum; HIS, Hyperemesis Impact of Symptoms questionnaire; MoM, multiple of the median; NVP, nausea and vomiting in pregnancy; NVPQoL, Nausea and Vomiting in Pregnancy Quality of Life questionnaire; PUQE-24, 24 Hour Pregnancy Unique Quantification of Emesis and Nausea questionnaire; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone.

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Abstract

Introduction: Little is known about the pathophysiology of hyperemesis gravidarum (HG). Proposed underlying causes are multifactorial and thyroid function is hypothesized to be causally involved. In this study, we aimed to assess the utility of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) as a marker and predictor for the severity and clinical course of HG.

Material and methods: We conducted a prospective cohort study including women admitted for HG between 5 and 20 weeks of gestation in 19 hospitals in the Netherlands. Women with a medical history of thyroid disease were excluded. TSH and FT4 were measured at study entry. To adjust for gestational age, we calculated TSH multiples of the median (MoM). We assessed HG severity at study entry as severity of nausea and vomiting (by the Pregnancy Unique Quantification of Emesis and nausea score), weight change compared with prepregnancy weight, and quality of life. We assessed the clinical course of HG as severity of nausea and vomiting and quality of life 1 week after inclusion, duration of hospital admissions, and readmissions. We performed multivariable regression analysis with absolute TSH, TSH MoMs, and FT4.

Results: Between 2013 and 2016, 215 women participated in the cohort. TSH, TSH MoM, and FT4 were available for, respectively, 150, 126, and 106 of these women. Multivariable linear regression analysis showed that lower TSH MoM was significantly associated with increased weight loss or lower weight gain at study entry (ΔKg; β = 2.00, 95% CI 0.47-3.53), whereas absolute TSH and FT4 were not. Lower TSH, not lower TSH MoM or FT4, was significantly associated with lower nausea and vomiting scores 1 week after inclusion (β = 1.74, 95% CI 0.36-3.11). TSH and FT4 showed no association with any of the other markers of the severity or clinical course of HG. Twenty-one out of 215 (9.8%) women had gestational transient thyrotoxicosis. Women with gestational transient thyrotoxicosis had a lower quality of life 1 week after inclusion than women with no gestational transient thyrotoxicosis (p = 0.03).

Conclusions: Our findings show an inconsistent role for TSH, TSH MoM, or FT4 at time of admission and provide little guidance on the severity and clinical course of HG.

KEYWORDS
disease severity marker, free thyroxine, hyperemesis gravidarum, nausea and vomiting in pregnancy, thyroid function, thyroid-stimulating hormone

1 | INTRODUCTION

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting in pregnancy (NVP) affecting 0.3%-3.6% of pregnancies.[1,2] HG is the most common reason for hospital admission in early pregnancy, but evidence-based effective treatment options are currently limited.[3,4] Because of the major impact of HG on maternal well-being and quality of life, a marker that could help to identify the severity and clinical course of HG would be of value for assessing a patient's prognosis and individualizing patient care.[5-8]

Little is known about the pathophysiology of HG. Proposed underlying causes are multifactorial and related to maternal endocrine and placental function as well as to gastrointestinal conditions, although recently genetic causes, including involvement of the growth differentiation factor-15 gene (*GDF15*), a cachexia gene, and its receptor have been implicated.[9,10]

Key message

Thyroid measurement in women admitted for hyperemesis gravidarum provides little guidance on predicting disease severity and course.

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Influence of Dietary Habits on Oxidative Stress Markers in Hashimoto's Thyroiditis

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Background: There is a growing awareness that nutritional habits may influence risk of several inflammatory and immune-mediated disorders, including autoimmune diseases, through various mechanisms. The aim of the present study was to investigate dietary habits and their relationship with redox homeostasis in the setting of thyroid autoimmunity.

Materials and Methods: Two hundred subjects (173 females and 27 males; median age, 37 years) were enrolled. None were under any pharmacological treatment. Exclusion criteria were any infectious/inflammatory/autoimmune comorbidity, kidney failure, diabetes, and cancer. In each subject, serum thyrotropin (TSH), free thyroxine, antithyroid antibodies, and circulating oxidative stress markers were measured. A questionnaire on dietary habits, evaluating the intake frequencies of food groups and adherence to the Mediterranean diet, was submitted to each participant.

Results: Among the 200 recruited subjects, 81 (71 females and 10 males) were diagnosed with euthyroid Hashimoto's thyroiditis (HT); the remaining 119 (102 females and 17 males) served as controls. In questionnaires, HT subjects reported higher intake frequencies of animal foods (meat, $p=0.0001$; fish, $p=0.0001$; dairy products, $p=0.004$) compared with controls, who reported higher intake frequencies of plant foods (legumes, $p=0.001$; fruits and vegetables, $p=0.030$; nuts, $p=0.0005$). The number of subjects who preferentially consumed poultry instead of red/processed meat was lower in HT subjects than in controls ($p=0.0141$). In logistic regression analysis, meat consumption was associated with increased odds ratio of developing thyroid autoimmunity, while the Mediterranean diet traits were protective. In HT subjects, serum advanced glycation end products (markers of oxidative stress) were significantly higher ($p=0.0001$) than in controls, while the activity of glutathione peroxidase and thioredoxin reductase, as well as total plasma antioxidant activity, were lower ($p=0.020$, $p=0.023$, and $p=0.002$, respectively), indicating a condition of oxidative stress. Stepwise regression models demonstrated a significant dependence of oxidative stress parameters on consumption of animal foods, mainly meat.

Conclusions: The present study suggests a protective effect of low intake of animal foods toward thyroid autoimmunity and a positive influence of such nutritional patterns on redox balance and potentially on oxidative stress-related disorders.

Keywords: Hashimoto's thyroiditis, diet, oxidative stress, vegetarianism, thyroid autoimmunity, antioxidants, Mediterranean diet

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PHYSICAL ACTIVITY, HEALTH AND EXERCISE

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Physical activity, sports participation and exercise-related constraints in adult women with primary hypothyroidism treated with thyroid hormone replacement therapy

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ABSTRACT

Awareness of physical activity (PA) constraints in patients with primary hypothyroidism on thyroid hormone replacement therapy (THR) is important. Hence, this cross-sectional matched case-control study aimed to determine PA and sports participation (SP) in patients with hypothyroidism on THR in comparison to control subjects. Accordingly, survey questions were selected from the National Survey on Injuries and Physical Activity in the Netherlands (IPAN), supplemented with questions related to self-reported clinical characteristics and exercise-related constraints (ERC) of patients. In total, 1,724 female patients (mean age 53.0 years ±11.6) and 1,802 controls (mean age 52.6 ± 13.2) were included. Compared to controls, patients were less likely to comply with the moderate-intensity PA guideline (OR 0.70; 95% CI: 0.611–0.803), although patients were more actively participating in sports (OR 1.40; 95% CI: 1.156–1.706). Two-thirds of patients reported that hypothyroidism was limiting their PA performance. These limitations were more pronounced in patients with autoimmune thyroiditis (AIT) than in patients with hypothyroidism from other aetiology (OR 1.93; 95% CI: 1.518–2.457), representing disease-specific exercise intolerance. In order to establish effective intervention programmes to encourage regular PA in hypothyroid patients on THR with exercise intolerance, further research is warranted to better understand PA barriers.

ARTICLE HISTORY
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KEYWORDS
Autoimmune thyroiditis; comorbid conditions; exercise tolerance; Hashimoto disease; physical fitness

1. Introduction

Primary hypothyroidism is the second most common endocrine disease worldwide after diabetes mellitus and is caused by thyroid hormone deficiency. Hypothyroidism can be categorised based on its time of onset (congenital or acquired) and its severity, as in overt (clinical), subclinical, and mild diseases (Biondi & Wartofsky, 2014). The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the USA and between 0.2% and 5.3% in Europe (Åsvold et al., 2013; Aoki et al., 2007; Canaris et al., 2000; Garmendia Madariaga et al., 2014; Hollowell et al., 2002), depending on the definition used (Chaker et al., 2017). Hypothyroidism affects women 10 times more frequently than men, and its rate increases with age (Vanderpump, 2011). Hashimoto's thyroiditis, which is also referred to as autoimmune thyroiditis (AIT), is characterised by the presence of thyroid peroxidase antibody (TPO-Ab) in serum and is the most common cause of hypothyroidism (Caturegli et al., 2014; Chaker et al., 2017; Vanderpump, 2011). The standard treatment of hypothyroidism is thyroid hormone replacement therapy (THR) with levothyroxine (Chaker et al., 2017), which is one of the main prescribed drugs worldwide (Korevaar et al., 2018).

Hypothyroidism can have a considerable negative impact on the quality of life (McMillan et al., 2004), including persistent fatigue and exercise intolerance (Lankhaar et al., 2014; McAllister et al., 1995). In general, it is presumed that adequate THR in hypothyroidism will improve quality of life and reverse impairments of cardiovascular, respiratory, and muscle functions at rest and during exercise. However, approximately 10–15% of patients on THR with levothyroxine continue to experience impaired quality of life (Hennessey & Espaillat, 2018; Peterson et al., 2018; Watt et al., 2006; Wiersinga, 2019), including physical constraints and exercise intolerance (Lankhaar et al., 2014). Moreover, the mere presence of TPO-Ab in AIT patients has been linked to a decreased quality of life (Ott et al., 2011; Wiersinga, 2019). As a result, continual physical constraints can lead to a negative spiral of deconditioning, resulting in a further loss of functional capacity and the ability to perform physical activity (PA) and exercise (Verbunt et al., 2003).

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Hedwig Hofstetter has changed jobs, whereas Pierre M.J. Zelissen has retired.

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ORIGINAL RESEARCH
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Statin Use and Benefits of Thyroid Function: A Retrospective Cohort Study

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Purpose: Previous studies have suggested that cholesterol may influence thyroid function. Since statins are widely used for their cholesterol-lowering effect, we aimed to assess the association between statin use and thyroid function, and also to explore the role of the cholesterol-lowering effect in it.

Methods: We performed a retrospective cohort study derived from REACTION study. Eligible subjects receiving statin therapy were included in the statin group, and sex-, age-, total cholesterol (TC)-, and thyroid function-matched participants without lipid-lowering therapy were included in the control group. The median follow-up time was three years. Outcomes of thyroid function were evaluated at the end of follow-up. We used multivariable regression models to assess the association between statin use and outcomes of thyroid function, and also performed mediation analyses to explore the role of cholesterol in it.

Results: A total of 5,146 participants were screened, and 201 eligible subjects in the statin group and 201 well-matched subjects in the control group were analyzed. At the end of follow-up, TC and thyroid-stimulating hormone (TSH) levels in the statin group were lower than those in the control group (both $p < 0.05$), and the percentage of euthyroid subjects was higher in the statin group (88.06% vs. 76.12%, $p = 0.002$). The incidence rate of subclinical hypothyroidism (SCH) in euthyroid subjects was lower in the statin group (6.29% vs. 14.86%, $p = 0.009$), and the remission rate among subjects with SCH was higher in the statin group (50.00% vs. 15.38%, $p = 0.008$). In multivariable regression analyses, statin use was independently associated with lower TSH levels and higher odds to be euthyroid (OR 2.335, $p = 0.004$) at the end of follow-up. Mediation analyses showed the association between statin use and TSH levels were mediated by TC changes during follow-up.

Conclusion: Statin use was associated with benefits of thyroid function, and TC changes serve as a mediator of the association between statin use and TSH levels. Further studies are needed to clarify the possible underlying mechanism.

Keywords: statin, thyroid function, thyroid-stimulating hormone, total cholesterol, mediation analysis

INTRODUCTION

Hypothyroidism is a common pathological condition of thyroid hormone deficiency, including overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) (1). In China, the prevalence of SCH has significantly increased from 3.22% in 1999 to 16.7% in 2011 (2). The most frequent cause of SCH is Hashimoto's thyroiditis in iodine-sufficient areas (3). However, risk factors contributing to the increasing prevalence of SCH remain unclear.

In recent years, studies have revealed the emerging role of the disturbance of lipid metabolism in the development of hypothyroidism (4–9). Our previous prospective observational study found that high baseline total cholesterol (TC) level was a risk factor of progression to OH in patients with SCH (10), which suggested that cholesterol may influence thyroid function. It is known that SCH is associated with an increased risk of cardiovascular disease (11, 12), and cholesterol is a key element in the development of cardiovascular disease (13). If cholesterol-lowering therapy can benefit thyroid function, we can not only find a possible way to relieve the disease burden of SCH, but also provide additional evidence that cardiovascular mortality and morbidity can be reduced by the proper control of cholesterol levels.

Statins are widely used due to their ability to lower cholesterol in clinical practice. Besides, statins also have pleiotropic actions such as anti-inflammatory and immunomodulatory properties (14, 15). Only a few studies have investigated the effects of statins on thyroid function, and the results were inconsistent (16–18). A reason for these findings could be due to small sample sizes that were limited to hospital-based patients only. It still remains inconclusive whether statin use is associated with improved thyroid function in the general population. We believe that it is worth clarifying this relationship, as well as investigating whether this is mediated by the cholesterol-lowering function of statins.

In this population-based retrospective cohort study, we aimed to assess the association between statin use and thyroid function, as well as to explore the role of the cholesterol-lowering effect in it.

MATERIALS AND METHODS

Study Design and Participants

This study involves retrospective analyses of the population derived from the community-based REACTION study, which was a prospective observational cohort study in China investigating the epidemiology of metabolic diseases in residents aged 40 years or older (19). The study protocol was approved by the ethics committee of Shanghai Jiao Tong University, and all participants provided written informed consent before data collection.

In this study, data were obtained from participants who enrolled in REACTION study in Ningyang County, Shandong Province between April 2011 and July 2017. We included 5,146 participants who had more than one visit during the study period and assessed for eligibility. As our primary focus was the relationship between statin use and the outcome of thyroid function, we excluded subjects using the following exclusion criteria: (1) Missing vital data, such as age, sex, body mass index (BMI), or thyroid function; (2) self-report history of thyroid tumor, thyroidectomy, or radioactive iodine therapy; (3) intake of medications that influence thyroid function or serum lipids except statins (including thyroid hormone, antithyroid drugs, amiodarone, lithium, β-adrenergic blockers, fibrates, and steroid hormone) within the past 3 months; and (4) complications or conditions that affect thyroid status or lipid metabolism, such as pregnancy, lactation, severe liver dysfunctions (either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) higher than 100 U/L), renal dysfunction (creatinine higher than 105 μmol/L and an estimated glomerular filtration rate (eGFR) generated from simplified MDRD equation below 60 ml/min), or malignant tumor (4).

