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001

Real-world evidence of the effect of adjunctive semaglutide on weight change, glycaemic control, and metabolic dysfunction associated steatotic liver disease in people with type 1 diabetes

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Introduction
Obesity is increasingly prevalent in type 1 diabetes (T1D), contributing to insulin resistance and metabolic-dysfunction associated steatotic liver disease (MASLD). While semaglutide has demonstrated weight loss, improved glycaemic control, and cardiovascular benefits in people with type 2 diabetes, its use in T1D remains unapproved.
Aims & Methods
This real-world study evaluates the effects of once-weekly semaglutide SQ in overweight/obese adults with T1D after 12 months of follow-up. Inclusion criteria were stable glycaemic control (ΔHbA1c $<0.3\%$), stable body weight (Δweight $<3\%$), and consistent total daily insulin requirement (TDI, ΔTDI $<5\%$) over the preceding year. Changes in weight, TDI, HbA1c, and metabolic markers, including controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), were analysed.
Results
Among 42 subjects (53% male, age 46 $\pm$ 12 years, diabetes duration 28 $\pm$ 12 years, HbA1c 7.4 $\pm$ 0.8%, BMI 32.2 $\pm$ 4.3 kg/m^2), 76.2% had obesity. Eight subjects discontinued treatment, mainly due to gastrointestinal intolerance. Mean relative weight loss was 13.3 $\pm$ 11.3% (P <0.001), with 76.4% attaining $\geq$ 5% weight loss and 61.7% attaining $\geq$ 10%. Obesity prevalence decreased to 29.4% (P <0.001). HbA1c decreased by 0.4 $\pm$ 0.6% (P <0.001), with 42% achieving a reduction of $\geq$ 0.5%. No significant changes in continuous glucose monitoring-derived parameters were observed in those with available data (n = 28). TDI reduced by 13.6 $\pm$ 16.0% (P <0.001), while TDI/kg of bodyweight remained stable. In 23 subjects with serial hepatic imaging, MASLD prevalence reduced from 82.6 to 30.4% (P <0.001), CAP decreased by 45 $\pm$ 33 dB/m, and significant fibrosis (based on LSM $>$ 8 kPa) declined from 20.6 to 4.5% (P $<$ 0.001).
Conclusion
Semaglutide in T1D was safe, well-tolerated, and led to significant weight loss, improved glycaemic control and amelioration of MASLD.
Keywords
Type 1 diabetes, semaglutide, obesity, MASLD
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DOI: 10.1530/endoabs.112.001

002

Continuous glucose monitoring metrics and pregnancy outcomes in type 1 diabetes: a secondary analysis of the cristal trial

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Introduction
More data are needed regarding specific continuous glucose monitoring (CGM) metrics and their association with pregnancy outcomes in women with type 1 diabetes (T1D). Therefore, this study aims to examine the association between various CGM metrics and pregnancy outcomes in women with T1D.
Methods
The CRISTAL study was a randomized controlled trial, comparing the MiniMed™ 780G with standard insulin therapy in 95 pregnant women with T1D and indicated improved pregnancy-specific time in range (TIRp) overnight (1). This secondary analysis assessed the association between CGM metrics and pregnancy outcomes. Logistic regression and Spearman correlations, adjusted for baseline HbA1c, were used to analyze binary and continuous outcomes. Data are presented as odds ratios with 95% confidence intervals.
Results
Each 5% increase in TIRp was associated with lower odds of gestational hypertension (0.63; 0.41-0.97), birthweight $<$4.5 kg (0.56; 0.32–0.96) and neonatal hypoglycemia requiring neonatal care (0.09; 0.01-0.57). Each 5% increase in TIRp overnight reduced the odds of gestational hypertension (0.71; 0.52- 0.98) and neonatal care for hypoglycemia (0.15; 0.03-0.79). Each 5% increase in time above the pregnancy-specific range (TARp) was associated with birthweight $<$4.5 kg (1.76; 1.05-2.96), respiratory distress (1.55; 1.02-2.37), and neonatal hypoglycemia requiring neonatal care (5.1; 1.14-22.78). Every 5 mg/dl increase in mean glycemia was associated with higher odds for respiratory distress (1.54; 1.07-2.23), while every 5 mg/dl increase in glucose standard deviation raised the odds of gestational hypertension (1.69; 1.02-2.80) and birthweight $<$4.5 kg (2.31; 1.20-4.43).
Conclusion
Our findings indicate that, along with TIRp and TARp, overnight TIRp, mean glycemia and glycemic variability are important predictors of pregnancy outcomes.
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Keywords
Continuous glucose monitoring, type 1 diabetes, pregnancy outcomes
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003

Who benefits most from advanced hybrid closed loop therapy in pregnancy based on baseline characteristics? a secondary analysis of the CRISTAL trial

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Introduction
The CRISTAL trial showed that advanced hybrid closed-loop (AHCL) therapy with the MiniMed™ 780G system in type 1 diabetes (T1D) pregnancy did not improve the pregnancy-specific time in range (TIRp) overall compared to standard insulin therapy (SoC), but improved TIRp overnight and reduced time below range (TBRp) (1). Identifying subgroups that may benefit most from AHCL use is crucial for optimizing treatment strategies. We aimed to identify subgroups that may benefit most from AHCL therapy in pregnancy based on baseline characteristics.
Methods
This is a secondary analysis of the CRISTAL study, a multicenter randomized controlled trial comparing MiniMed™ 780G AHCL with SoC in 95 pregnant women with T1D. The primary outcome (TIRp) and key secondary outcomes (TIRp overnight, TBRp overall and overnight) were evaluated according to various baseline characteristics.
Results
AHCL users with baseline HbA1c $<7.0\%$ (n = 35) had a significantly higher TIRp than SoC (n = 37), with a mean difference of 5.64% (95% CI: 1.32-9.96), corresponding to 1h21min more TIRp per day and 11.89% (95% CI: 7.01-16.76) higher TIRp overnight. In women without prior AHCL use, TIRp was 6.29%

(95% CI:0.90-11.68) higher in the AHCL group ($n = 24$) with an 11.91% (95% CI: 5.65-18.16) higher overnight TIRp compared to SoC ($n = 28$). TIRp was significantly higher in AHCL users ($n = 14$) compared to SoC ($n = 14$) in women without higher education (7.33%, 95% CI: 0.88-13.78). TBRp was significantly lower in AHCL users with baseline HbA1c $<7.0\%$ and in women without prior AHCL use compared to SoC.

Conclusion

AHCL use with the MiniMed™ 780G system improved glycemic control in pregnant women with baseline HbA1c $<7.0\%$, women without prior AHCL use, and women without higher education, indicating that AHCL use might particularly benefit these subgroups.

Reference

1. Benhalima K, Beunen K, Van Wilder N, *et al*. Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, openlabel, randomised controlled trial.12(6),390–403 (2024).

Keywords

Diabetes in pregnancy, Technology and diabetes, Artificial pancreas

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004

Correlations between fear and perception of hypoglycemia and continuous glucose monitoring metrics in adults with type 1 diabetes using diabetes technology: a one-year retrospective study

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Introduction

Although the use of technology in type 1 diabetes (T1D) has been shown to improve fear and perception of hypoglycemia and continuous glucose monitoring (CGM) metrics, their underlying associations remain unclear. This study examines the correlations between fear and perception of hypoglycemia and CGM-measured time in hypoglycemia along with other CGM-metrics.

Methods

This retrospective secondary-use study assessed correlations between 12-month changes in questionnaires scores and 12-month changes in CGM-metrics in 1370 adults with T1D who used either real-time CGM (rtCGM; ALERTT1-study (1), $n = 254$) or hybrid closed-loop (HCL; INRANGE-study (2), $n = 1116$). Questionnaires included the Hypoglycemia Fear Survey II (HFS) and the perceived frequency of hypoglycemia item from the Diabetes Treatment Satisfaction Questionnaire - status (DTSQs-hypo). Delta (Δ) represents the change from baseline to 12 months after rtCGM or HCL initiation. Data are reported as mean $\pm$ SD.