Participants who had statin therapy (including atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) during the follow-up period were defined as the statin group. Considering non-random treatment allocation and potential confounding covariates, we used baseline sex-, age-, TC-, and thyroid function-matched participants without lipid-lowering therapy as the control group (1:1 match). Ultimately, 201 participants in the statin group and 201 participants in the control group were included in the final analysis. The selection process is illustrated in **Figure 1**.

Data Collection

The data collection process has been described in the previous study (4). Briefly, all investigators went through a training program successfully to minimize instructor variability. Data collection was conducted at local health stations near the participants' residential area. Trained investigators obtained information on demographic characteristics, medical history (including statin use), and other essential information from a well-established questionnaire through a face-to-face interview. Weight and height were measured in kilograms and centimeters, respectively. BMI was calculated by

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Clinical Research Article

Clinical Research Article

Statins Decrease the Risk of Orbitopathy in Newly Diagnosed Patients with Graves Disease

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Abbreviations: ATC, Anatomical Therapeutic Chemical; GD, Graves disease; GO, Graves orbitopathy; HMG CoA, 3-Hydroxy-3-methylglutaryl-coenzyme; HR, hazard ratio; ICD, International Classification of Diseases; IGF-1R, insulin-like growth factor 1 receptor; IQR, interquartile range; LDL, low-density lipoprotein; TSHR, thyrotropin receptor.

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Abstract

Context/objective: The aim of this study was to examine the effect of statins and other lipid-lowering agents on the development of Graves orbitopathy (GO) in patients with newly diagnosed Graves disease (GD).

Methods: Our sample included the full adult population of individuals living in Sweden with newly diagnosed GD between 2005 and 2018 (n = 34 894). We compared the GO incidence in statin users (n = 5574) and nonusers (n = 34 409) by applying Cox regression with a time-varying exposure variable. We adjusted for age, sex, and treatment for hyperthyroidism in the multivariate analyses.

Results: Periods of nonusage lasted for a median of 4.3 years (interquartile range [IQR] 1.2-8.4), whereas periods of usage lasted for a median of 4.7 years (IQR 2.0-8.1). Among statin users, 77.1% had used simvastatin, 28.9% atorvastatin, and 8.2% had used other statins. Statin users were found to be significantly less likely to develop GO. In the main analysis based on the full cohort, the unadjusted hazard ratio (HR) was 0.74 (CI 0.65-0.84, $P < .001$), whereas full adjustment altered the effect to 0.87 (CI 0.76-1.00, $P = .04$). The main results were largely driven by men; the fully adjusted HR was 0.78 (CI 0.58-1.04, $P = .09$) for men and 0.91 (CI 0.79-1.06, $P = .24$) for women. Lipid-lowering agents other than statins did not exhibit a similar protective effect.

Conclusion: In newly diagnosed patients with GD, treatment with statins may protect against the development of GO. Statins should be investigated in a clinical trial as a preventive treatment for GO in newly diagnosed patients with GD.

Key Words: Graves disease, Graves orbitopathy, 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, statins

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Patient-Reported Outcomes Following Total Thyroidectomy for Graves' Disease

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Background: Graves' disease accounts for ~80% of all cases of hyperthyroidism and is associated with significant morbidity and decreased quality of life. Understanding the association of total thyroidectomy with patient-reported quality-of-life and thyroid-specific symptoms is critical to shared decision-making and high-quality care. We estimate the change in patient-reported outcomes (PROs) before and after surgery for patients with Graves' disease to inform the expectations of patients and their physicians.
Methods: PROs using the MD Anderson Symptom Inventory (MDASI) validated questionnaire were collected prospectively from adult patients with Graves' disease from January 1, 2015, to November 20, 2020, on a longitudinal basis. Survey responses were categorized as before surgery (≤120 days), short term after surgery (<30 days; ST), and long term after surgery (≥30 days; LT). Negative binomial regression was used to estimate the association of select covariates with PROs.
Results: Eighty-five patients with Graves' disease were included. The majority were female (83.5%); 47.1% were non-Hispanic white and 35.3% were non-Hispanic black. The median thyrotropin (TSH) value before surgery was 0.05, which increased to 0.82 in ST and 1.57 in LT. In bivariate analysis, the Total Symptom Burden Score, a composite of all patient-reported burden, significantly reduced shortly after surgery (before surgery mean of 56.88 vs. ST 39.60, $p < 0.001$), demonstrating improvement in PROs. Furthermore, both the Thyroid Symptoms Score, including patient-reported thermoregulation, palpitations, and dysphagia, and the Quality-of-Life Symptom Score improved in ST and LT (thyroid symptoms, before surgery 13.88 vs. ST 8.62 and LT 7.29; quality of life, before surgery 16.16 vs. ST 9.14 and LT 10.04, all $p < 0.05$). After multivariate adjustment, the patient-reported burden in the Thyroid Symptom Score and the Quality-of-Life Symptom Score exhibited reduction in ST (thyroid symptoms, rate ratio [RR] 0.55, confidence interval [CI]: 0.42–0.72; quality of life, RR 0.57, CI: 0.40–0.81) and LT (thyroid symptoms, RR 0.59, CI: 0.44–0.79; quality of Life, RR 0.43, CI: 0.28–0.65).
Conclusions: Quality of life and thyroid-specific symptoms of Graves' patients improved significantly from their baseline before surgery to both shortly after and longer after surgery. This work can be used to guide clinicians and patients with Graves' disease on the expected outcomes following total thyroidectomy.

Keywords: Graves' disease, patient-reported outcomes, quality of life, thyroidectomy

Introduction

GRAVES' DISEASE ACCOUNTS for nearly 80% of all cases of hyperthyroidism (1), and causes significant morbidity and decreased quality of life (2–4). Treatment options include medications, radioactive iodine ablation (RAI), and surgical management; the treatment choice is based on patient preference as well as the clinical presentation (2,3,5). Surveys indicate that RAI is the dominant treatment modality in the United States, accounting for more than half of the treatment, however, the use of antithyroid medication is increasing (6,7). Recent analysis showed that even though surgery is the most definitive treatment (99%), it is only used as first-line treatment for 6% of patients and subsequently in 9% of patients with first-line treatment failure, and 3% with second-line treatment failure (7,8). With the use of shared

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Pralsetinib for patients with advanced or metastatic *RET*-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study

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Summary

Background Oncogenic alterations in *RET* represent important therapeutic targets in thyroid cancer. We aimed to assess the safety and antitumour activity of pralsetinib, a highly potent, selective RET inhibitor, in patients with *RET*-altered thyroid cancers.

Methods ARROW, a phase 1/2, open-label study done in 13 countries across 71 sites in community and hospital settings, enrolled patients 18 years or older with *RET*-altered locally advanced or metastatic solid tumours, including *RET*-mutant medullary thyroid and *RET* fusion-positive thyroid cancers, and an Eastern Co-operative Oncology Group performance status of 0–2 (later limited to 0–1 in a protocol amendment). Phase 2 primary endpoints assessed for patients who received 400 mg once-daily oral pralsetinib until disease progression, intolerance, withdrawal of consent, or investigator decision, were overall response rate (Response Evaluation Criteria in Solid Tumours version 1.1; masked independent central review) and safety. Tumour response was assessed for patients with *RET*-mutant medullary thyroid cancer who had received previous cabozantinib or vandetanib, or both, or were ineligible for standard therapy and patients with previously treated *RET* fusion-positive thyroid cancer; safety was assessed for all patients with *RET*-altered thyroid cancer. This ongoing study is registered with clinicaltrials.gov, NCT03037385, and enrolment of patients with *RET* fusion-positive thyroid cancer was ongoing at the time of this interim analysis.

Findings Between Mar 17, 2017, and May 22, 2020, 122 patients with *RET*-mutant medullary and 20 with *RET* fusion–positive thyroid cancers were enrolled. Among patients with baseline measurable disease who received pralsetinib by July 11, 2019 (enrolment cutoff for efficacy analysis), overall response rates were 15 (71%) of 21 (95% CI 48–89) in patients with treatment-naive *RET*-mutant medullary thyroid cancer and 33 (60%) of 55 (95% CI 46–73) in patients who had previously received cabozantinib or vandetanib, or both, and eight (89%) of nine (95% CI 52–100) in patients with *RET* fusion-positive thyroid cancer (all responses confirmed for each group). Common (≥10%) grade 3 and above treatment-related adverse events among patients with *RET*-altered thyroid cancer enrolled by May 22, 2020, were hypertension (24 patients [17%] of 142), neutropenia (19 [13%]), lymphopenia (17 [12%]), and anaemia (14 [10%]). Serious treatment-related adverse events were reported in 21 patients (15%), the most frequent (≥2%) of which was pneumonitis (five patients [4%]). Five patients [4%] discontinued owing to treatment-related events. One (1%) patient died owing to a treatment-related adverse event.

Interpretation Pralsetinib is a new, well-tolerated, potent once-daily oral treatment option for patients with *RET*-altered thyroid cancer.

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Introduction

The incidence of thyroid cancer has increased over the past decade, with medullary thyroid cancer representing 1–5% of all thyroid cancer cases (75% sporadic and 25% hereditary) and papillary thyroid cancer accounting for 80–85% of all differentiated thyroid cancer.[1–3] Despite its low prevalence, medullary thyroid cancer accounts for almost 14% of all thyroid cancer-related deaths.[4] Activating alterations in the RET proto-oncogene (*RET*), which encodes a transmembrane receptor tyrosine kinase (proto-oncogene tyrosine-protein kinase receptor *RET*), are known oncogenic drivers in both medullary thyroid cancer and differentiated thyroid cancer, and represent a promising therapeutic target.[5,6] Medullary thyroid cancer originates from parafollicular C cells and can be hereditary, associated with two subtypes of multiple endocrine neoplasia syndrome type 2 (MEN2; MEN2A and MEN2B), or sporadic.[7] *RET* mutations occur in more than 95% of hereditary and approximately 50% of sporadic medullary thyroid cancer.[8] In the hereditary form, these include

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Article

Active Surveillance in *RET* Gene Carriers Belonging to Families with Multiple Endocrine Neoplasia

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Simple Summary: MEN2 has a very high penetrance for the development of medullary thyroid cancer. However, intra- and inter-familial variabilities have been described. Accordingly, in this precision medicine era, a personalized approach should be adopted in subjects harboring *RET* mutations. In these subjects, we showed that thyroid surgery could be safely timed according to basal and stimulated calcitonin, especially in children who can reach adulthood, avoiding the risks of thyroid surgery and decreasing the period of a long-life hypothyroidism treatment.

Abstract: Multiple Endocrine Neoplasia 2 (MEN2) is a hereditary cancer syndrome for developing medullary thyroid cancer (MTC) due to germline mutations of *RET* gene. Subjects harboring a germline *RET* mutation without any clinical signs of MTC are defined as gene carriers (GCs), for whom guidelines propose a prophylactic thyroid surgery. We evaluate if active surveillance of GCs, pursuing early thyroid surgery, can be safely proposed and if it allows safely delaying thyroid surgery in children until adolescence/adulthood. We prospectively followed 189 GCs with moderate or high risk germline *RET* mutation. Surgery was planned in case of: elevated basal calcitonin (bCT) and/or stimulated CT (sCT); surgery preference of subjects (or parents, if subject less than 18 years old); other reasons for thyroid surgery. Accordingly, at *RET* screening, we sub-grouped GCs in subjects who promptly were submitted to thyroid surgery (Group A, $n = 67$) and who were not (Group B, $n = 122$). Group B was further sub-grouped in subjects who were submitted to surgery during their active surveillance (Group B1, $n = 22$) and who are still in follow-up (Group B2, $n = 100$). Group A subjects presented significantly more advanced age, bCT and sCT compared to Group B. Mutation RET^{V804M} was the most common variant in both groups but it was significantly less frequent in Group A than B. Analyzing age, bCT, sCT and genetic landscape, Group B1 subjects differed from Group B2 only for sCT at last evaluation. Group A subjects presented more frequently MTC foci than Group B1. Moreover, Group A MTCs presented more aggressive features (size, T and N) than Group B1. Accordingly, at the end of follow-up, all Group B1 subjects presented clinical remission, while 6 and 12 Group A MTC patients had structural and biochemical persistent disease, respectively. Thank to active surveillance, only 13/63 subjects younger than 18 years at *RET* screening have been operated on during childhood and/or adolescence. In Group B1, three patients, while actively surveilled, had the possibility to reach the age of 18 (or older) and two patients the age of 15, before being submitted to thyroid surgery. In Group B2, 12 patients become older than 18 years and 17 older than 15 years. In conclusion, we demonstrated that an active surveillance pursuing an early thyroid surgery could be safely recommended in GCs. This patient-centered approach permits postponing thyroid surgery

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in children until their adolescence/adulthood. At the same time, we confirmed that genetic screening allows finding hidden MTC cases that otherwise would be diagnosed much later.

Keywords: medullary thyroid cancer; calcitonin; MEN2; gene carriers

1. Introduction

Multiple Endocrine Neoplasia 2 (MEN2) is an hereditary cancer syndrome characterized by the development of medullary thyroid cancer (MTC), variably associated with other endocrine neoplasia, such as pheochromocytoma and primary hyperparathyroidism [1–3]. MEN2 is an autosomal dominant disease with a very high penetrance due to missense gain-of-function mutation of the *RET* gene (Rearranged during Transfection) [4,5]. Germline *RET* mutation is present in about 99% of familial and about 6.0% of apparently sporadic cases of MTC [6]. Accordingly, germline *RET* screening must be offered to all patients with MTC and, if positive, all first-degree relatives should be screened [7,8]. Subjects harboring a germline *RET* mutation without any clinical signs of MTC are defined as Gene Carriers (GCs) [8].

In the case of a GC, guidelines propose a prophylactic thyroid surgery as "the removal of the thyroid before MTC develops or while it is clinically unapparent and confined to the gland" [8]. Its timing is essentially based on subject *RET* mutation and age; in cases of *RET* mutation at highest risk (*M918T*) surgical therapy must be performed within the first year, in cases at high risk (*C634F/G/R/S/W/Y* and *A883F*) the timing of thyroidectomy can be based on serum calcitonin (CT). However, in any case before 5 years and in cases at moderate risk (other mutations), basal and stimulated CT (bCT and sCT) should guide thyroid surgery timing [8]. This latter suggestion is not always followed in the real clinical world and several centers still follow the indication to operate immediately after the *RET* screening, warning against the use of serum CT in this clinical scenario [9].

By many years, in the case of GCs harboring high and moderate risk mutations, in our center we are performing an active surveillance by timing the thyroid surgery on bCT and sCT levels, regardless of *RET* mutation and age, pursuing an early, instead of a prophylactic, thyroid surgery [10]. The main reasons are related to both the higher risk of surgical complications in children, particularly permanent hypoparathyroidism that implies long-life therapy [11], and to the need of early medication with levothyroxine during childhood and adolescence in subjects who actually have normal thyroid function.

In this study, we evaluated if an active surveillance with an early thyroid surgery can be safely proposed in *RET* GCs and for how many years the surgery could be safely delayed in children. Moreover, we looked also at the relevance of genetic screening in finding hidden MTC cases that, otherwise, would be diagnosed much later.

2. Materials and Methods

2.1. Subjects

After 1993, we performed *RET* genetic screening in all patients with diagnosis of MTC, either familial or apparently sporadic and, if positive, to all their first-grade relatives [6].

All adult patients signed informed consent to perform *RET* genetic screening. Parents or guardians signed the informed consent in the case of subjects less than 18 years of age. As per the policy of the University Hospital, all patients provided written informed consent to both the genetic screening and the use of their clinical and biochemical data for scientific purposes.

2.2. Clinical Evaluation

We evaluated GCs by using clinical, biochemical (i.e., bCT and sCT (pentagastrin (Pg) stimulation test up to 2013, and then calcium (Ca) stimulation test, as elsewhere described [12]), urinary metanephrine and normetanephrine, serum PTH, calcium and

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Clinical Utility of Circulating Cell-Free DNA Mutations in Anaplastic Thyroid Carcinoma

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Background: Anaplastic thyroid carcinoma (ATC) is an aggressive thyroid cancer that requires a rapid diagnosis and treatment to achieve disease control. Gene mutation profiling of circulating cell-free DNA (cfDNA) in peripheral blood may help to facilitate early diagnosis and treatment selection. The relatively rapid turnaround time compared with conventional tumor mutation testing is a major advantage. The objectives of this study were to examine the concordance of ATC-related mutations detected in cfDNA with those detected in the corresponding tumor tissue, and to determine the prognostic significance of cfDNA mutations in ATC patients.
Methods: The ATC patients who were diagnosed and treated at The University of Texas MD Anderson Cancer Center between January 2015 and February 2018 and who had cfDNA testing were included in this study. cfDNA was collected by blood draw and was analyzed by next-generation sequencing (NGS) using the Guardant360-73 gene platform.
Results: A total of 87 patients were included in the study. The most frequently mutated genes detected in cfDNA were *TP53, BRAF*, and *PIK3CA*. In 28 treatment naive ATC patients, the concordance rate of detected mutations in *TP53, BRAF*^{V600E}, and *PIK3CA* between cfDNA and matched tissue NGS was 82.1%, 92.9%, and 92.9%, respectively. Patients with a *PIK3CA* mutation detected on cfDNA had worse overall survival (OS) ($p = 0.03$). This association was observed across various treatment modalities, including surgery, cytotoxic chemotherapy, radiation, and BRAF inhibitor (BRAFi) therapy. With regard to treatment, BRAFi therapy significantly improved ATC OS ($p = 0.003$).
Conclusions: cfDNA is a valuable tool to evaluate a tumor's molecular profile in ATC patients. We identified high concordance rates between the gene mutations identified via cfDNA analysis and those identified from the NGS of the corresponding tumor tissue sequencing. Identified mutations in cfDNA can potentially provide timely information to guide treatment selection and evaluate the prognosis in patients with ATC.

Keywords: anaplastic thyroid carcinoma, BRAF inhibitor, cell free DNA, PIK3CA, prognosis

Introduction

Anaplastic thyroid carcinoma (ATC) is rare but is one of the most aggressive solid tumors in humans. The ATC accounts for 1–2% of all thyroid cancers (1). The historical median overall survival after diagnosis is 3–6 months and only 10–15% ATC patients have a survival of 2 years after presentation. The disease-specific mortality rate approaches 100% (1).

The clinical course of ATC is characterized by rapid and invasive local tumor growth, frequent distant metastases, and fatal outcomes. Therefore, ATC requires rapid diagnosis and prompt treatment. Targeted therapy, such as BRAF inhibitor (BRAFi) treatment for patients with *BRAF*^{V600E} mutated ATC, shows promising results in ATC treatment (2) and the U.S. Food and Drug Administration (FDA) has approved the BRAF/MEK inhibitor combination dabrafenib/trametinib for ATC patients with *BRAF*^{V600E} mutated tumors. Understanding ATC genetic features and their clinical significance has become essential for ATC management.

Liquid biopsies to detect circulating cell-free DNA (cfDNA) for cancer genotyping have been increasingly used in clinical practice as reliable and minimal invasive methods for many solid tumors, including lung cancer and gastric cancer (3). Compared with the molecular testing performed on tissue biopsies, cfDNA-based analysis has several

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Metformin Reduces Thyroid Cancer Tumor Growth in the Metastatic Niche of Bone by Inhibiting Osteoblastic RANKL Productions

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Background: Metformin has antitumoral actions in human cancers, including the thyroid, while its effects on metastatic lesions are unclear. Patients with bone metastasis (BM) from thyroid cancers have poor survival. Because metformin inhibits the activation of osteoclasts, which has essential roles in BM, the aim of this study was to investigate the therapeutic effects of metformin on thyroid cancer BM and osteoclast activation in the bone microenvironment.
Methods: The anaplastic thyroid cancer (ATC) cell lines FRO and SW1736 were used to test the antitumoral effect of metformin *in vitro* and *in vivo*. A murine model of BM was established by intratibial injection of cancer cells. To mimic the BM microenvironment, osteoblasts were treated with conditioned media from the FRO (FRO-CM) and SW1736 (SW1736-CM) cells. Thyroid cancer patients with or without BM were recruited, and the serum receptor activator of nuclear factor kappa-B ligand (RANKL) levels was measured.
Results: Metformin treatment significantly reduced the viabilities of the FRO and SW1736 cells *in vitro* and the tumor growth of SW1736 *in vivo*. In the murine model of BM, metformin delayed tumor growth in the bone and decreased the numbers of tartrate-resistant acid phosphatase-positive osteoclasts on the bone surface with reduced RANKL in the bone marrow. Furthermore, FRO- or SW1736-CM significantly increased the osteoblastic RANKL productions and activated osteoclast differentiation in whole marrow cultures, which were blocked by metformin treatment. Among 67 thyroid cancer patients, the serum RANKL levels were significantly increased in BM patients compared with patients with lung-only metastasis or no distant metastasis. In addition, the interleukin-6 superfamily in the FRO- or SW1736-CM stimulated STAT3 phosphorylation, which was inhibited by gp130 blocking. Metformin treatment decreased the FRO- or SW1736-CM-induced STAT3 phosphorylation by AMPK phosphorylation. Metformin also inhibited the FRO- or SW1736-CM-induced osteoclastic differentiation of bone marrow-derived monocyte/macrophage by RANK/c-Fos/NFATC1 signaling.
Conclusions: In the microenvironment of BM, metformin effectively reduced ATC tumor growth by inhibiting cancer cell viability, blocking cancer cell-induced osteoblastic RANKL production, which further activated osteoclastogenesis, and directly reduced osteoclast differentiation. These multifactorial actions of metformin suggest that it has potential therapeutic effects in thyroid cancer BM.

Keywords: metformin, bone metastasis, thyroid cancer, osteoblast, osteoclast, OPG/RANKL

Introduction

THYROID CANCER IS the most common endocrine malignancy and its incidence has increased rapidly in the past three decades. Although differentiated thyroid cancer (DTC) has a good prognosis with 80–95% 10-year survival rates, 1–7% of papillary thyroid cancer (PTC) and 7–20% of follicular thyroid cancer (FTC) patients have bone metastasis, which is associated with a worse prognosis (1). The overall 10-year survival rate for patients with DTC bone metastasis is 0–34% (2–9). The mean survival for those patients is estimated to be about four years (6,10). Furthermore, anaplastic thyroid cancer (ATC), which accounts for 1% of all thyroid cancers, commonly has features of marked invasiveness with an extremely poor survival (11–13), and ~5–15% of ATC patients have distant metastasis in the bone (14).

Radioactive iodine therapy is the standard treatment of choice for iodine-avid tumors for DTC bone metastasis

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Influence of endocrine multidisciplinary tumor board on patient management and treatment decision making

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ABSTRACT

Background: Multidisciplinary Tumor Boards (MDT) are used to obtain input regarding cancer management. This study assessed the impact of our institutional Endocrine MDT.
Methods: MDT notes on patients with thyroid cancer treated during 2012–2018 were abstracted retrospectively from the electronic medical record. Management change (MC) was prospectively collected by the MDT coordinator. Biannual evaluations reviewed the impact of the MDT as observed by attendees.
Results: MC was recommended in 47 (15%) of 286 presentations, with additional imaging being the most frequent (43%). Presentation of recurrences were more likely to result in MC (24% vs. 13% initial, $p = 0.03$). Overall, 98% of attendees found the conference exceeded educational expectations. About 24% reported intending to use a more evidence/guideline-based approach after attending and this trend increased over time ($p = 0.002$).
Conclusion: MDT presentations led to a higher rate of MC particularly in recurrent TC patients and increased evidenced-based practice for attendees.

Introduction

Multidisciplinary Tumor Boards (MDT) are frequently used forums for presenting patients with various cancers for input regarding management. The idea of an MDT to discuss the care of cancer patients was first developed in 1975 and has expanded significantly since that time.[1] A MDT generally consists of several health care specialists including surgeons, oncologists, radiologists, pathologists, nursing providers as well as other specialized support staff such as nutritionists and genetic counsellors who meet with the intent of discussing and coordinating the care of cancer patients.[2] MDT have been shown to result in changes in management as well as improved patient and clinician satisfaction, and may also improve survival.[2]

Cancer care is complex and varies widely based on cancer type. Additionally, advances are continually made, and guidelines are adjusted to reflect these new developments. The utility of MDT has been shown recently in a variety of different cancer types, including pancreatic cancer, colorectal cancer, gynecological tumors, lung cancer, head and neck squamous cell cancers, and breast cancer.[3–9] MDT have been shown to identify and improve specific quality markers based on the type of cancer discussed. As an example, Quero et al. identified that MDT resulted in a change in the resectability status of 29.7% of pancreatic cancers discussed.[10] For rectal cancer patients, Richardson et al. identified that MDT improved the completeness of total mesorectal excision.[11] In patients with breast cancer, MDT have been shown to result in avoidance of immediate surgery, alteration of the type of surgery performed and may also result in the identification of new suspicious breast lesions.[9]

Thyroid cancer is the 12th most common cancer in the United States, with approximately 50,000 new cases diagnosed each year,

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Real-World Performance of the American Thyroid Association Risk Estimates in Predicting 1-Year Differentiated Thyroid Cancer Outcomes: A Prospective Multicenter Study of 2000 Patients

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National Survey of Endocrinologists and Surgeons Regarding Active Surveillance for Low-Risk Papillary Thyroid Cancer

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Abstract

Objective: Active surveillance for low-risk papillary thyroid cancer (PTC) was endorsed by the American Thyroid Association guidelines in 2015. The attitudes and beliefs of physicians treating thyroid cancer regarding the active surveillance approach are not known.

Methods: A national survey of endocrinologists and surgeons treating thyroid cancer was conducted from August to September 2017 via professional society emails. This mixed-methods analysis reported attitudes toward potential factors impacting decision-making regarding active surveillance, beliefs about barriers and facilitators of its use, and reasons why physicians would pick a given management strategy for themselves if they were diagnosed with a low-risk PTC. Survey items about attitudes and beliefs were derived from the Cabana model of barriers to guideline adherence and theoretical domains framework of behavior change.

Results: Among 345 respondents, 324 (94%) agreed that active surveillance was appropriate for at least some patients, 81% agreed that active surveillance was at least somewhat underused, and 76% said that they would choose surgery for themselves if diagnosed with a PTC of ≤1 cm. Majority of the respondents believed that the guidelines supporting active surveillance were too vague and that the current supporting evidence was too weak. Malpractice and financial concerns were identified as additional barriers to offering active surveillance. The respondents endorsed

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improved information resources and evidence as possible facilitators to offering active surveillance.

Conclusion: Although there is general support among physicians who treat low-risk PTC for the active surveillance approach, there is reluctance to offer it because of the lack of robust evidence, guidelines, and protocols.

Keywords

thyroid cancer; microcarcinoma; active surveillance; low-risk; survey; papillary

Introduction

In 2015, the American Thyroid Association (ATA), for the first time, endorsed active surveillance as a management option for select patients with low-risk papillary thyroid cancer (PTC), including papillary microcarcinoma (≤1 cm).[1] The data supporting active surveillance at that time included 2 cohort studies of patients from Japan with a biopsy-proven PTC of ≤1 cm in size, which collectively showed no deaths among more than 1200 patients managed with active surveillance, some of whom were followed up for more than 10 years.[2–8] In these case series, 7% to 8% of cancers grew over time, eventually requiring surgery. Since the publication of the ATA guidelines, additional data from the first North American cohort of patients managed with active surveillance has been published, this time including patients with tumors of up to 1.5 cm in size.[9] These data again showed no deaths among 291 patients followed up for a median of 25 months (range: 6–166), with 11 of 291 (3.8%) showing growth of tumors >3 mm and 36 (12.7%) showing growth of tumors >50% in volume. Collectively, data from Italy, Japan, and North America have shown that younger patients' tumors are more likely to grow and that the rate of cancer spread to lymph nodes during active surveillance is between 0% and 3.8%.[10]

Despite the endorsement of active surveillance in the respected guidelines, much remains unknown about active surveillance for low-risk PTC. The published cohorts have been from single institutions, and there have been no trials, randomized or otherwise, directly comparing patients managed with active surveillance versus those managed with surgery. Because the protocols, guidelines, and outcome data regarding active surveillance are not yet mature, physicians who manage patients with low-risk PTC in the current era face uncertainty about the best practices. Physicians' attitudes and beliefs regarding active surveillance have not been studied. Their attitudes and beliefs are likely to be important in elucidating both how patients diagnosed with low-risk PTC are managed today and the trajectory of future efforts to study and advance the practice of active surveillance.