Results

Mean age was 41.0 $\pm$ 13.7 years, 55.9% were female. At baseline, HbA1c was 7.6 $\pm$ 1.0%, time in range (TIR; 70-180 mg/dl) 61.1 $\pm$ 15.5%, time <70 mg/dl 3.4 $\pm$ 3.5% and time <54 mg/dl 0.8 $\pm$ 1.4%. Delta HFS-worry scores were not correlated with Δtime <70 mg/dl ($r = 0.037$, $P = 0.240$) or Δtime <54 mg/dl ($r = 0.012$, $P = 0.708$). Similarly, ΔHFS-behavior showed no correlation with Δtime <70 mg/dl ($r = -0.036$, $P = 0.257$) and only very weak correlation with Δtime <54 mg/dl ($r = -0.071$, $P = 0.025$). For other CGM-metrics only weak or no correlations were found with ΔHFS-worry, including Δtime >250 mg/dl ($r = 0.067$, $P = 0.033$) and Δcoefficient of variation ($r = 0.092$, $P = 0.005$). Similarly, ΔHFS-behavior showed only very weak correlation with ΔTIR ($r = -0.081$, $P = 0.010$) and Δtime in tight range [70-140 mg/dl] ($r = -0.068$, $P = 0.040$). Also ΔDTSQs-hypo showed only weak correlations with Δtime <70 mg/dl ($r = 0.188$, $P < 0.001$) and Δtime <54 mg/dl ($r = 0.115$, $P < 0.001$)

Conclusion

No clear correlations were found between changes in fear and perception of hypoglycemia and CGM-metrics, suggesting that factors beyond glucose management alone likely contribute to these psychological responses in adults using rtCGM or HCL over a one-year period.

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Keywords

Type 1 diabetes, hypoglycemia, continuous glucose monitoring

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005

Inflammatory stimuli induce profound transcriptome and translatome changes in induced pluripotent stem cell-derived β cells that mimic type 1 diabetes βcell gene signatures

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Introduction

Human induced pluripotent stem cells (iPSCs) differentiated into β-like cells represent an exciting model to investigate the pathogenesis of type 1 diabetes (T1D). The unlimited source of iPSC-β cells enables comprehensive omics studies of gene expression (transcriptomics) and protein synthesis (translatomics). Here, we examined how β cells respond to inflammatory stimuli known to play a role in T1D, aiming to better understand disease mechanisms and uncover potential therapeutic targets. We focused on interferon alpha (IFNα), that is linked to early, preclinical stages and triggers initial immune activation, interferon gamma (IFNγ) and interleukin-1 beta (IL1β), that are produced by autoreactive T cells and macrophages during the active β cell destruction phase, and tumor necrosis factor alpha (TNFα), that is involved in amplifying inflammation and cellular stress.

Methods

iPSCs were differentiated into β cells and purified by MACS using the iPSC-β cell surface marker CD49a. The cells were exposed for 24h to the individual cytokines IFNα, IFNγ, IL1β, TNFα or to the combination IFNγ + IL1β. RNA sequencing was used to study the transcriptome and ribosome profiling to examine which RNAs are actively translated into proteins (translatome). These analyses link gene expression changes to altered protein production.

Results

MACS purification generated 80 $\pm$ 7% pure iPSC-β cells. Among all treatments, IFNγ + IL1β had the greatest impact, changing the expression of over 5,600 genes. Of the single cytokines, IFNs had the strongest impact (especially IFNy). Pathway analyses showed that translation was affected in all conditions. The comparison between transcriptome and translatome showed common upregulation of immune reaction pathways and downregulation of metabolic pathways and regulation of insulin secretion. In iPSC-β cells cytokines inhibited glucose-stimulated insulin secretion, from 4.5-fold stimulation in control to 3.5-fold for IL1β and TNFα and 1.5-fold for IFNα, IFNγ and IFNγ + IL1β. Notably, this occurred without a reduction in insulin content, indicating that the problem lies in secretion, not production. This aligns with T1D pathophysiology, where early β cell dysfunction induces impaired insulin release before full βcell destruction occurs. When comparing our data with FACS-purified β cells from T1D organ donors, high overlap was seen in particular for IFNα, IFNγ + IL1β and IFNγ confirming the clinical relevance of this in vitro model. Using the Connectivity Map (a resource linking gene expression signatures to drug effects), we identified novel therapeutic targets that may counteract the overlapping gene signatures. Among the most promising classes of drugs were bromodomain inhibitors (known to reduce cytokine-induced inflammation), leucine-rich repeat kinase (LRRK) inhibitors and a farnesyltransferase inhibitor.

Conclusion

Transcriptome, translatome and functional analyses suggest a preferential translation of genes which increase visibility of βcells to the immune system at the expense of βcell function. This functional imbalance mimics early T1D pathology. The high transcriptome overlap between T1D patients' β cells and the iPSC-βcells supports the use of the latter model to identify new therapeutic strategies to delay or prevent T1D.

Keywords

Induced pluripotent stem cells, βcells, transcriptome, insulin secretion, type 1 diabetes

DOI: 10.1530/endoabs.112.005

006

The value of free cortisol estimates in healthy individuals undergoing an insulin tolerance test and synacthen test to evaluate adrenal function

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Introduction
Increased CBG (corticosteroid binding globulin) concentrations can mask low free cortisol levels by showing normal total cortisol values, potentially leading to missed diagnoses of adrenal insufficiency (AI). Free cortisol estimates in serum and saliva may provide a more accurate assessment of adrenal function in these situations. The aim of this study is to describe the dynamic responses of calculated and measured free cortisol, salivary cortisol, and salivary cortisone in healthy individuals during the insulin tolerance test (ITT) and 250µg short Synacthen test (SST), and to evaluate the degree of discordance. Due to lower total cortisol values measured by modern immunoassays, a new cut-off value of 13.5 µg/dl (instead of 18 µg/dl) for endocrine dynamic function tests has been suggested in the literature to prevent overdiagnosis of AI. We aimed to compare the peak total cortisol levels (measured by electrochemiluminescence immunoassay and liquid chromatography–mass spectrometry (LC-MS/MS)) with the new proposed cut-off value of 13.5 µg/dl.
Methods
24 healthy individuals underwent an ITT with collection of plasma and salivary samples at baseline and 15, 30, 45 and 60 minutes after insulin injection. 23 healthy individuals underwent an SST with sample collection at baseline, 30 and 60 minutes after Synacthen injection. Free cortisol was measured using equilibrium dialysis followed by LC-MS/MS and calculated by using an in-house formula based on the law of mass-action, comparable to the Vermeulen formula (1) for free testosterone. During the ITT, total cortisol was measured using electrochemiluminescence immunoassay and LC-MS/MS for method comparison.
Results
Calculated free cortisol values were significantly lower than measured free cortisol values in both dynamic tests. Salivary cortisol peaked at significantly different time points during the ITT compared to other variables (with earlier peaks in a substantial proportion of participants). We observed a significant higher relative increase of salivary cortisol and free cortisol in serum compared to total cortisol. During the ITT, 8/24 individuals (LC-MS/MS) and 3/24 (immunoassay) did not reach the 18 µg/dl total cortisol cutoff, whereas only one fell below the 13.5 µg/dl threshold (using both immunoassay and LC-MS/MS). During the SST (using LC-MS/MS), 1/23 missed the 18 µg/dl cutoff, and 23/23 reached a peak value above 13.5 µg/dl.
Conclusion
Free cortisol estimates may be a potential alternative to total cortisol; however further research is required to assess their role in individuals with altered cortisol-binding states as well as a clinical suspicion of adrenal insufficiency. Larger studies are needed to establish universally accepted cutoff values that consider the specific analytical method used.
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Keywords
Adrenal insufficiency, endocrine dynamic function tests, free cortisol
DOI: 10.1530/endoabs.112.006

007

Effect of elexacaftor-tezacaftor-ivacaftor on glucose metabolism in patients with cystic fibrosis

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Introduction
Cystic fibrosis-related diabetes (CFRD) is a common complication among people with cystic fibrosis (pwCF), contributing to significant morbidity and mortality. The introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators has markedly improved pulmonary outcomes and quality of life in pwCF. However, the impact of these modulators — particularly the combination therapy Elexacaftor/Tezacaftor/Ivacaftor (ETI) — on glucose metabolism remains unclear and controversial. This study aimed to evaluate changes in oral glucose tolerance following ETI initiation in a relatively large cohort.
Methods
We conducted a retrospective, observational, single-center study involving pwCF receiving ETI therapy aged 10 years and older. All participants underwent 2-hour oral glucose tolerance testing (OGTT) prior to starting ETI and again at 12 and 24 months post-initiation. Participants were stratified into three subgroups based on baseline glucose tolerance: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and CFRD (managed with diet al one or <10 IU/day of insulin). Secondary outcomes included absolute changes in body weight, evaluation of excessive weight gain (≥ 10 kg) (only in ≥ 18 years), and absolute changes in HbA1c, at two years after starting ETI.
Results
We included 68 pwCF with a median age of 23 (IQR 18-31) years. At baseline, 38 (56%) patients had NGT, 17 (26%) IGT, and 13 (19%) CFRD. Among those with NGT at baseline, 29/38 (76%) remained stable. Deterioration of OGTT was observed in 9/38 subjects (24%); of which eight developed IGT and one CFRD. Of those with baseline IGT, 11/17 subjects (65%) showed an improvement in OGTT with 9 subjects having NGT after one year. However, five of them experienced a reversal to IGT at year two. 2/17 IGT subjects (12%) developed CFRD. Among those with baseline CFRD, 5/13 (38%) experienced improved OGTT results at year one. Three reverted to NGT and two to IGT, although CFRD returned in one case at year 2. Bodyweight was assessed in 54 adult pwCF demonstrating an overall significant weight gain at year two (median 4 [IQR 0.9-6.8] kg vs. baseline; $P<0.001$). Excessive weight gain was present in 11 cases (20%). Absolute weight gain did not differ between subjects with deteriorated glucose tolerance and those who maintained stable or improved glucose tolerance. However, all subjects who developed IGT gained weight. Development of CFRD was accompanied by excessive weight gain in two subjects. All three subjects developing CFRD carried homozygosity for the F508del mutation. In the total cohort, median HbA1c decreased from 5.5% (IQR 5.2-5.8) to 5.1% (IQR 5.1-5.6) at year two ($P<0.001$).
Conclusion
ETI may improve glucose tolerance in pwCF. However, this effect is heterogeneous, appears to diminish over time and may be abolished by excessive weight gain. Preventing excessive weight gain associated with ETI therapy may therefore lower the risk for deterioration of glucose tolerance and development of CFRD, especially in high-risk subjects.
Keywords
Cystic fibrosis, Bodyweight, CFRD, CFTR-modulator, glucose metabolism
DOI: 10.1530/endoabs.112.007

008

Exploration of phenotypic age in gender-affirming hormone therapy

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Introduction
Biological or 'epigenetic' age reflects physiological integrity more accurately than chronological age, with established associations to morbidity and mortality. While DNA methylation-based estimators are the gold standard for assessing biological ageing, surrogate models using standard blood biomarkers, such as PhenoAge®, offer a clinically feasible alternative (1). This study applies PhenoAge ® and its ageing acceleration metric, PhenoAccel, to individuals undergoing gender-affirming hormone therapy (GAHT).
Methods
A retrospective analysis was performed on data from the Ghent arm of the European Network for the Investigation of Gender Incongruence (ENIGI) cohort, a longitudinal study of gender-diverse individuals. PhenoAge® was calculated in a hormone-naïve state at baseline and after 36 months of GAHT using apanel of nine routinely-measured biomarkers (1). Data gaps were addressed through imputation, andadjustment factors were applied to account for GAHT-induced changes in muscle mass. PhenoAccelwas derived from residuals of a regression model comparing PhenoAge to chronological age, built usingmerged data from ENIGI and NHANES (National Health and Nutrition Examination Survey), a large,population-based study in the United States. Multiple regression analysis

was used to identify predictorsof accelerated ageing. Analyses were conducted in RStudio.
Results
Of 651 participants, 97 (53 on feminizing GAHT, 44 on masculinizing GAHT) had complete data for both time points. At baseline, ageing rates did not differ significantly between groups. After 36 months, individuals on masculinizing GAHT showed a significant reduction in ageing rate, with median PhenoAccel decreasing from 0.14 to -0.12 standardized residuals ($P = 0.003$), while those on feminizing GAHT showed no significant change (from -0.05 to -0.02 residuals). Older age at baseline predicted greater changes in ageing rate ($P < 0.001$), explaining 63% of the variance. Smoking status was associated with higher baseline ageing acceleration. Rapid agers tended to have medical comorbidities or substance use.
Conclusion
PhenoAge® and PhenoAccel offer promising, though preliminary, insights into biological ageing duringGAHT. During the first three years of GAHT, aging rates remained stable in those receiving feminizingtherapy, whilst they significantly decreased in participants using masculinizing GAHT. These findingssupport the safety of GAHT from a biological ageing perspective and highlight the potential of DNAmbasedtools in future gender-diverse health research.
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Keywords
Epigenetic Age, Aging, Transgender, Biomarkers
DOI: 10.1530/endoabs.112.008

009

The one-hour oral glucose tolerance test to predict glucose intolerance postpartum in women with prior gestational diabetes

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Background and aims
Women with a history of gestational diabetes (GDM) are at higher risk of developing type 2 diabetes (T2DM) postpartum. The 2-hour oral glucose tolerance test (OGTT) is the preferred method to screen for glucose intolerance in early postpartum, while the clinical value of the 1-hour value on the OGTT remains unclear. We aimed to evaluate the predictive value of the 1-hour OGTT glucose level in early postpartum for the development of T2DM in women with a history of GDM.
Materials and methods
This is a secondary analysis of a multi-center randomized controlled trial (MELINDA), which evaluated the effectiveness of a mobile-based lifestyle intervention in early postpartum in women with prediabetes after a pregnancy complicated by GDM (1). Glucose tolerance was assessed using a 75-gram OGTT at 12 months postpartum. Women were categorized based on their 1-hour glucose value during the OGTT at 3 months postpartum, following recent guidelines from the International Diabetes Federation (2). A value of ≥ 155 mg/dl (8.6 mmol/l) was used to indicate an increased risk of future T2DM. In addition, a 1-hour value of ≥ 209 mg/dl (11.6 mmol/l) is diagnostic for diabetes.
Results
Of the 166 women with prediabetes in early postpartum based on the 2-hour OGTT, 106 women (63.9%) had a 1-hour glucose value ≥ 155 mg/dl at baseline. All 8 (4.8%) cases of T2DM diagnosed at 12 months postpartum occurred in the high risk group (glycemia ≥ 155 mg/dl), compared to none in the < 155 mg/dl group ($P = 0.029$). Additionally, any form of prediabetes or T2DM was significantly more prevalent in the high risk group compared to those with lower values [65/106 (61.3%) vs. 26/60 (43.8%), $P = 0.025$]. At 12 months, 21 women had a 1-hour value ≥ 209 mg/dl, of whom only 5 were diagnosed with T2DM based on the 2-hour value on the OGTT according to the ADA guidelines.
Conclusion
In this high-risk cohort of women with a recent history of GDM, a 1-hour glucose value ≥ 155 mg/dl during early postpartum OGTT predicted all cases of T2DM diagnosed at 12 months postpartum and identified more women with T2DM at 1 year postpartum compared to the 2h glucose value on the OGTT. These findings support the use of the 1-hour post-load glucose measurement as a valuable early marker for identifying women at increased metabolic risk after a recent history of GDM.
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Keywords
Gestational diabetes, diabetes, risk prediction, oral glucose test, postpartum
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010

GLP-1 receptor agonists for weight loss in adults without diabetes: perspectives from primary care

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Introduction
The incidence of obesity is growing worldwide. Although lifestyle interventions form the cornerstone of treatment, their effectiveness and sustainability are often limited. In recent years, there has been growing interest in the use of glucagon-like peptide 1 receptor agonists (GLP1-RAs) for weight loss, since their effectiveness and safety are now well-established. Although general practitioners (GPs) are increasingly receiving questions about these medications, uniform guidelines on their use in primary care are lacking. Moreover, differences exist between guideline-based indications and reimbursement criteria, which may form an additional barrier. In this context, the present study aimed to investigate the experiences and perspectives of Flemish GPs regarding the use of GLP1-RAs for overweight and obesity in primary care.
Methods
We developed an online questionnaire using the Qualtrics platform. The survey was distributed to Flemish GPs between August 20, 2024 and December 29, 2024 and was anonymously filled in by 102 GPs. The results were descriptively analyzed, and statistical tests were performed using SPSS to explore associations between certain variables.
Results
Whereas a majority (96%) of Flemish GPs are willing to manage follow-up for patients on GLP-1 agonists, only one-third are comfortable initiating treatment. While some GPs see potential in these agents for preventing weight-related comorbidities or as a bridge to bariatric surgery, hesitations persist. Concerns include long-term safety and effectiveness, cost, limited availability, and the risk of undermining lifestyle changes. Some physicians also report feeling pressured by patients to prescribe these medications.
Conclusion
GLP-1 receptor agonists may be integrated into a multimodal strategy for treating overweight and obesity, when they are combined with lifestyle changes. Many GPs emphasized the importance of lifestyle interventions, even when prescribing GLP-1 agents. Future efforts should focus on a multidisciplinary approach that supports this treatment model from various perspectives, while also considering financial implications for the patients. The diversity of opinions among GPs underlines the need for clear, evidence-based guidelines in primary care, particularly regarding indications. These guidelines should be regularly updated because of rapid developments in this field.
Keywords
GLP-1 receptor agonists, weight loss, obesity, primary health care
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011