We performed a national survey of surgeons and endocrinologists who manage patients with thyroid cancer to understand the current landscape of physicians' beliefs during the early years since the introduction of the active surveillance approach. This analysis reports data on physicians' attitudes and beliefs regarding active surveillance, barriers and facilitators to increasing its use, and a qualitative analysis of physicians' beliefs related to why they would choose various management strategies for themselves if diagnosed with low-risk PTC.

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Thyrotropin Suppression for Papillary Thyroid Cancer: A Physician Survey Study

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Background: Current guidelines recommend against thyrotropin (TSH) suppression in low-risk differentiated thyroid cancer patients; however, physician practices remain underexplored. Our objective was to understand treating physicians' approach to TSH suppression in patients with papillary thyroid cancer.
Methods: Endocrinologists and surgeons identified by thyroid cancer patients from the Surveillance, Epidemiology, and End Results registries of Georgia and Los Angeles were surveyed in 2018–2019. Physicians were asked to report how likely they were to recommend TSH suppression (i.e., TSH <0.5 mIU/L) in three clinical scenarios: patients with intermediate-risk, low-risk, and very low-risk papillary thyroid cancer. Responses were measured on a 4-point Likert scale (extremely unlikely to extremely likely). Multivariable logistic regressions were performed to determine physician characteristics associated with recommending TSH suppression in each of the aforementioned scenarios.
Results: Response rate was 69% (448/654). Overall, 80.4% of physicians were likely/extremely likely to recommend TSH suppression for a patient with an intermediate-risk papillary thyroid cancer, 48.8% for a patient with low-risk papillary thyroid cancer, and 29.7% for a patient with very low-risk papillary thyroid cancer. Surgeons were less likely to recommend TSH suppression for an intermediate-risk papillary thyroid cancer patient (odds ratio [OR] = 0.36 [95% confidence interval, CI, 0.19–0.69]) compared with endocrinologists. Physicians with higher thyroid cancer patient volume were less likely to suppress TSH in low-risk and very low-risk papillary thyroid cancer patients (i.e., >40 patients per year, OR = 0.53 [CI 0.30–0.96]; OR = 0.49 [CI 0.24–0.99], respectively, compared with 0–20 patients per year). Physicians who estimated higher likelihood of recurrence were more likely to suppress TSH in a patient with very low-risk papillary thyroid cancer (OR = 2.34 [CI 1.91–4.59]).
Conclusions: Many patients with low-risk thyroid cancer continue to be treated with suppressive doses of thyroid hormone, emphasizing the need for more high-quality research to guide thyroid cancer management, as well as better understanding of barriers that hinder guideline adoption.

Keywords: physician survey, thyroid cancer, TSH suppression

Introduction

PAPILLARY THYROID CANCER is the most common and least aggressive type of thyroid malignancy, accounting for ∼90% of differentiated thyroid cancers (DTC) (1). Owing to the widespread use of ultrasonography and fine-needle aspiration biopsy of incidentally detected thyroid nodules in recent years, the most commonly occurring papillary thyroid cancers in the United States are low-risk papillary thyroid cancers and very low-risk papillary thyroid microcarcinomas (2–6), with risk denoting the risk of cancer recurrence after initial treatment as outlined in the 2015 American Thyroid Association (ATA) guidelines (7). Specifically, very low-risk and low-risk papillary thyroid cancers carry a ≤5% risk of recurrence, while intermediate-risk papillary thyroid cancers carry a recurrence risk of ∼5% to 30% (7).

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Effects of thyroxine on apoptosis and proliferation of mammary tumors

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Highlights

- Thyroxine treatment reverted the cancer-protective effects of hypothyroidism.
- •Proliferative and antiapoptosis mechanisms of T4 varied regarding the thyroid status.
- •The cross-talk with other hormone receptors was critical in EUT tumors.
- •The non-genomic pathway of T4 was the main mechanism involved in HypoT tumors.
- •Overdoses of T4 can increase breast cancer risk.

Abstract

Hypothyroidism is a protective factor against breast cancer but long-term exposure or overdoses of thyroid replacement therapy with thyroxine (T_4) may increase breast cancer risk. Objective: to study, *in vivo* and *in vitro*, the effects of T4 on the proliferation and apoptosis of mammary tumors of hypo- and euthyroid rats, and the possible mechanisms involved in these effects. Material and Methods: Female Sprague-Dawley rats were treated with a single dose of dimethylbenzathracene (15 mg/rat) at 55 days of age and were divided into three groups: hypothyroidism (HypoT; 0.01% 6-N-propyl-2-thiouracil -PTU- in drinking water, n = 20), hypothyroidism treated with T_4 (HypoT + T_4; 0.01% PTU in drinking water and 0.25 mg/kg/day T_4 via sc; n = 20) and EUT (untreated control, n = 20). At sacrifice, tumor explants from HypoT and EUT rats were obtained and treated either with 10^{-10} M T_4 in DMEM/F12 without phenol red with 1% Charcoalized Fetal Bovine Serum or DMEM/F12 only for 15 min to evaluate intracellular signaling pathways associated with T_4, and 24 h to evaluate changes in the expression of hormone receptors and proteins related to apoptosis and proliferation by immunohistochemistry and Western Blot. Results: *In vivo*, hypothyroidism retards mammary carcinogenesis but its treatment with T_4 reverted the protective effects. *In vitro*, the proliferative and anti-apoptosis mechanisms of T_4 were different regarding the thyroid status. In EUT tumors, the main signaling pathway involved was the cross-talk with other receptors, such as ERα, PgR, and HER2. In HypoT tumors, the non-genomic signaling pathway of T_4 was the chief mechanism involved since αvβ3 integrin, HER2, β-catenin and, downstream, PI3K/AKT and ERK signaling pathways were activated. Conclusion: T_4 can regulate mammary carcinogenesis by mainly activating its non-genomic signaling pathway and by interacting with other hormone or growth factor pathways endorsing that overdoses of thyroid replacement therapy with T4 can increase the risk of breast cancer.

Keywords

Thyroxine; TRβ1; αvβ3 integrin; HER2; β-catenin; Breast cancer

[1] These two authors equally contributed to the study.

ΓΟΝΙΔΙΑΚΗ ΘΕΡΑΠΕΙΑ: ΠΑΡΟΝ - ΜΕΛΛΟΝ

ΚΩΣΤΑΣ ΣΤΡΑΤΑΚΗΣ

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What is gene therapy?

1. A normal gene inserted to compensate for a non-functional gene
2. An abnormal gene replaced by a normal gene
3. An abnormal gene repaired through selective repair
4. Simply, change the regulation of expression of a gene

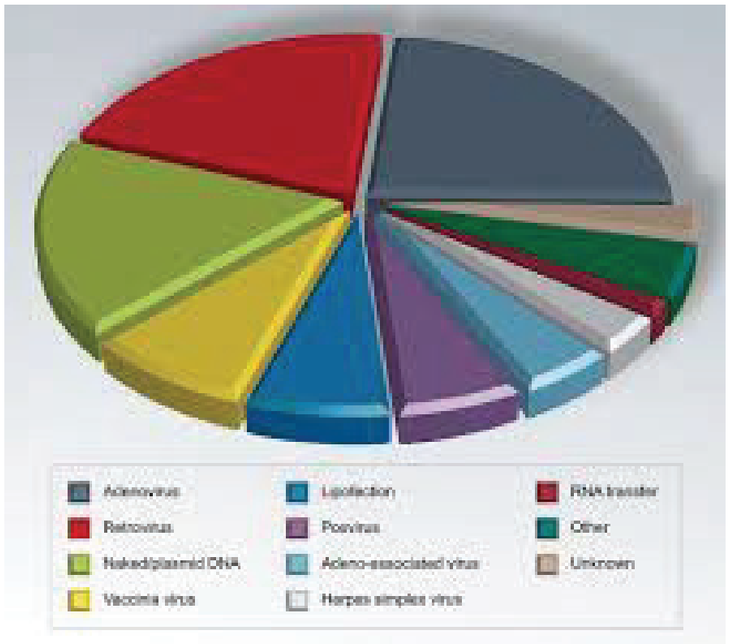
What is needed for successful gene therapy?

1. To know exactly what the molecular defect is
2. A molecule that will fix somehow the defect (by inserting itself, or blocking the defective one etc)
3. A way to deliver the molecule to the patient cells

• Several viral vectors and non-viral gene delivery methods have been developed and found their applications in gene therapy.

• There are mainly five viral vectors: Adenovirus (AV), Adeno-Associated Virus (AAV), Lentivirus (LV), Retrovirus (RV), and Herpes Viruses (HSV).

• Non-viral gene delivery methods could be liposomes, polymers or dendrimers, and even cell-penetrating methods



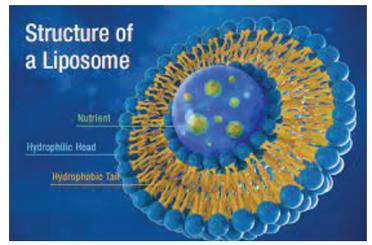
VIRAL VECTORS

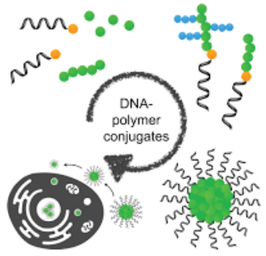
1. DNA-polymer conjugates
2. Naked DNA

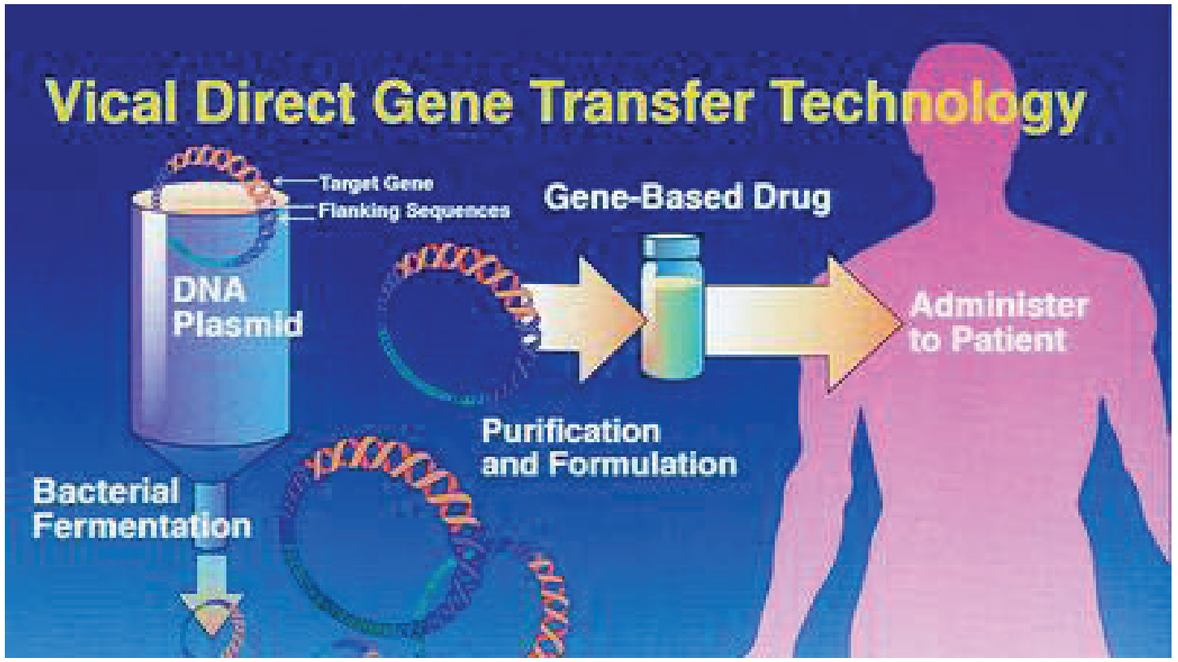
Vector class	Efficacy	Safety	Expression	Approaches	Injection
Nonviral vectors	Low	High	Brief	Ex vivo	Unsuitable
Viral vectors					
Adenoviral vectors	Very high	Low	Brief	In vivo	Adapted
HSV-based vectors	High	Low	Brief	In vivo	Adapted
Retro–/lentiviral vectors	Low	Low	Prolonged	Ex vivo	Unsuitable
rAAV vectors	Very high	High	Prolonged	In vivo	Adapted

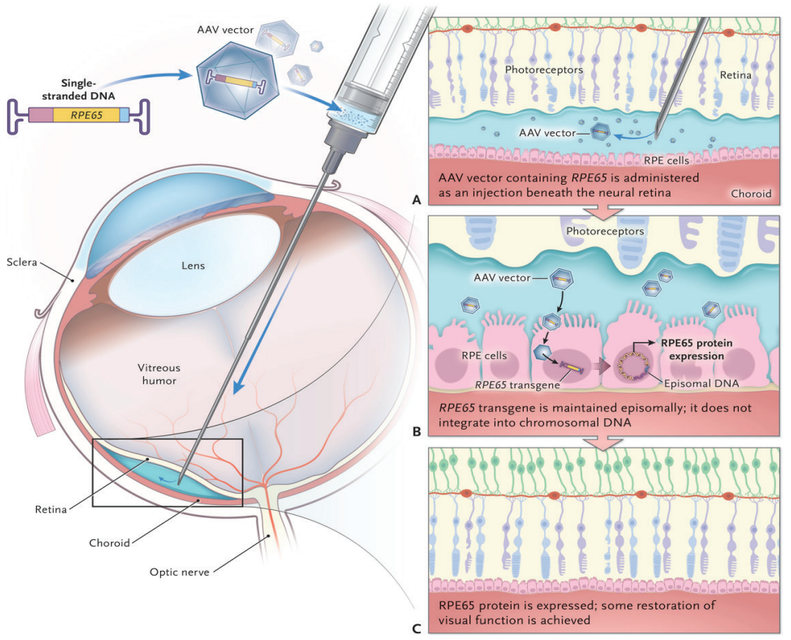
NON-VIRAL WAYS OF DELIVERY

1. Liposomes
2. DNA-polymer conjugates
3. Naked DNA



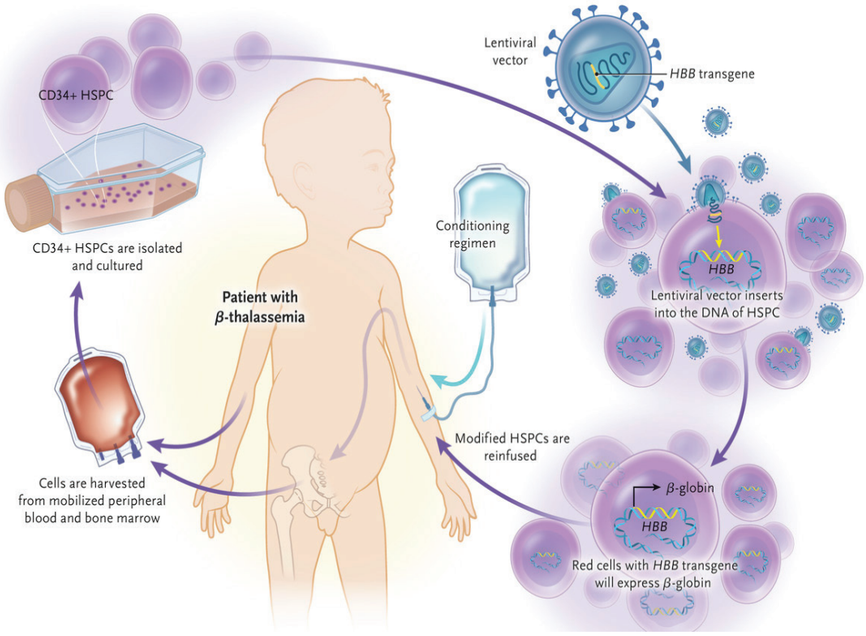






In Vivo Delivery of Gene Therapy.

KA High, MG Roncarolo. N Engl J Med 2019;381:455



Ex Vivo Delivery of Gene Therapy.

KA High, MG Roncarolo. N Engl J Med 2019;381:455

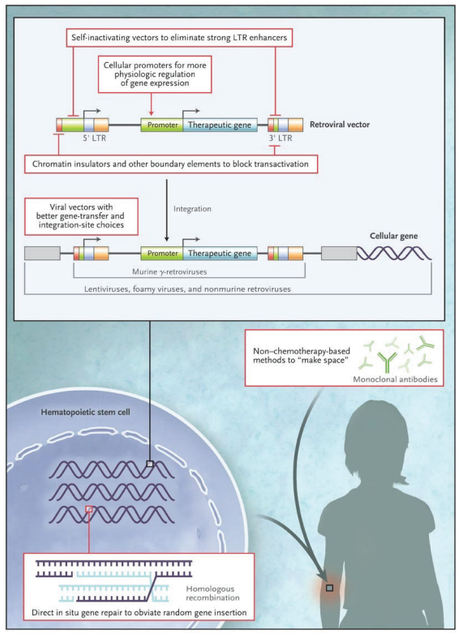
Potential and Observed Complications of Gene Therapy

Table 1. Potential and Observed Complications of Gene Therapy.*

Complication	Clinical Presentation	Vector	Evidence
Gene silencing	Gradual loss of gene expression without evidence of immune response	—	Theoretical; not reliably described clinically
Genotoxicity: integration events and insertional mutagenesis	Development of leukemia or solid tumors	Retroviral	Documented in studies of gene therapy for X-linked SCID,[1,2] Wiskott–Aldrich syndrome,[3] and chronic granulomatous disease[4]
Phenotoxicity: overexpression or ectopic or dysregulated expression of the transgene	Dependent on transgene, tissue in which transgene is expressed, or both	—	Theoretical
Immunotoxicity	Dependent on tissue transduced — for example, elevated aminotransferase levels when liver is transduced or elevated creatine kinase levels when muscle is transduced	More likely with AAV (in vivo delivery)	Documented in experiments involving muscle[5] and trials of treatment for hemophilia,[6,7] spinal muscular atrophy,[8] Leber's hereditary optic neuropathy,[9] and retinal dystrophy caused by mutations in *RPE65*[10]
Horizontal transmission	Household contacts seropositive	AAV	Not documented; vector not infectious after 72 hr[11]
Vertical transmission	Offspring positive for vector transgene	More likely with AAV (in vivo delivery)	No documented cases; vector has been detected in semen transiently[7,12,13]

* AAV denotes adeno-associated virus, and SCID severe combined immunodeficiency.

KA High, MG Roncarolo. N Engl J Med 2019;381:455



In 2020, Lu et al. delivered the first clustered regularly interspaced short palindromic repeats (CRISPR)-edited T cell therapy for patients with refractory non-small-cell lung cancer. This is a milestone that marks an upgrade to the next generation of gene therapy. Gene therapy is an emerging experimental treatment that delivers functional genes into the human body and may be applicable to a wide range of diseases, with the first approved human gene therapy trial conducted by Rosenberg et al. in 1989, using retroviral vectors to deliver the gene coding for resistance to neomycin to patients with advanced melanoma (Rosenberg et al., 1990).

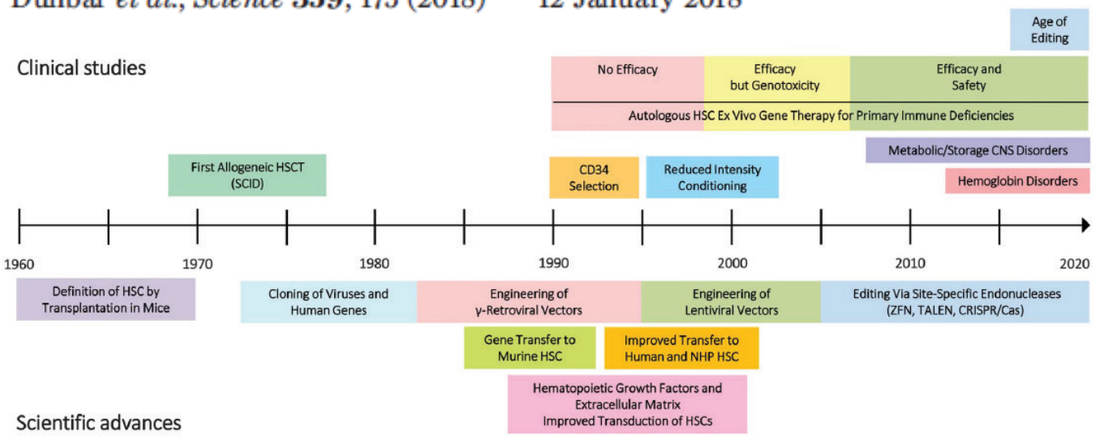
Gene therapies faced severe setbacks in 1990–2002, but the resurgent interest in offering gene therapy-based treatments from 2015 is one of the most defining pharmaceutical industry developments.

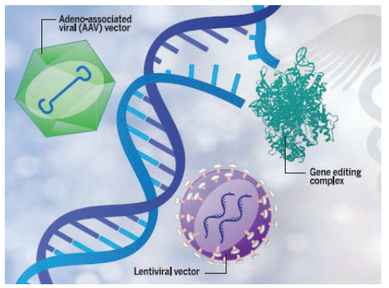
It is expected to have far-reaching implications on curing dangerous diseases in the future and benefit both clinical trials and the pharmaceutical industry immensely.

Gene therapy comes of age

Cynthia E. Dunbar,* Katherine A. High, J. Keith Joung, Donald B. Kohn, Keiya Ozawa, Michel Sadelain*

Dunbar *et al.*, *Science* **359**, 175 (2018) 12 January 2018





Gene therapy comes of age

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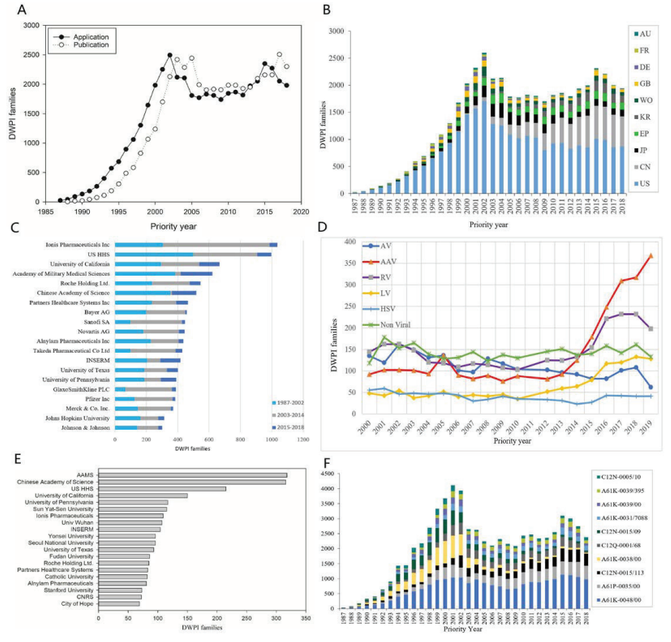
Dunbar *et al.*, *Science* **359**, 175 (2018) 12 January 2018

Table 1. Clinical and product development landmarks for ex vivo gene therapies.

Cell type	Disease	Vector/transgene	Key publication(s) or clinicaltrials.gov no.	Primary institution and/or company	Breakthrough designation or product approval
T cells	Adult ALL*	γRV CD19 (CD28) CAR-T	(*134*,*143*,*144*)	Memorial Sloan Kettering Cancer Center	FDA 2016
	Pediatric ALL	LV CD19 (4-1BB) CAR-T	(*145*)	University of Pennsylvania/Novartis	FDA Oncology Advisory Committee recommended approval 2017; EMA 2016
		γRV CD19 (CD28) CAR-T	(*146*)	National Cancer Institute/Kite	
		LV CD19 CAR-T, TALEN knockout of TCR and CD52	(*74*) NCT02808442	Cellectis/Servier/Pfizer	
	Diffuse large B cell lymphoma	γRV CD19 (CD28) CAR-T	(*147*) NCT00924326	National Cancer Institute/Kite	FDA 2014
		γRV CD19 (CD28) CAR	NCT02348216	Multiple academic sites/Kite	FDA 2015; EMA 2016
		LV CD19 (4-1BB) CAR-T	(*148*) NCT02631044	Multiple academic sites/Juno	FDA 2016; EMA 2016
		LV CD19 (4-1BB) CAR-T	NCT02445248	Multiple academic sites/Novartis	FDA 2017
	CLL/indolent lymphoma	LV CD19 (4-1BB) CAR-T	(*149*)	University of Pennsylvania/Novartis	
		γRV CD19 (CD28) CAR-T	(*150*)	National Cancer Institute	
	Multiple myeloma	γRV BCMA (CD28) CAR-T	(*136*) NCT02215967	National Cancer Institute/Kite	
		γRV BCMA (4-1BB) CAR T	NCT03070327	Memorial Sloan Kettering Cancer Center/Juno	
		LV-BCMA CAR-T	NCT03090659	Nanjing Legend Biotech	
	Synovial sarcoma	γRV-NY-ESO-TCR	(*151*)	National Cancer Institute	
		LV-NY-ESO-TCR	NCT03096659	Multiple academic sites/Adaptimmune	FDA 2016; EMA 2016
	Human immunodeficiency virus	ZFN CCR5 electroporation	(*73*)	University of Pennsylvania/Sangamo	
HSPCs	β-Thalassemia	LV anti-sickling β-hemoglobin	(*120*) NCT01745120 NCT02151526 NCT03207009	Hopitaux de Paris/academic centers worldwide/Bluebird Bio	FDA 2015; EMA 2016
		LV β-hemoglobin	NCT02453477	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	
		LV β-hemoglobin	NCT01639690	Memorial Sloan Kettering Cancer Center	
	Sickle cell anemia	LV anti-sickling β-hemoglobin	(*121*) NCT02151526, NCT02140554	Hopitaux de Paris/US academic sites/Bluebird Bio	
		LV anti-sickling β-hemoglobin	NCT02247843	UCLA/California Institute of Regenerative Medicine	
	Wiskott-Aldrich syndrome	LV WAS	(*114*)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	
		LV WAS	(*152*)	Hopital Necker-Enfants/ University College/Genethon	
	Adenosine deaminase deficiency	γRV ADA	(*116*)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	EMA 2016 approved "Strimvelis"
		LV ADA	NCT02999984	University College/UCLA/ Orchard Therapeutics	FDA 2015
	IL2Rγ-deficient X-SCID	γRV SIN IL2Rγ	(*115*)	Hopital Necker-Enfants/Great Ormond Street	
		LV IL2Rγ	(*153*)	National Institute of Allergy and Infectious Diseases	
	Adrenoleukodystrophy	LV ABCD1	(*118*)	St. Vincent de Paul, Paris	
		LV ABCD1	(*119*)	Multiple academic sites/Bluebird Bio	
	Metachromatic leukodystrophy	LV ARSA	(*117*,*154*)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	EU Orphan Drug 2007
	Human Immunodeficiency virus	ZFN CCR5 electroporation	NCT02500849	City of Hope/Sangamo	

*Abbreviations: FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; γRV, murine γ-retrovirus; LV, lentivirus; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; HSPC, hematopoietic stem and progenitor cells; X-SCID, X-linked severe combined immunodeficiency; ZFN, zinc finger nuclease; BCMA, B cell maturation antigen; ARSA, arylsulfatase A; ABCD1, transporter gene mutated in adrenoleukodystrophy.

Patents in gene therapy

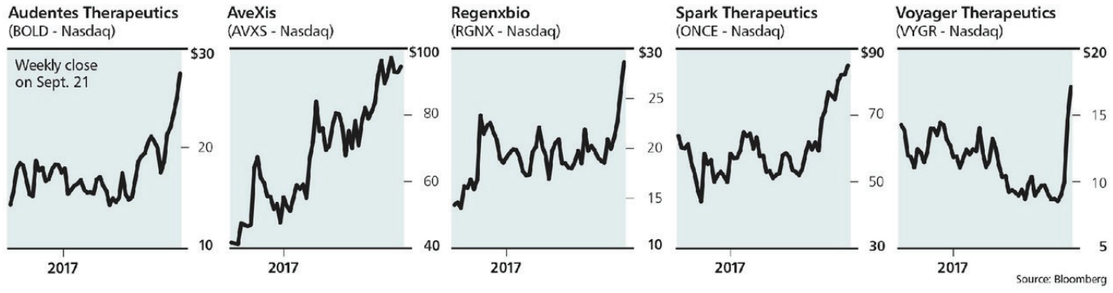


GENE THERAPY PLAYS...

These five companies are developing replacement gene therapy for different hereditary diseases. The stocks have moved up sharply this year, but could add to gains if treatments get approval from the Food and Drug Administration. Any unexpected setbacks, however, could hurt the shares.