Evaluation of predictive clinical and biological factors for weight reduction and metabolic improvement following remission of Cushing's syndrome

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Introduction
Cushing's syndrome (CS) is a rare endocrine disorder caused by chronic exposure to excess gluco - corticoids. Despite surgical remission, cardiometabolic comorbidities frequently persist. Identifying clinical and biological predictors of weight loss and metabolic improvement after remission may help personalize follow-up.
Methods
This retrospective longitudinal study included 85 adult patients with CS in remission for at least one year after surgery. Anthropometric and cardiometabolic comorbidities (type 2 diabetes [T2D], hypertension, dyslipidaemia) were assessed before the onset of symptoms, at diagnosis, and at 12, 24 and 60 months post-remission. Outcomes and potential predictors of weight loss and cardiometabolic improvement were analysed using statistical comparisons and logistic regression models.
Results
At diagnosis, 44% of patients had obesity, 33% had T2D, 67% had hypertension and 82% had dyslipidemia. One year after remission, mean body weight was significantly decreased (-8,5%, $P < 0{,}001$), as did the prevalence of hypertension (-21%, $P < 0{,}001$) and T2D (-13%, $P < 0{,}001$), while the frequency of dyslipidemia remained unchanged. Greater weight gain before diagnosis was correlated with greater weight loss after remission ($r = 0{,}41$, $P = 0{,}003$). However, no disease characteristics (aetiology, duration or severity of hypercorticism) and no clinical or biological factors independently predicted weight loss or metabolic comorbidity remission.
Conclusion
Remission of CS leads to a significant but partial and highly variable improvement in overweight and cardiometabolic comorbidities. Factors explaining this unpredictable outcome remain however elusive. Nevertheless, our findings highlight the persistent impact of previous chronic hypercortisolism on the metabolic status and the importance of personalized and long-term care in this population.
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Keywords
Cushing's syndrome, weight loss, metabolic comorbidities, predictive factors
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012

Relationship between macrovascular complications and time in range in adults with type 1 diabetes

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Introduction
People with T1D have greater cardiovascular mortality and morbidity compared to healthy individuals (1). Since the advent of continuous glucose monitoring (CGM), new data ("glucometrics") have been introduced such as time in range (TIR: 70 –180 mg/dl) and time in tight range (TITR: 70 –140 mg/dl), changing the standard of care in diabetes management (2). We examined an association between TIR and macrovascular complications (MACE).
Methods
Data from adults with T1D who were using CGM (MDI or pump) were analyzed over a 5-year period. Macrovascular complications were present if one of the following was documented: coronary heart disease (ischemic heart damage detected in cardiologic work-up or symptomatic AMI), the need for a revascularization procedure, cerebrovascular events including TIA (transient ischemic attack) and stroke (CVA) and the presence of peripheral arterial disease.
Results
We included 147 adults with T1D (51.7% were male) with a mean age of 46 } 16 years, mean diabetes duration of 28 $\pm$ 14 years. Mean BMI was 24.9 $\pm$ 3.9 kg/m^2. This cohort had a median HbA1c of 7.5 (6.9–8.1) %, a TIR of 49 $\pm$ 15% and TITR of 34 $\pm$ 11%. At the five-year time point, HbA1c decreased to 7.1 (6.5–7.6, $P < 0.001$) %, TIR increased to 63 $\pm$ 16% ($P < 0.001$) and TITR to 41 $\pm$ 14% ($P = 0.005$). 15 acute coronary events were recorded, 6 of which were symptomatic and 9 asymptomatic. 3 people died of non-cardiovascular causes. No cardiovascular mortality was reported. 6 cerebrovascular events occurred (3 TIAs,3 CVAs) and 14 people had peripheral arterial disease of whom one underwent surgical intervention. Patients who experienced MACE were more likely to report a familial history ($P = 0.016$), had a higher chance of taking antihypertensive medication at start of the study (34.8 vs 65.2%, $P = 0.003$) or at 60 months (39.5 vs 63.6%, $P = 0.036$) or lipid lowering medication at start (30.4 vs 65.2%, $P = 0.004$). No statistically significant differences between groups were reported concerning HbA1c or TIR. Family history of a major cardiovascular event and use of antihypertensive medication at start of the study were independently associated with macrovascular complications as identified using logistic regression analysis. This was the case in the model using HbA1c as well as in the model using TIR.
Conclusion
In this small study cohort, no association was found between TIR and macrovascular complications. Family history of cardiovascular events and use of antihypertensive medication were found to be independently associated with the presence of MACE.
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Keywords
Type 1 diabetes, continuous glucose monitoring, macrovascular complications, time in range
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013

Directly measured free testosterone may better predict sexual symptoms of hypogonadism than calculated approximations

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Introduction
Several clinical guidelines suggest assessment of serum free testosterone (FT) for diagnosis of hypo - gonadism in men. Mathematical approximations of FT (cFT) are most used. However, direct measurement of FT (mFT) using equilibrium dialysis followed by mass spectrometry (ED LC-MS/MS) is considered the gold-standard. We evaluated whether low mFT or low cFT are differentially associated with sexual symptoms of hypogonadism.
Methods
Serum samples were selected of 525 men aged 55 to 85 years participating in the EMAS study (1). Total T and SHBG levels were measured using LC-MS/MS and immunoassay, respectively. FT levels were calculated using the Vermeulen formula and measured using ED LC-MS/MS. Sexual symptoms of hypogonadism were assessed using the EMAS Sexual Function Questionnaire. The cFT threshold was placed at 220 pmol/l (2). The mFT threshold was placed at 190 nmol/l, based on the lower reference for healthy adult men aged 18-39. Logistic regression was used to determine altered probabilities of symptoms compared to the group with normal FT levels.
Results
Participants were divided in four groups: normal mFT/normal cFT ($n = 242$), normal mFT/low cFT ($n = 13$), low mFT/normal cFT ($n = 128$) and low mFT/low cFT ($n = 142$). The low mFT/normal cFT and low mFT/low cFT groups had an increased risk of insufficient erections (OR: 2.2 and 2.9), less frequent sexual thoughts (OR: 1.9 and 2.5) and lower sexual desire (OR: 2.2 and 2.2).
Conclusion
The low mFT groups had increased odds of sexual symptoms, even with normal cFT levels. As such, mFT levels may be more accurate to assess androgen exposure than cFT levels.
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Keywords
Male hypogonadism, free testosterone, sexual function
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014

One-year effectiveness and safety in young children aged 2-6 years with type 1 diabetes using an advanced hybrid closed-loop system: a real-world prospective cohort study

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Purpose of the study
The MiniMed™ 780G is currently not approved for use in children with type 1 diabetes (T1D) under seven years of age. This prospective study aims to complement recent findings from the LENNY randomized controlled trial by evaluating one-year changes in glycemic management, parent-reported outcomes and safety following initiation of the MiniMed™ 780G in children aged 2-6 years with T1D in real-world clinical practice.
Methods
Children aged 2-6 years whose parents agreed to initiate the MiniMed™ 780G were enrolled at 15 Belgian centers between October 2022 and December 2023. Data were collected quarterly over one year during routine follow-up. Parent-reported outcomes were assessed using questionnaires (HAPPID and Hypoglycemia Fear Survey [HFS] – Parent). Data are reported as mean ± SD or least-squares mean (95% CI).
Results
A total of 149 children were included (mean age 4.2 ± 1.4 years; 56.4% girls). At start, mean T1D duration was 22.0 ± 13.0 months and 75.2% used an insulin pump. After one year, time in range (70-180 mg/dl) increased from 56.8% (54.4-59.2) to 66.6% (64.7-68.5) and HbA1c decreased from 7.6% (7.4-7.8) to 7.2% (7.1-7.4) (all $P < 0.001$). Time <70 mg/dl remained stable (5.0% [4.2-5.8] at start vs 4.6% [3.9-5.3] at 12 months, $P = 0.172$). Parents reported less diabetes-related burden on the HAPPI-D questionnaire (22.9 points [21.7-24.0] at start vs 21.7 points [20.5-22.8] at 12 months, $P = 0.001$), while scores on the HFS-Parent questionnaire did not change. There were no hospitalizations for severe hypoglycemic events and one hospitalization for diabetic ketoacidosis due to infusion set occlusion.
Conclusion
One year use of the MiniMed™ 780G in children with T1D aged 2-6 years was safe and associated with improved glycemic management and reduced burden on parents, with limited impact on hypoglycemia and related parental fear. These results underscore the need to expand regulatory approval and access to hybrid closed-loop technology for this population.