Company / Ticker	Recent Price	YTD Change	Market Value (mil)	2017E EPS	Cash and Equivalents* (mil)	Current or Completed Phase of Clinical Trials	1st Potential Year of Profit	Diseases Targeted
Audentes Therapeutics / BOLD	$27.41	50%	$762	–$3.51	$145	Phase 1/2	N.A.	X-linked myotubular myopathy, Crigler-Najjar syndrome
AveXis / AVXS	96.14	101	3,069	–6.04	418	Phase 3	2020	Spinal muscular atrophy
Regenxbio / RGNX	29.40	58	910	–3.08	209	Phase 1/2	2022	Age-related macular degeneration, HoFH, MPS 1
Spark Therapeutics / ONCE	87.10	75	3,120	–7.37	239	Phase 3	2019	RPE-65 mediated retinal disease, Hemophilia A & B
Voyager Therapeutics / VYGR	17.72	39	477	–2.84	141	Phase 1/2	2023	Parkinson's disease

E=Estimate. *As of 6/30/17. Subsequently, Spark raised an additional $380 million. N.A.=Not available. Sources: Chardan; Bloomberg



Epigenetic Therapies for Cancer

Susan E. Bates, M.D.

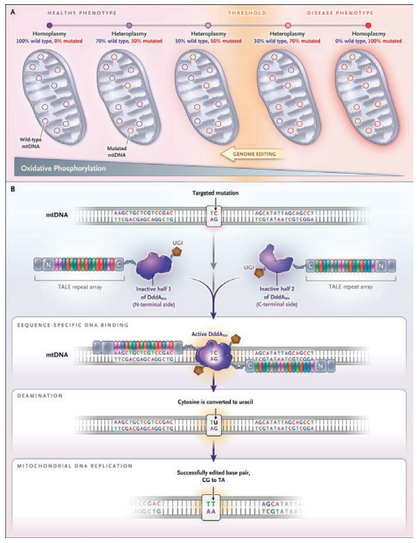
From the Department of Medicine, Division of Hematology/Oncology, Columbia University Irving Medical Center and James J. Peters Veterans Affairs Medical Center, New York.

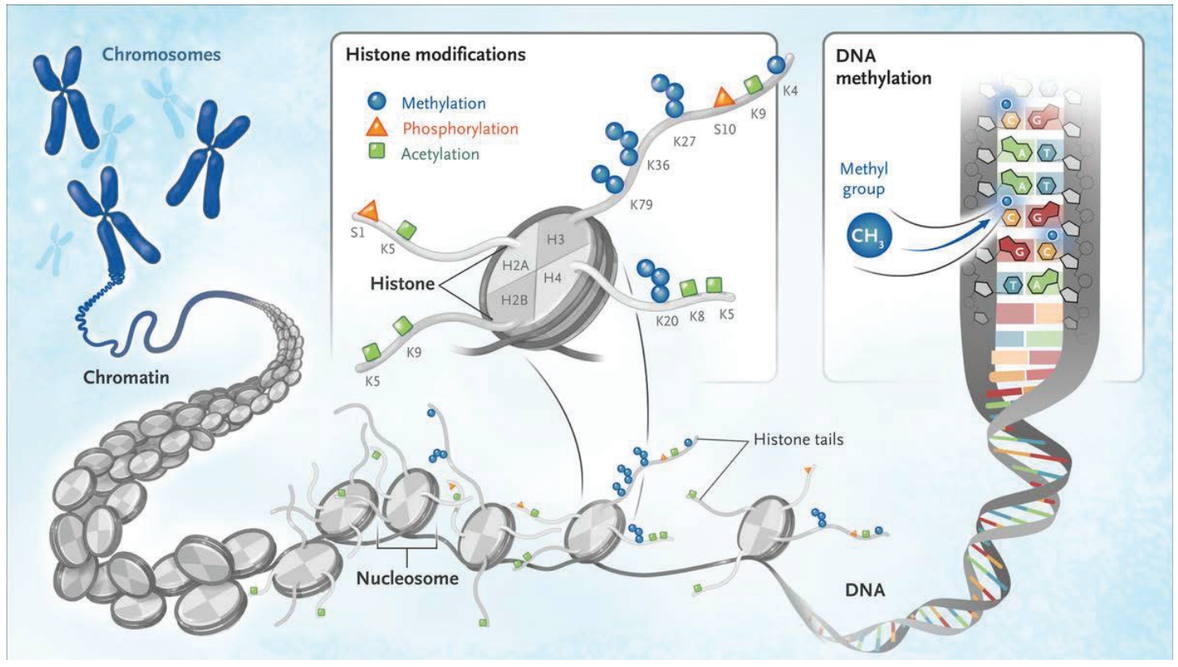
N Engl J Med 2020;383:650-63.
DOI: 10.1056/NEJMra1805035

CHROMATIN IS ONE OF THE EARLIEST IDENTIFIED TARGETS FOR CANCER therapeutics. Drug development aimed at altering chromatin can be traced to the differentiating agents of the 1970s and their link to DNA methylation.[1] A more precise understanding of the complexity of chromatin and its role in oncogenesis began to emerge when sequencing of the cancer genome revealed mutations in numerous genes encoding proteins that regulate chromatin. In many cases, these mutations proved to be critical in maintaining the malignant process, an observation that led to new therapeutics. This review summarizes approved agents and their clinical activity, describes therapies in development, and delineates challenges in the field of epigenetics.

Editing the Mitochondrial Genome

Maria Falkenberg, Ph.D., and Michio Hirano, M.D.



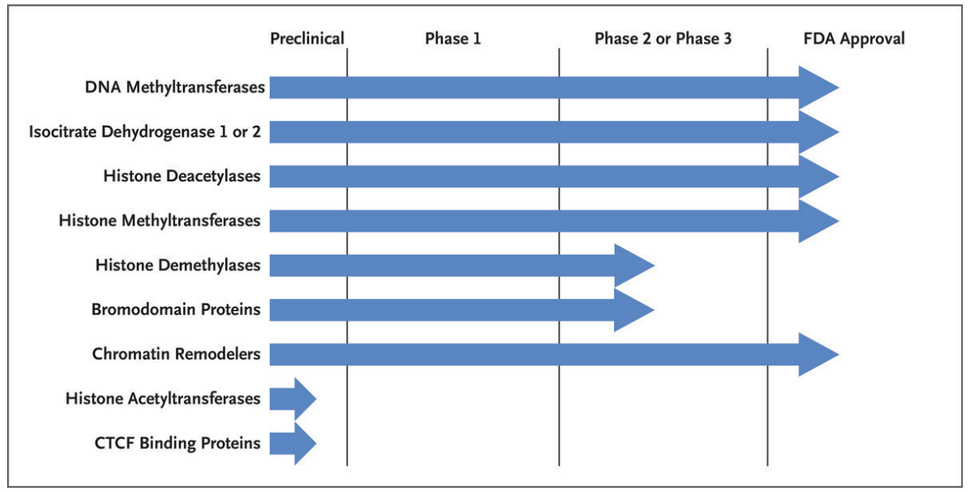


Commonly Altered Epigenetic Regulatory Proteins Implicated in Cancer.

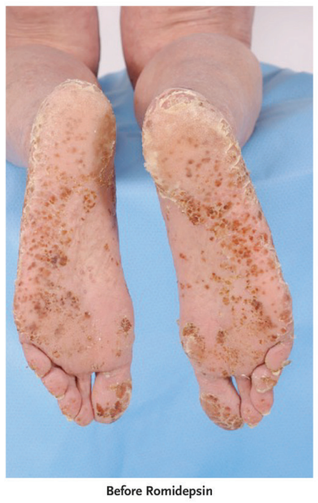
Category	Epigenetic Regulators	Function	FDA-Approved Drug
Writers	**DNMT1, 3A, and 3B**	Methylates cytosines on DNA, and mutation can lead to aberrant methylation	Azacitidine, decitabine
	EZH2	Methylates histone H3K27	Tazemetostat
	DOT1L	Methylates histone H3K79	
	KMT2A–D, SETD2, NSD1	Methylate histone lysines	
	EP300, CREBBP	Acetylate histone lysines	
Erasers	**TET2**	Is the first step in cytosine demethylation; is inhibited by 2-hydroxyglutarate (2-HG)	Azacitidine, decitabine
	IDH1, IDH2	Mutated protein produces 2-HG from isocitrate that inhibits TET2 and lysine demethylases	Ivosidenib, enasidenib
	HDAC1–3, 8 HDAC6	Deacetylase removes acetyl groups from histone lysines	Vorinostat, belinostat, panobinostat, romidepsin
	KDM1A, **KDM6A (UTX)**	Demethylates histone lysines	
Readers	BRD4	Bromodomain proteins read acetyl groups on histone lysines	
	CBX family, CHD1	Chromodomain proteins read methyl groups	
Movers	**ARID1A, ARID1B, ARID2** SMARCA2, **SMARCA4, SMARCB1,** CHD1	Proteins in the chromatin remodeling complex use ATP to move nucleosomes away from DNA; loss-of-function mutations common in cancer	
Shapers	**HIST1H1B, HIST1H1C, HIST1H3B, H3F3A, H3F3B**	Structural histone proteins acquire mutations that can be oncogenic	
Insulators	**CTCF, STAG2, RAD21,** CHD8	Normal binding to CTCF sites on DNA defines and protects gene neighborhoods from inappropriate expression	

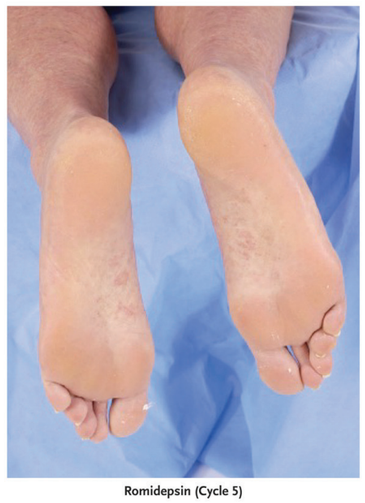
SE Bates. N Engl J Med 2020;383:650-663.

Epigenetic Regulators under Investigation or Approved by the Food and Drug Administration (FDA), According to Protein Family.



Clinical Images Obtained before and after Treatment with Romidepsin in a Patient with Cutaneous T-Cell Lymphoma (CTCL).

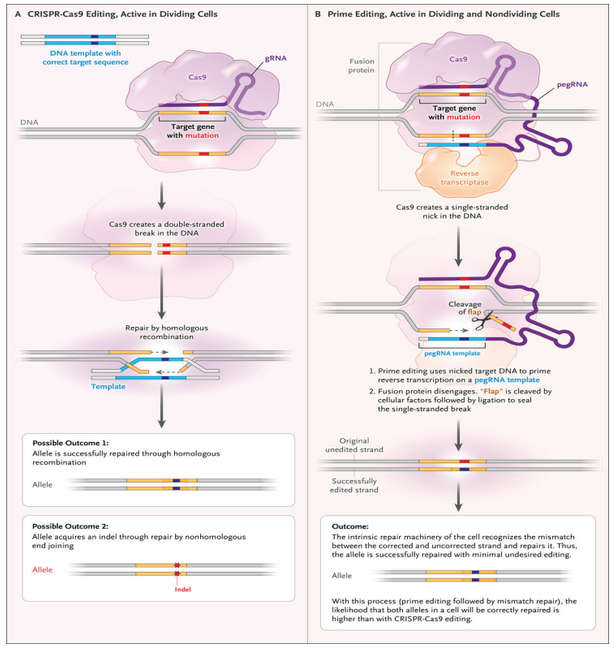

Before Romidepsin


Romidepsin (Cycle 5)

SE Bates. N Engl J Med 2020;383:650-663.

Prime Time for Genome Editing?

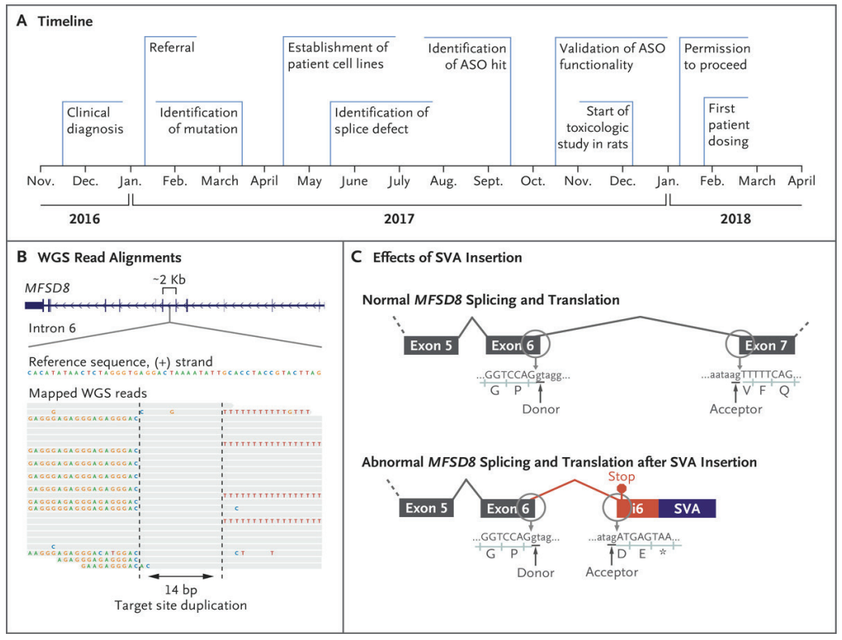
Fyodor D. Urnov, Ph.D.



FD Urnov. N Engl J Med 2020;382:481-484.