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015

Role of steroid hormone-binding proteins on the bioactivity of 11-oxygenated androgens

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Introduction
Recently, 11-oxygenated androgens (11OA), particularly 11-ketotestosterone (11KT), have emerged as contributors to the bioactive androgen pool. However, unlike classic androgens testosterone (T) and dihydrotestosterone (DHT), which bind to steroid hormone-binding proteins (sex hormone-binding globulin (SHBG), albumin), little is known about how these proteins interact with 11KT. Observational data from saliva (reflecting free hormone) and serum (reflecting total hormone) suggest that steroid hormone- binding proteins may influence 11KT bioavailability. We aimed to examine 11-ketotestosterone's (11KT) interaction with steroid hormone receptors and the effect of SHBG on its androgenic activity.
Methods
We used *in vitro* luciferase reporter assays to assess 11KT's ability to activate glucocorticoid (GR), mineralocorticoid (MR), progesterone (PR), and oestrogen receptors (ER) in HEK293T cells transiently coexpressing a specific receptor and a steroid receptor–inducible luciferase construct (Sri_Luc). Increasing concentrations of 11KT were added to the cell culture medium. To assess SHBG's impact on 11KT's androgenic activity, the cell culture medium of HEK293T cells stably expressing the androgen receptor (AR) and response element (ARE)-driven luciferase reporter was supplemented with a fixed concentration of 11KT (EC50 = 10-7 M) and varying SHBG concentrations (6–56 nM). The SHBG concentration range was designed to mimic both sub-physiological and physiological levels, reflecting typical values observed in healthy adult men (24–55 nM). Additionally, computational docking (AutoDock Vina) was used to model 11KT's fit in the SHBG DHT-binding pocket. The docking parameters include the coordinates of the SHBG residue that anchors DHT in its binding pocket.
Results
In addition to its strong androgenic activity, 11KT was found to activate Erα and ERβ, but only at concentrations more than 1,000-fold higher than oestradiol. However, 11KT did not activate GR, MR, or PRα. Interestingly, SHBG co-treatment did not reduce 11KT-induced luciferase activity, as luminescence remained stable even at higher SHBG concentrations. In contrast, T and DHT showed dose-dependent decreases in luminescence with SHBG addition. Exploratory *in silico* modelling suggests that 11KT may bind SHBG with relatively high affinity.
Conclusion
11KT is an AR agonist that can also activate ERα and ERβ, though only at supraphysiological concentrations. Our in vitro findings suggest that 11KT maintains its androgenic activity in the presence of SHBG. Albumin, which also binds classic androgens, may play a more prominent role in 11KT binding. Further experimental validation is needed to confirm these findings and investigate the in silico prediction of 11KT's relatively high SHBG binding affinity.
Keywords
Steroid hormone-binding proteins, 11-oxygenated androgens, free hormone hypothesis, androgen bioactivity, steroid hormone receptors
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016

Graves' orbitopathy: burden of the disease in the belgian patient population

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Introduction
Graves' orbitopathy (GO) is a potentially disfiguring and sight-threatening autoimmune condition that affects 25% to 50% of individuals with Graves' thyroid disease. Patients often experience disfiguring symptoms which diminish their health-related quality of life. The objective is to investigate in Belgium quality of life in patients with active GO, compared with patients with Graves' thyroid disease (GD) only and healthy controls.
Methods
At Ghent University Hospital, we included 34 patients with active GO (CAS ≥ 3), 32 patients with GD only and 39 sex- and age- matched healthy controls. Participants completed a survey consisting of demographic questions, medical outcomes, the 21-question version of the Depression Anxiety Stress Scale (DASS21); Study 36-items Form Health Survey (SF-36) and the Illness Cognition Questionnaire.

Results
Both GO an GD group demonstrate a significant *mental health burden* compared to controls. On measures of anxiety, stress, emotional well-being, and social functioning, both GO and GD reported significantly poorer outcomes than the control group. There was no significant difference between the GO and GD group, suggesting the psychological impact is linked to having GD itself, rather than the complication of orbitopathy. The *physical burden* of the disease appears to be primarily driven by the presence of orbitopathy. Only the GO group reported significantly worse outcomes for energy/fatigue and limitations due to physical health, compared to the normal controls. GD did not show a significant difference from controls on these physical measures. Comparison between the two patient groups using the *Illness Cognition Questionnaire* scale showed that the GO group reported significantly higher levels of helplessness, which reflects the more complex and visually prominent nature of their condition.
Conclusion
Having GD delivers a high psychological impact. The physical implications and helplessness are significantly linked to the presence of GO.
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Keywords
Belgian patient, burden of disease, Graves' orbitopathy, Graves' thyroid disease
DOI: 10.1530/endoabs.112.016

017

Discrepancy between haemoglobine A1c and continuous glucose monitoring derived glucose management indicator and its link to microvascular complications in type 1 diabetes

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Introduction
Haemoglobin A1c (HbA1c) is the gold standard for evaluating glycaemic control in people with diabetes (1). In recent years continuous glucose monitoring (CGM) has introduced new parameters, including glucose management index (GMI), a calculation based on mean glucose that provides an estimation of HbA1c (2-4). However, in some patients GMI and HbA1c differ significantly (2, 5-9). The aim of this study is to investigate whether a difference between HbA1c and GMI, expressed as haemoglobin glycation index (HGI), has an impact on the prevalence of microvascular complications in people with type 1 diabetes mellitus.
Methods
This retrospective, cross-sectional study included adults with type 1 diabetes using CGM. Exclusion criteria included pregnancy, dialysis or insufficient sensor use ($<$70% over 28 days). The presence of microvascular complications was compared across HGI subgroups (low $\leq$-0.5%, moderate -0.5% to 0.5%, high $\geq$0.5%). Logistic regression analyses evaluated the independent association between HGI and microvascular complications.
Results
Three hundred sixty-nine adults (57.7% men, median diabetes duration 27.7 years) were included. The median HbA1c was 7.1% (6.5-7.6), GMI was 7.1% (6.7-7.5), and HGI was -0.10% (-0.47 to 0.26). In 144 participants (39%), the absolute difference between HbA1c and the GMI was $\geq$0.5%, and in 31 individuals (8.4%) the difference was even $\geq$1% (Figure 1). Eighty-five participants (23%) had a low HGI and 59 (16%) had a high HGI. Compared to low HGI high HGI was associated with significantly higher rates of nephropathy (4% vs 19%, $P = 0.016$), neuropathy (6% vs 20%, $P = 0.011$) and severe retinopathy (15% vs 33%, $P = 0.026$, figure 2). Logistic regression showed that high HGI was associated with nephropathy (OR 2.23), neuropathy (OR 3.15), and severe retinopathy (OR 2.26). However, after adjusting for co-variates (diabetes duration, smoking, hypertension) the associations lost significance.
Conclusion
This study demonstrates that a high HGI based on CGM data may serve as a valuable parameter in daily clinical practice for identifying individuals at higher risk of microvascular complications. These results strengthen the rationale for prospective studies to confirm the clinical relevance of HGI and to further define its role in complication risk stratification.