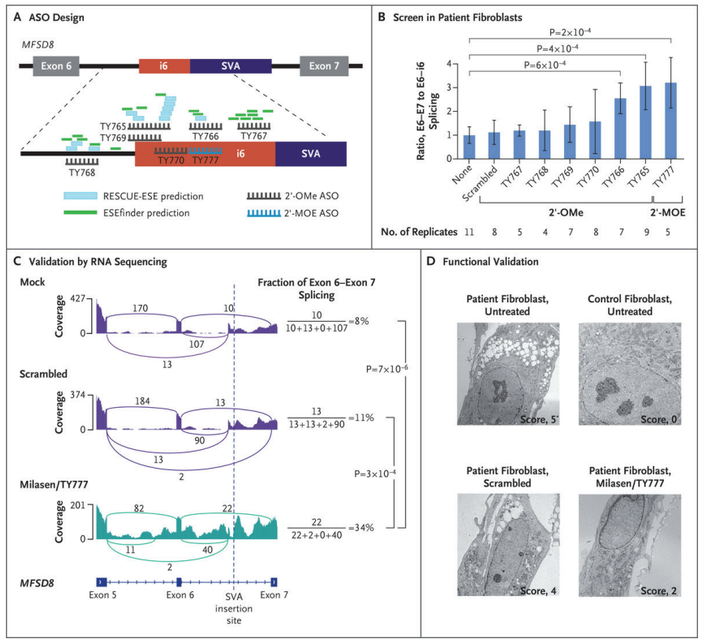
Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu



Neuronal Ceroid Lipofuscinosis Gene Therapy

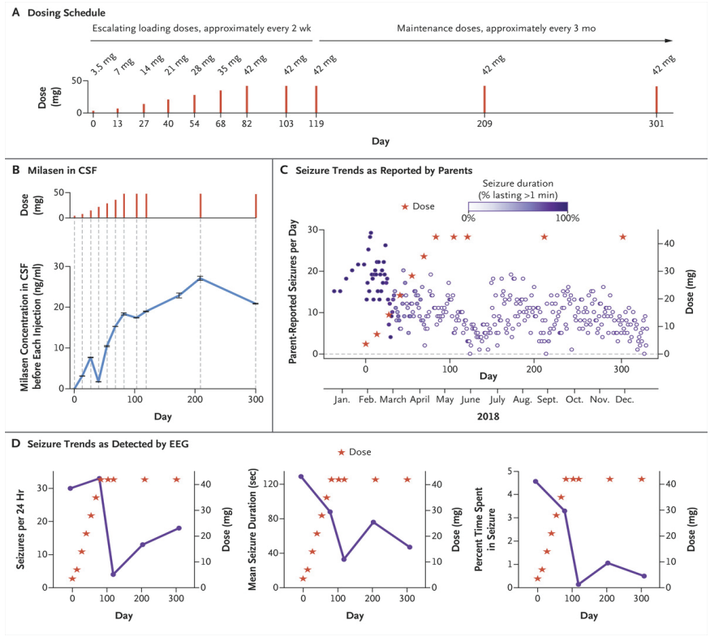
J Kim et al. N Engl J Med 2019;381:1644-1652



Neuronal Ceroid Lipofuscinosis Gene Therapy

Antisense Oligonucleotide Drug Development

J Kim et al. N Engl J Med 2019;381:1644-1652



Neuronal Ceroid Lipofuscinosis Gene Therapy

Antisense Oligonucleotide Drug Development

J Kim et al. N Engl J Med 2019;381:1644-1652

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Gillmore JD et al. DOI: 10.1056/NEJMoa2107454

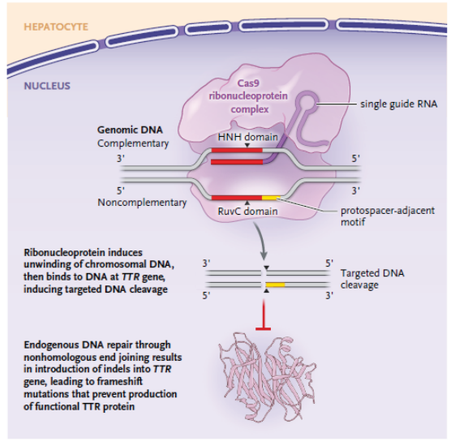
CLINICAL PROBLEM

In transthyretin amyloidosis, misfolded transthyretin (TTR) protein accumulates, primarily in the nerves and heart, and is ultimately fatal. Current therapies reduce amyloid formation through repeated infusions that can have serious adverse effects or require infusion premedications. These treatments slow but do not stop disease progression.

CLINICAL TRIAL

Study Design: An open-label, phase 1 clinical study evaluated the safety and pharmacodynamic effects of NTLA-2001, a CRISPR-Cas9–based in vivo gene-editing therapy targeting *TTR* in human hepatocytes, in adults with hereditary transthyretin amyloidosis and polyneuropathy with or without cardiomyopathy.

Intervention: 6 patients received a single intravenous infusion of NTLA-2001 at a dose of either 0.1 or 0.3 mg per kilogram of body weight.



Efficacy: At 28 days after infusion, TTR levels were reduced from baseline with both doses; the reduction was greater with the larger dose.

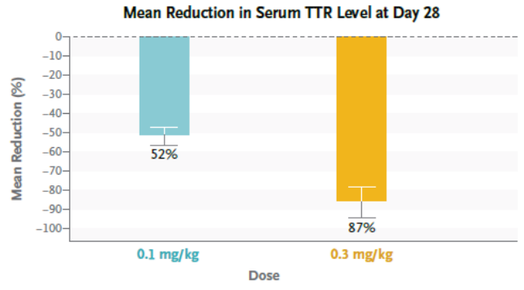
Safety: Adverse effects occurred in 3 patients and were mild.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- The duration of TTR reduction after a single infusion of NTLA-2001 at the doses used in this study and at higher doses
- Clinical outcomes in these 6 patients and in larger trials
- Whether other adverse effects, including off-target gene editing, occur in the longer term

Links: Full Article | NEJM Quick Take | Editorial



CONCLUSIONS

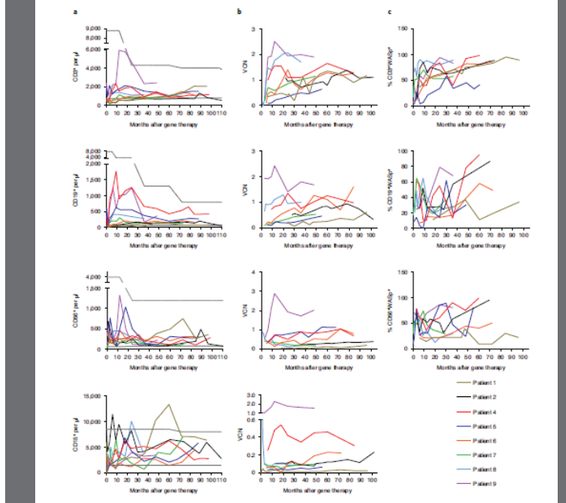
This trial involving a small number of patients with hereditary transthyretin amyloidosis provides proof-of-concept evidence that CRISPR-Cas9–based gene editing with NTLA-2001 greatly reduces TTR levels after a single infusion, with only mild adverse events.

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01641-x
Check for updates

OPEN

Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott–Aldrich syndrome

NATURE MEDICINE | VOL 28 | JANUARY 2022 | 71–80 |



news & views
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GENE THERAPY

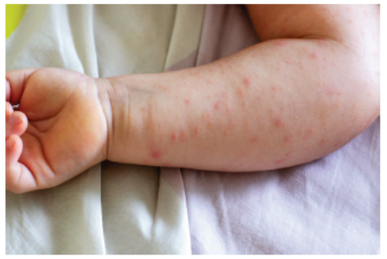
Gene therapy goes the distance in Wiskott–Aldrich syndrome

Long-term follow-up data reinforce the curative potential of hematopoietic stem-cell gene therapy for this rare primary immunodeficiency disorder.

Alessandra Biffi

Wiskott–Aldrich syndrome (WAS) is a rare X chromosome-linked primary immunodeficiency caused by mutations in the gene that encodes the WAS protein (WASP), an essential regulator of the actin cytoskeleton in hematopoietic cells. WAS-affected patients present with thrombocytopenia, eczema, recurrent infections, autoimmune disease and malignancy. Severe disease occurs in those with no functional WASP and is typically associated with a very dismal prognosis — life expectancy is less than 15 years in the absence of curative treatments[1,2].

Allogeneic hematopoietic stem-cell transplantation (HSCT) from HLA-matched donors has become the gold-standard treatment for patients with WAS[3,4], offering a potential cure and correction of the underlying immunodeficiency and thrombocytopenia. However, as related identical donors are rare and the use of matched-unrelated donors (if available) carries a risk of complications, hematopoietic stem-cell (HSC) gene therapy has also been explored as a potential



Credit: Zanobilis / Alamy Stock Photo

First sickle cell patient treated with CRISPR gene-editing still thriving

December 31, 20215:05 AM ET

https://www.npr.org/sections/health-shots/2021/12/31/1067400512/first-sickle-cell-patient-treated-with-crispr-gene-editing-still-thriving?t=1643720490885

For more than a year, Victoria Gray's life had been transformed. Gone were the sudden attacks of horrible pain that had tortured her all her life. Gone was the devastating fatigue that had left her helpless to care for herself or her kids. Gone were the nightmarish nights in the emergency room getting blood transfusions and powerful pain medication.

But would the experimental treatment she got to genetically modify her blood cells keep working, and leave her free from the complications of sickle cell disease that had plagued her since she was a baby?

More than another year later, the answer appears to be: Yes. "I'm doing great," Gray, now 36, said -
"I haven't any problems with sickle cell at all. I did get a cold about a week ago," she says with a nervous chuckle. Victoria's so traumatized by a life of sickle cell: a simple cold had been one of many things that could trigger a terrible attack of the painful symptoms of the disease.

Multiyear Factor VIII Expression after AAV Gene Transfer for Hemophilia A

Lindsey A. George, M.D., Paul E. Monahan, M.D., M. Elaine Eyster, M.D., Spencer K. Sullivan, M.D., Margaret V. Ragni, M.D., M.P.H., Stacy E. Croteau, M.D., M.M.S., John E.J. Rasko, M.B., B.S., Ph.D., Michael Recht, M.D., Ph.D., Benjamin J. Samelson-Jones, M.D., Ph.D., Amy MacDougall, B.S.N., Kristen Jaworski, M.S.N., F.N.P., Robert Noble, Ph.D., Marla Curran, Dr.P.H., Klaudia Kuranda, Ph.D., Federico Mingozzi, Ph.D., Tiffany Chang, M.D., Kathleen Z. Reape, M.D., Xavier M. Anguela, Ph.D., and Katherine A. High, M.D.

N ENGL J MED 385;21 NEJM.ORG NOVEMBER 18, 2021

The NEW ENGLAND JOURNAL of MEDICINE

Betibeglogene Autotemcel Gene Therapy for Non–β^0/β^0 Genotype β-Thalassemia

OPEN-LABEL, PHASE 3 STUDY

23
Adult and pediatric patients with transfusion-dependent β-thalassemia and a non–β^0/β^0 genotype

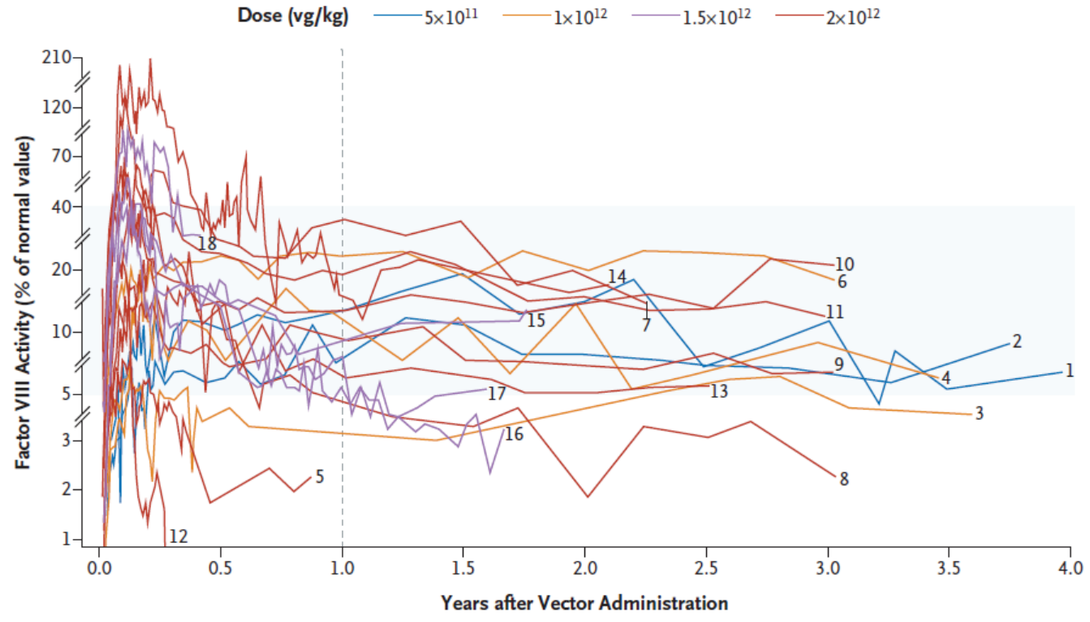
Beti-cel gene therapy
(after myeloablation with busulfan)

HSPCs → Lentivirus → Modified HSPCs

Transfusion independence (median follow-up, 29.5 mo)	20 of 22 patients
Average hemoglobin level during transfusion independence	11.7 g/dl (range, 9.5–12.8)
Median gene therapy–derived adult hemoglobin level at 12 mo	8.7 g/dl (range, 5.2–10.6)

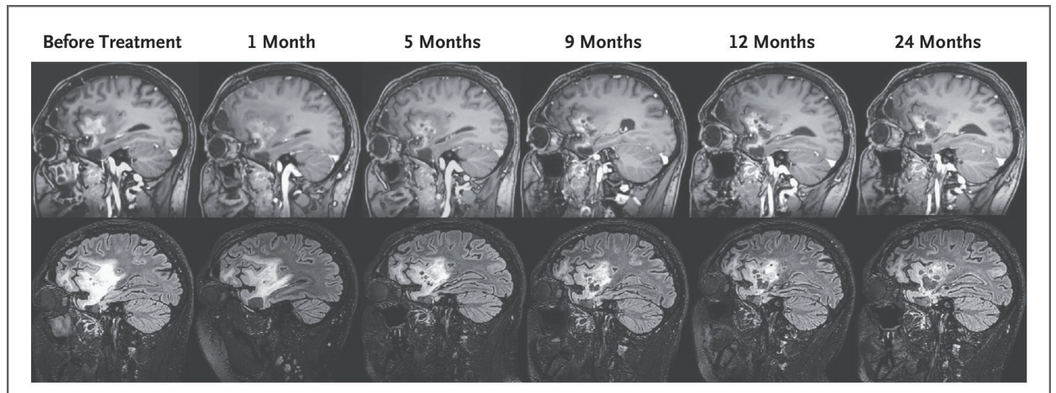
Beti-cel treatment resulted in transfusion independence in most patients.