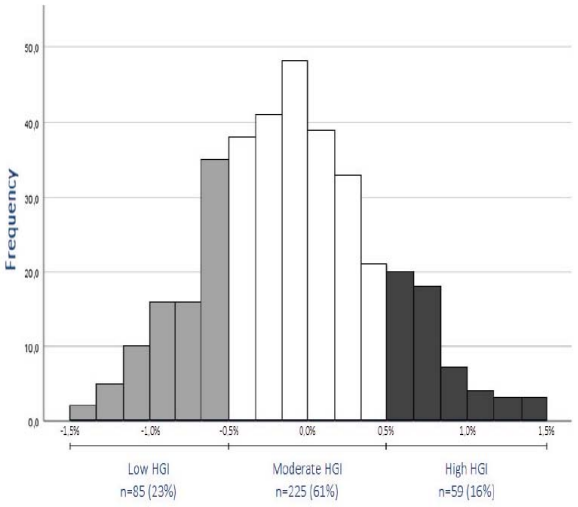

Figure 1: Discrepancy between HbA1c and GMI

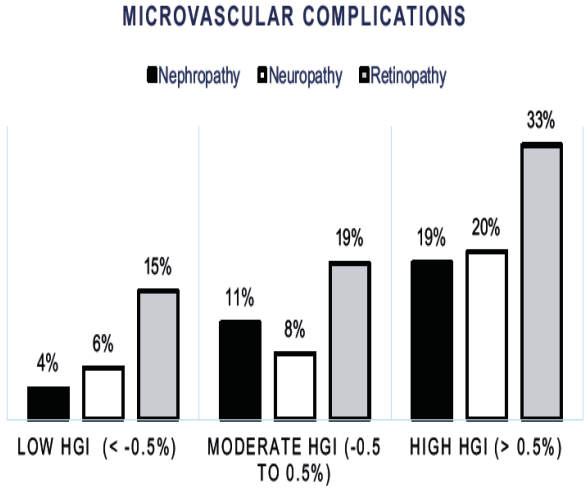

Figure 2: Microvascular complications as function of different HGI groups

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Keywords
Microvascular complications, type 1 diabetes, CGM, HbA1c, HGI
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018

Vascularization of islet organoids derived from human pluripotent stem cells

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Introduction
Stem cell-derived βcells are currently in phase 3 cell therapy trials in people with type 1 diabetes. Human induced pluripotent stem cells (iPSC) represent an inexhaustible source of functional islet cells. Generation of iPSC from a patient eliminates the problem of allogeneic rejection and allows grafts to be engineered prior to transplantation to stimulate vascularization, glucose sensing and insulin release, ultimately promoting graft survival. This unique model allows to create new organoids composed of different cells designed to form a niche. Beyond the supply of oxygen and nutrients, intra-islet endothelial cells (EC) and secreted components of the extracellular matrix form a niche necessary for the correct function of βcells and adaptation to their environment. We therefore generated "vascularized" islet organoids containing EC and endocrine cells derived from the same human iPSC, ensuring genetic concordance. The impact of EC on the maturation, self-organization and function of endocrine cells was assessed *in vitro*.
Methods
Our laboratory has implemented a 7-step protocol to generate functional islet-like aggregates from iPSC on a large scale. Following our coculture strategy, we generated functional iPSC-derived EC and islets from the same iPSC line to generate isogenic endothelial-endocrine organoids. The two cell types were characterized independently and then in coculture in terms of identity and function by immunostaining, RT-qPCR and dynamic insulin secretion in response to glucose.
Results
Our iPSC-derived EC and islets showed the expression of specific markers, both at the gene (*VEGFR1/2, CD144 and PDX1, NKX6.1, MAFA*, respectively) and protein level (CD31, von Willebrand factor, vimentinand insulin, glucagon, somatostatin, respectively). Oxidized-low density lipoprotein incorporation assaysconfirmed the functional maturity of iPSC-EC. We incorporated highly differentiated iPSC-EC at the endof the 7-step endocrine differentiation. Kinetic monitoring of the morphology of the organoids showedaggregates with endothelial characteristics (migration, assembly). Two distinct cell populations wereobserved in the vascularized condition, with larger and smaller clusters. No changes in endocrine geneexpression were observed at 1 and 2 weeks, but the expression of endothelial markers declined progressivelyto low levels after 2 weeks of coculture. Dynamic glucose-stimulated insulin secretion studiesshowed a similar secretory profile (stimulation index: vascularized 2.53 vs control 2.54) but reduced insulincontent in the vascularized condition compared with control.
Conclusion
We have succeeded in generating functional EC and islets from the same iPSC line and established coculture that durably preserves insulin secretion. To counteract the gradual disappearance of EC, we will establish a new culture method involving the progressive mixing of endocrine and endothelial media to improve EC survival. The human "vascularized" islet organoids will be tested in a preclinical *in vivo* model by transplantation into mice. Ultimately, these strategies will advance iPSC-islet replacement therapies in type 1 diabetes.
Keywords
iPSC, βcells, endothelial cells, vascularized organoids, large scale.
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019

Levothyroxine use in belgium in 2003-2020: a longitudinal population-level registry-based cohort analysis

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Background and objectives
Levothyroxine (LT4) is among the most frequently used medications in the Western world. In Belgium, where health insurance is mandatory, 5.85% of the population was prescribed LT4 in 2023, raising concerns regarding overdiagnosis and overtreatment. (1) We investigated prevalence and incidence of LT4 use in relation to TSH screening intensity, treatment threshold, and risks of over-treatment.
Methods
Retrospective registry-based cohort analysis from 2003 to 2020, based on aggregated data from the largest Belgian health insurance provider, representing 42% of the Belgian population (around 4.5 million individuals).
Results
Prevalence of LT4 use steadily increased from 2.59% in 2003 to 5.29% in 2020 (slope over time +0.153; $P < 0.0001$), whereas incidence of LT4 use was stable around 0.40%/year (slope +0.003; $P = 0.0628$) (adjusted for age category, sex, region, and socioeconomic status). In the 80+ age category, prevalence rose from 5.36% in 2003 to 11.63% in 2020 (slope +0.418; $P < 0.0001$), but incidence decreased from 0.70%/year to 0.53%/year (slope -0.005; $P = 0.046$). Among non-LT4 users, the proportion with high TSH testing rate ($\geq$1 TSH test/year) steadily rose from 26.05% to 38.53% over time. Prescription (first and following) of exclusively the lowest dose (25 µg) rose from 8.33% to 19.83%. Incidence of thyroid surgery was stable at around 0.05%/year. First-time LT4 use was associated with high TSH testing rate in the preceding year (Rho 0.86; $P < 0.0001$), prescription of exclusively the lowest dose (Rho 0.736; $P = 0.0007$), and incidence of thyroid surgery (Rho 0.552; $P = 0.0252$). Among LT4 starters, a low subsequent TSH testing rate ($\leq$1 TSH test within two years after start) was present in 16.52% in 2003 and 14.19% in 2018. The proportion of low TSH testing rate was negatively associated with the calendar year (Rho -0.915; $P < 0.0001$). Compared to non-LT4 users, those using LT4 for $\geq$2 years had a higher risk of subsequent initiation of antiarrhythmic (RR 1.113; $P = 0.0284$) and antiresorptive drugs (RR 1.129; $P = 0.0305$), but a lower mortality risk (RR 0.885; $P = 0.0082$). Additionally, we found a higher risk of statin use (RR 1.483; $P < 0.0001$), flu vaccination (RR 1.273; $P < 0.0001$), and $\geq$2 GP visits/year (RR 1.165; $P < 0.0001$).
Conclusion
These findings suggest that increased LT4 use may partially be attributed to increased detection (TSH testing rate) of subclinical hypothyroidism (prescription of only the lowest LT4 dose), and highlight the need for better TSH monitoring after starting LT4. Whether the higher use of antiarrhythmic and antiresorptive medications in LT4 users is causally related or explained by other factors, such as more intensive medical follow-up, needs to be further explored on a subject-level basis.
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Keywords
Levothyroxine, prevalence, subclinical hypothyroidism
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020

The use of rapid on-site evaluation during thyroid fine needle aspiration might help improve samples representativity

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Introduction
Thyroid fine needle aspiration (FNA) is routinely performed in thyroid nodular disease. It provides precious information about nodules' cellular constitution and can help therapeutic management, notably through the use of Bethesda classification. Unfortunately, this test encounters a significant number of non-diagnostic (class I) results, which leads to uncertainty in providing the most appropriate support and potentially increasing patients' anxiety. In our study, we

were interested in appreciating the improvement of sample quality by checking the cellular content during FNA with the help of a microscope and using rapid on-site evaluation (ROSE) directly in the consultation room.

Design and methods

We conducted a retrospective study on 297 (69 males, 228 females; mean ages 54 and 55 respectively) fine needle aspirations, made between 2017 and 2024. Ultrasound appearance according to EU-TIRADS classification were respectively 131 EU-TIRADS 3 (44%), 68 EU-TIRADS 4 (23%), and 98 EU-TIRADS-5 (33%). In group A (ROSE, 67 patients), FNA was performed by the same operator (Operator A), spreading out a drop of the sample over a microscope slide. Samples were coloured using Diff-Quick method, and cellularity was evaluated under a microscope. If the cellularity was insufficient, another aspiration was made. Group B (230 patients) comprises cases of FNA performed without microscopic quality-control by operator A and others.

Results

9 samples were classified as non-diagnostic in group A (13%) against 118 in group B (51%), $P < 0{,}0001$. Looking at the samples taken by operator A ($n = 146$), ROSE procedure was performed in 67 cases whereas standard FNA procedure was used in 79 cases. 9 needle aspirations were classified as nondiagnostic in the first subgroup (13%) against 31 (39%) in the second one. $P < 0{,}0001$. The proportion of different EU-TIRADS nodules in groups A and B was not significantly different.

Conclusion

Our study suggests the use of microscope and ROSE during FNA might improve the yield of fine needle aspiration by reducing the number of non-diagnostic samples. This method would help reduce the overall number of repeated biopsy sessions and allow the practician to offer a more refined exploration of thyroid nodular disease.

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Keywords

Fine needle aspiration, rapid on-site evaluation, Bethesda classification

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021

HbA1c-GMI relative gap as emerging risk factor for early onset retinopathy in type 1 diabetes

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Introduction

To evaluate the phenotype of individuals with type 1 diabetes wearing Continuous Glucose Monitoring (CGM), identified as hyperglycators based on discrepancy between haemoglobin A1c (HbA1c) and Glucose Management Indicator (GMI). The primary outcome was to determine whether hyperglycators are at higher risk of diabetic retinopathy (DR) compared to individuals whose GMI is concordant or lower than HbA1c. The secondary outcome aimed at identifying factors associated with hyperglycation.

Methods

This retrospective study investigated 411 CGM-wearing patients with type 1 diabetes as regards HbA1c-GMI and cardiometabolic phenotype, including micro- and macroangiopathies, with longitudinal followup for onset of DR. Patients, with underlying conditions altering red blood cell lifespan, were excluded. We hypothesized that defining hyperglycation as relative HbA1c-GMI difference ($\Delta_{HbA1c\text{-}GMI}$) was appropriate, given heteroskedasticity between HbA1c and GMI (White test $P < 0.001$). A Delphi panel established a $\Delta_{HbA1c\text{-}GMI}$ of $\pm 5\%$ as clinically relevant, thus defining hyperglycation as an HbA1c value $\geq 5\%$ above the corresponding GMI figure. Patients were categorized into 3 groups according to $\Delta_{HbA1c\text{-}GMI}$ ($\geq 5\%$; hyperglycator, < 5 & $> -5\%$; normoglycator, $\leq -5\%$; hypoglycator) of equivalent periods.

Results

143 patients (35%) were hyperglycators. Hyperglycation was associated with higher odds of new-onset DR over the retrospective study period (adjusted Cox hazard ratio 1.78). On average, retinopathy was diagnosed 6 and 7 years earlier in hyperglycators compared to hypoglycators and normoglycators, respectively. Current smoking, and non-HDL-C were associated with hyperglycation (adjusted OR 2.41 and 1.01, respectively). Association of hyperglycation approached statistical significance with metformin use, red blood cell distribution width coefficient of variation, and reduced glomerular filtration rate. Using an absolute difference of 0.4% yielded similar results, equally classifying absolute hyperglycators at higher microvascular risk.

Conclusion

An HbA1c value $\geq 5\%$ greater than matching GMI is associated with earlier onset DR among patients with type 1 diabetes. Current smoking and non-HDL-C were significantly associated with hyperglycation.

Keywords

Type 1 diabetes, hyperglycation, glycation gap, HbA1c-GMI discordance, retinopathy

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Clinical Case Reports

022

Malignant hypertension and pseudohyperaldosteronism associated with rifampicin therapy

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Introduction
Rifampicin is a widely prescribed antibiotic primarily used in the treatment of tuberculosis and other serious infections. Arterial hypertension destabilisation during rifampicin therapy is frequent but remains under-recognised, despite the drug's widespread and prolonged use. Rifampicin is well known for its potent induction of cytochrome P450 (CYP) enzymes, which leads to significant pharmacokinetic interactions with various drugs, including antihypertensives. However, beyond these pharmacokinetic interactions, rifampicin might induce hypertensive effects by other mechanisms.
Case presentation
A 64-year-old woman with a 10-year history of reasonably controlled arterial hypertension, was hospitalized for spondylodiscitis and treated with rifampicin. Soon, severe grade III hypertension emerged despite maximal doses of five antihypertensive drugs, alongside worsening hypokalemia despite supplementation. Extensive workup excluded secondary causes of arterial hypertension, revealed suppressed renin and aldosterone with increased kaliuria, and showed elevated serum free cortisol and ACTH. Adjustments of antihypertensive treatment for rifampicin's drug interactions failed to improve blood pressure control. Rifampicin was discontinued after six weeks, resulting in gradual normalization of blood pressure, potassium levels, and endocrine markers.
Discussion
Rifampicin induces CYP3A4, which lowers the potency of many antihypertensives. However, in this case, the use of drugs that demonstrate minimal or no interaction with rifampicin fails to control blood pressure, suggesting the existence of other mechanisms leading to arterial hypertension destabilisation. Our patient developed pseudohyperaldosteronism associated with rifampicin therapy. This could be mediated by accelerated cortisol metabolism by CYP3A4, which increases ACTH-driven corticosterone with mineralocorticoid effects. Rifampicin is also an agonist of the pregnane X receptor, an emerging receptor with hypertensive effects.
Conclusion
This case highlights rifampicin as a cause of severe hypertension. This effect is mainly, but not exclusively, linked to pharmacokinetic drug interactions. Rifampicin-driven pseudohyperaldosteronism and pregnane X receptor agonisation may also be involved.
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Keywords
Malignant hypertension, Rifampicin, Cytochrome P450, Pseudohyperaldosteronism, Pregnane X receptor
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023

Severe hypocalcemia due to osteoblastic bone metastases in a patient with hypoparathyroidism: a case report

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Objectives
Bone metastases in breast cancer are typically osteolytic but can rarely be osteoblastic. While malignancy-related hypercalcemia is well-known, malignancy-related hypocalcemia is rare and often multifactorial.
Case presentation
We present a case of a 48-year-old woman with metastatic breast cancer who developed severe hypocalcemia due to a combination of expanding osteoblastic bone metastases and hypopara - thyroidism after total thyroidectomy. Despite oral and intravenous calcium supplementation, adequate calcium levels were not achieved until the patient responded to systemic therapy with Trastuzumab Deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate.
Conclusion
This case underscores the challenges in finding the cause of and managing hypocalcemia in patients with complex oncological histories and emphasizes the need for close calcium monitoring in patients with bone metastases, particularly those with additional risk factors such as hypoparathyroidism or treatment with anti-resorptive drugs.
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Keywords
Breast cancer, hypocalcemia, hypoparathyroidism, osteoblastic metastases
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024

Macroprolactinoma revealed by progressive vision loss at the end of pregnancy

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Introduction
During pregnancy, macroprolactinomas may grow to become symptomatic in 30% of cases (1). This has been reported in women diagnosed with prolactinoma before the onset of pregnancy. We report a rare case of a woman presenting with vision loss due to a previously undiagnosed compressive macroprolactinoma at the end of pregnancy.
Case report
A 31-year-old woman, at 35 weeks and 5 days of gestation, was referred for progressive visual loss in the left eye evolving over 4 months, with rapid worsening during the two weeks prior to presentation. Ophthalmologic assessment revealed a compressive optic neuropathy with visual acuity decreasing from 6/10 to 1/10 in two weeks on the left side. Optical coherence tomography showed no papillary atrophy, indicating a recent and potentially reversible visual loss. Pituitary MRI demonstrated a pituitary macroadenoma measuring 15×20×21 mm with an internal cystic component of 11×15×18 mm, compressing the optic chiasm. Serum prolactin was 368 µg/l, with normal thyroid and cortisol axes. The patient had no prior history of hyperprolactinemia. This was her third pregnancy, following two previous deliveries by cesarian section. After multidisciplinary discussions, a cesarean section (CS) was performed at 36 weeks and one day of gestation to safely deliver the baby and to prepare the mother for transsphenoidal decompression. At the same time, we started cabergoline 0.25 mg/day in an attempt to decrease the size of the adenoma and normal pituitary gland. Because no visual improvement was noted four days after CS and cabergoline initiation, a trans-sphenoidal resection of the tumor was performed. Histopathological examination showed a prolactin-secreting pituitary adenoma, PIT-1 positive, with a Ki-67 proliferation index of 6% and p53 positivity. Visual acuity improved markedly immediately after surgery. Two months post-surgery, serum prolactin had normalized to 14.3 µg/l without cabergoline and no pituitary hormone deficit was noted. Ophthalmological follow-up confirmed normalization of visual fields. Given the elevated proliferative index observed histologically, long-term follow-up is warranted to monitor for potential recurrence.
Conclusion
This case highlights the symptomatic enlargement of a previously undiagnosed prolactinoma during the third trimester leading to severe optic chiasm compression. Neurosurgical decompression was performed after cesarian section because of the advanced gestational age and in order to minimize maternal complications.