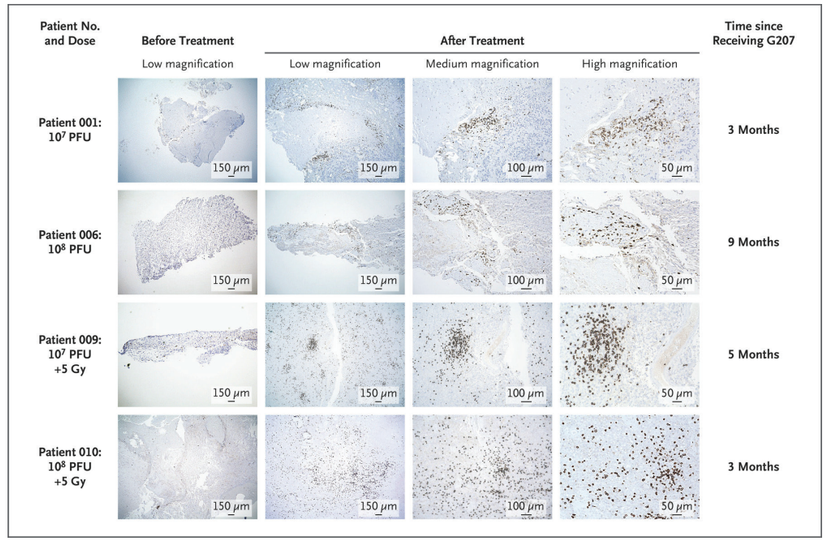
F. Locatelli et al. 10.1056/NEJMoa2113206



Oncolytic HSV-1 G207 Immunovirotherapy for Pediatric High-Grade Gliomas

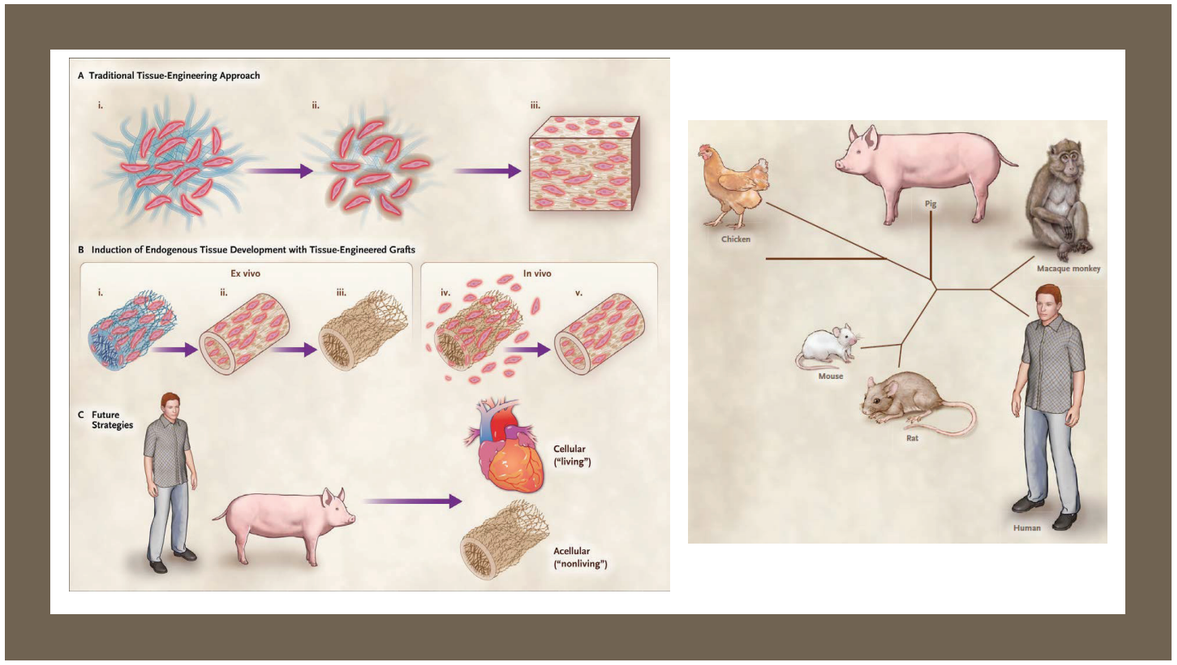
G.K. Friedman, J.M. Johnston, A.K. Bag, J.D. Bernstock, R. Li, I. Aban, K. Kachurak, L. Nan, K.-D. Kang, S. Totsch, C. Schlappi, A.M. Martin, D. Pastakia, R. McNall-Knapp, S. Farouk Sait, Y. Khakoo, M.A. Karajannis, K. Woodling, J.D. Palmer, D.S. Osorio, J. Leonard, M.S. Abdelbaki, A. Madan-Swain, T.P. Atkinson, R.J. Whitley, J.B. Fiveash, J.M. Markert, and G.Y. Gillespie

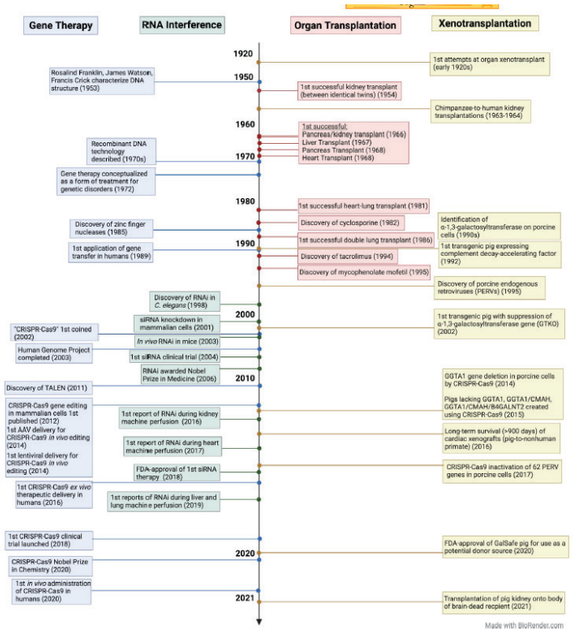




Immune and Genome Engineering as the Future of Transplantable Tissue

Jennifer Elisseeff, Ph.D., Stephen F. Badylak, M.D., D.V.M, Ph.D., and Jef D. Boeke, Ph.D., D.Sc.





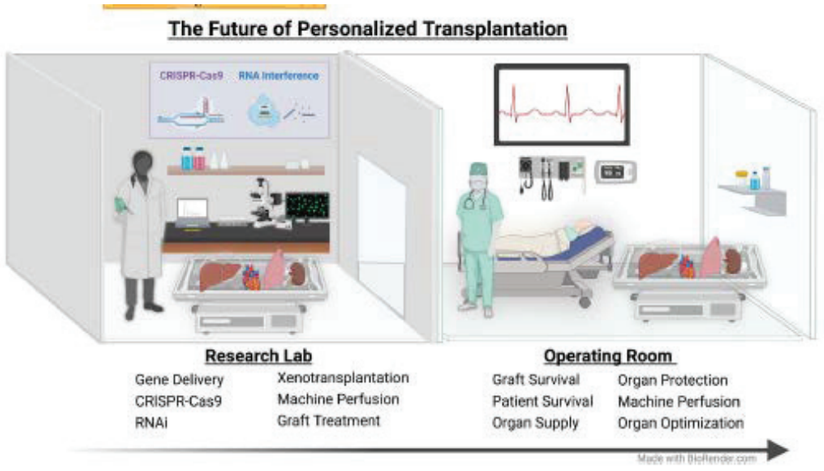
Advances in transplantation

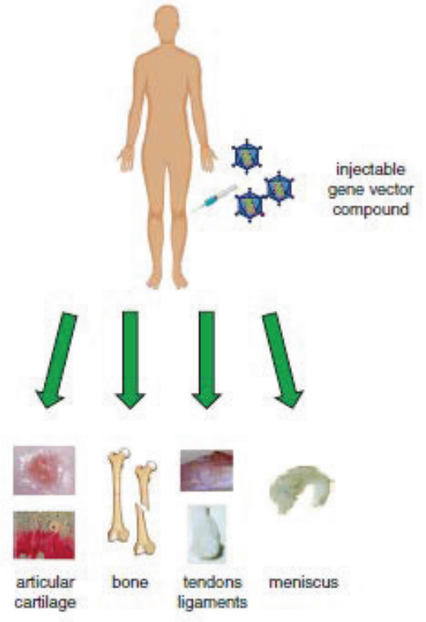
-

note the acceleration of pace recently

Designer organs: The future of personalized transplantation

Julianna E. Buchwald[1,2] | Paulo N. Martins[1]





Application	Vectors	Genes	Models
Cartilage	Adenoviral vectors	IL-1Ra	OA reduction (mouse, horse)
		IL-1Ra/sTNF-RI	OA reduction (rabbit)
		IL-1Ra/IGF-I	Focal repair (horse)
			OA reduction (rabbit)
		TGF-β/Smad7	OA reduction (mouse)
		Kallistatin	OA reduction (rat)
		FGF-2, FGF-2/IL-1Ra, FGF-2/IL-1Ra/IGF-I	OA reduction (rabbit)
		TSP-1	OA reduction (rat)
		BMP-2, BMP-6	Focal repair (horse)
		POMC	OA reduction (rat)
		Dkk-1	OA reduction (mouse)
		Prg4	
		Prg4/IL-1Ra	OA reduction (rat)
		RHEB	OA reduction (mouse)
		HDAC	OA reduction (rat)
		LOXL2	OA reduction (mouse)
	rAAV vectors	Dkk-1	OA reduction (rat)
		CRISPR-Cas9 editing of IL-1β or MMP-13	OA reduction (mouse)
Bone	Adenoviral vectors	BMP-2	Bone healing (rabbit)
			Bone healing (rat)
			Bone healing (sheep)
			Bone healing (horse)
		TGF-β	Bone healing (rabbit)
		VEGF	
	rAAV vectors	COX-2	Bone formation (mouse)
		siRNA (ApoE)	
Tendons, ligaments	Adenoviral vectors	BMP-12	Tendon healing (chicken)
			Ligament healing (rabbit)
		GDF-5	Tendon healing (rat)
	rAAV vectors	FGF-2	Tendon healing (chicken)
		VEGF	

Gene Therapy - Can it Cure Type 1 Diabetes?

Mirra Srinivasan [1] , Santhosh Raja Thangaraj [1] , Hadia Arzoun [1]

1. Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA

Author	Year	Key Findings
Xia et al. [7]	2015	Lentiviral vector-encoding Reg3g contributes to β cell regeneration and prevents β cells from autoimmune destruction by strengthening regulatory T-cells and generating highly resistant dendritic cells.
Gautham et al. [8]	2016	Targeted lentiviral transduction of the insulin gene into primary cMSCs makes these cells capable of secreting insulin in adequate quantities in vitro, indicating that they could be used in insulin gene therapy.
Fishman et al. [9]	2017	In vivo, mRNA-transfected T-cells expressing chimeric MHC complexes can selectively immunotarget pathogenic T-cells, thus preventing or minimizing the incidence of autoimmune diabetes in NOD mice.
Matsuoka et al. [10]	2017	Pdx1's ability to promote β-cell development from Ngn3-positive endocrine precursors was discovered to be potentiated by MafA, as well as Pdx1's ability to develop β-cells from α-cells.
Mallol et al. [11]	2017	Transgenic NOD mice overexpressing IGF1 specifically in β-cells (NOD-IGF1) and IGF1-encoding AAV of serotype 8 (AAV8-IGF1-dmiRT) treated NOD mice exhibited significantly reduced islet infiltration, preserved β-cell mass, and normalized insulin levels than controls.
Xie et al. [12]	2017	In overtly diabetic mice, an integration of Ngn3-Btc gene therapy and anti-TCRβ mAb treatment resulted in the development of periportal insulin-producing cells in the liver.
Yeh et al. [13]	2017	Transduced lentivirus Treg avatars are more likely to clear islet infiltration/inflammation and contribute to sustained engraftment in the long run.
Xiao et al. [14]	2018	The pancreatic duct was infused with adeno-associated virus containing Pdx1 and MafA expression cassettes in both β cell-toxin-induced diabetic mice and autoimmune NOD animals which then converted α cells into functional β cells and restored blood glucose that persisted for four months prior to reestablishment of autoimmune T1D.

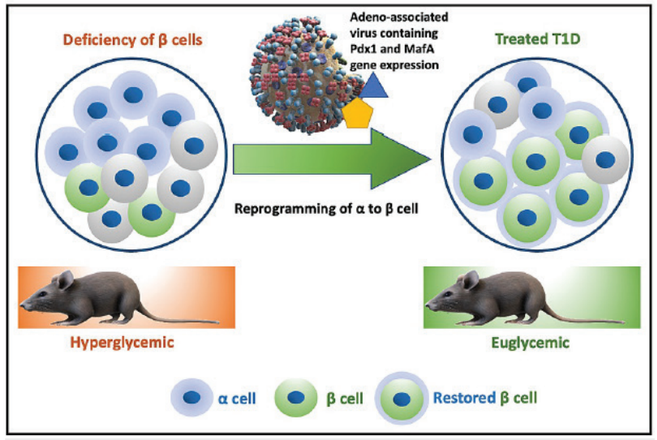


FIGURE 3: Reprogramming α cells into β cells through gene therapy

CONCLUDING STATEMENTS

- Gene therapy is now mature enough to be tried in several diseases
- Technology has led to many new applications beyond the classic gene replacement one
- There is convergence of gene therapy technology and tissue regeneration
- The transplantation field will soon be completely transformed due to gene therapy

Gene therapy and other novel therapies: the future is here!

Challenges faced by the medical systems:

- Infrastructure?
- Knowledgeable staff; training?
- Complications that may lead to new diseases

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Senior Investigator, Human Genetics & Precision Medicine, FORTH (ITE), Heraklion, Greece
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Email: castratakis@elpen.gr or castratakis@verizon.net

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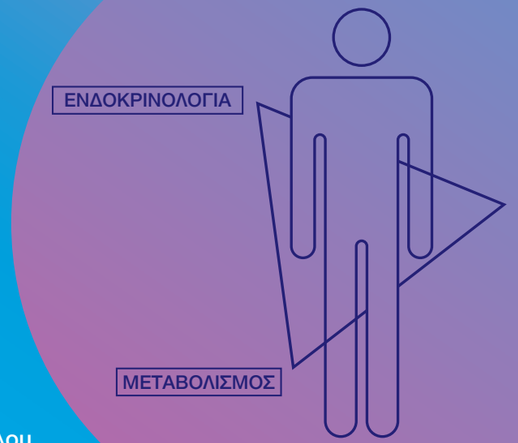

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