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Keywords
Macroprolactinoma, pregnancy, optic chiasm, neurosurgery
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025

Severe hyperglycemia induced by enfortumab vedotin: a case report

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Introduction
Guidelines recommend enfortumab vedotin as therapy for patients with locally advanced or metastatic urothelial cell carcinoma (UCC) combined with pembrolizumab in first line or as monotherapy in third line. Enfortumab vedotin is an antibody drug conjugate (ADC) directed against nectin-4, a transmembrane protein highly expressed in malignant urothelial cells.
Case description
A 62-year-old man, known with a locally advanced UCC and obesity (BMI 36.2 kg/m^2), was hospitalised with complaints of vomiting and diarrhoea. We report severe hyperglycemia after two administrations of enfortumab vedotin, requiring up to 600 units of intravenous insulin per day. The course was complicated with acute renal failure and development of circulatory shock, with suspicion of septic shock. The patient died on day 4 after initiation of palliative sedation.
Discussion
Literature review revealed 16 case reports of enfortumab vedotin – associated hyperglycemia. The underlying mechanism is severe insulin resistance, as evidenced by massive insulin requirement, hypertriglyceridemia, increased C-peptide and negative diabetes autoantibodies. Vedotin (monomethyl auristatin E, MMAE) is suspected to be the causal agent as the complication was also observed with other ADC with MMAE as payload. The mortality rate is high, but the complication is reversible if the patient can clear the medication.
Conclusion
Hyperglycemia as a side effect of enfortumab vedotin occurs frequently, with the possibility of rapid deterioration to refractory diabetic ketoacidosis based on severe insulin resistance. Patients with known risk factors such as obesity or increased hemoglobin A1c should be closely monitored. The treatment requires aggressive escalation in insulin therapy, sometimes necessitating more than 1000 units of insulin per day. Continuous hemodialysis may play a role by exogenously removing MMAE. Additional studies are needed to better understand the pathophysiology of insulin resistance and to safely support treatment with enfortumab vedotin.

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Keywords
Enfortumab vedotin, hyperglycemia, diabetic ketoacidosis
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026

Endoscopic ultrasound-guided trans-gastric radiofrequency ablation: an effective and safe alternative treatment for left-sided unilateral aldosterone-producing adenoma

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Introduction
Unilateral aldosterone-producing adenoma (APAs) represents a potentially curable cause of hyper - tension through laparoscopic adrenalectomy. However, surgical intervention may not be suitable for all patients, particularly those with significant comorbidities or a preference for less invasive management. Endoscopic ultrasound (US)-guided trans-gastric (TG) radiofrequency ablation (RFA) offers a minimally invasive alternative to treat left-sided APAs which are in close proximity with the stomach. This new approach was successfully performed in our center.
Case report
A 35-year-old woman with a history of familial adenomatous polyposis syndrome and previous total colectomy was referred for assessment of hypertension associated with severe hypokalemia at 2.14 mmol/l. Biochemical evaluation confirmed primary aldosteronism with high plasma aldosterone (47.1ng/dl; nl < 14), suppressed renin concentration (0.8 mU/l; nl>4.0) and a high aldosterone-to-renin ratio of 58.9 (nl < 2.4). Abdominal CT-scan imaging showed bilateral adrenal nodules (left: 23 x 16 mm and right: 17 x 12 mm), both evoking benign adenomas. Adrenal vein sampling showed a clear lateralization ratio (10.0) of aldosterone secretion from the left side. As the patient expressed a clear desire for a minimally invasive curative treatment with preservation of left adrenal tissue, endoscopic US-TG-RFA was considered after informed consent. After a medical preparation with spironolactone 50 mg/day and an alpha-blocker (terazosin 2.5 mg twice daily for 2 weeks), the left adrenal nodule could be successfully ablated under light general anesthesia, using a 10 mm STARMed needle (Taewoong Medical, Seoul, South Korea) and generator set at 30 W.
Follow-up
No immediate complication was noted after the procedure and blood pressure and heart rate remained normal. Complete clinical remission of hypertension was achieved within one week, allowing discontinuation of spironolactone. After one month, the patient's blood pressure remained consistently below 104/84 mmHg without medication, and CT scan imaging showed a stable size of the left adrenal lesion with focal areas of necrosis but no evidence of delayed complication. Biochemical cure of PA was confirmed by normalization of kalemia (4.68 mmol/l), aldosterone (9.7 ng/dl) and renin concentrations (4.1 mU/l).
Conclusion
Endoscopic ultrasound-guided trans-gastric RFA is an effective and safe, minimally invasive, adrenalsparing alternative to surgery for patients with unilateral left-sided APA.
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Keywords
Radiofrequency ablation, left-sided aldosterone producing adenoma, primary hyperaldosteronism
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027

A case of steroid-resistant dysthyroid optic neuropathy treated with teprotumumab

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Introduction
The 2021 EUGOGO guidelines suggest first-line treatment for Dysthyroid Optic Neuropathy (DON) to consist of high-dose intravenous methylprednisolone treatment. However, this often needs to be combined with orbital decompression surgery. Here, we present a case of steroid-resistant DON treated with Teprotumumab in a subject who declined orbital decompression.
Methods
A 56-year old male treated for Graves hyperthyroidism with a standard block-replace regimen developed Thyroid Eye Disease (TED) three months after treatment initiation. His initial Clinical Activity Score (CAS) was 2 and progressed to 6 within that timeframe with associated papilledema of the right eye. Because no alternative aetiology of the papilledema was identified, this was considered part of the TED which was thus diagnosed as DON. Corticosteroid pulse therapy was administered twice without clinically significant response. In line with the current EUGOGO guidelines for DON, orbital decompression surgery was proposed but was declined by the patient. Alternative treatment with the anti-IGF-1R monoclonal antibody Teprotumumab was made available through early access program.
Results
Teprotumumab infusion resulted to improved vision and partial regression of the papilledema from the first dose. During subsequent treatments, his CAS decreased to 0, proptosis drastically improved and papilledema regressed completely. Thyroid-stimulating immunoglobulin level declined steadily during treatment but remained positive (TSI: 4.23 U/l; reference: < 1.75 U/l) about six weeks after the last dose of Teprotumumab. Baseline HbA1c was 5.3%, peaked at 6.1% and declined at 5.8% six weeks post-treatment without glucose lowering therapy other than lifestyle measures. The patient experienced transient tinnitus after the first dose of teprotumumab; control audiometry ruled-out treatment-related hearing impairment.
Conclusion
We describe a case of steroid-resistant TED with features of DON treated successfully with teprotumumab. This suggest that IGF-1R targeting therapy could be used as second-line therapy in steroid-resistant DON before considering surgery. Robust assessment of treatment-response and recurrence rate in randomized clinical trials is nonetheless needed.
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Keywords
Thyroid Eye Disease, Dysthyroid Optic Neuropathy, Teprotumumab
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028

A rare cause of glucosuria and aminoaciduria in a patient with well-controlled diabetes mellitus

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Introduction
Familial renal glucosuria (FRG) is a rare renal tubular disorder characterized by increased urinary glucose excretion despite normoglycemia (1). It is most commonly caused by pathogenic variants in the solute carrier family V member 2 (SLC5A2) gene (1-3). This gene encodes the sodium-glucose cotransporter 2 (SGLT2), crucial for glucose reabsorption (1,2).
Case presentation
We report the case of a 44-year-old male who was referred for unexplained glucosuria despite well-controlled diabetes mellitus (HbA1c 6,5%) with metformin and gliclazide therapy. His main complaints were nocturia and unintentional 5-kg weight loss in one year. A 24-hour urinary collection revealed overt glucosuria (23,3 g/1,73 m^2/24h), generalized aminoaciduria and increased uric acid excretion (fractional excretion 6,4%). Whole exome sequencing revealed a novel heterozygous c.469-1G>A likely pathogenic variant in the *SLC5A2* gene (NM_003041.4). A maturity-onset diabetes of the young type (MODY) gene panel showed no pathogenic variants in the hepatocyte nuclear factor-1A (HNF-1A; MODY3), nor in other MODY-associated genes. We assume that the association of glucosuria, aminoaciduria and hyper-uricosuria can be explained by the combination of diabetes and the likely pathogenic *SLC5A2* variant in this patient.
Conclusion
We describe a well-controlled diabetic patient with FRG, associated with a novel heterozygous c.469-1G > A likely pathogenic variant in the *SLC5A2* gene. Our case highlights the importance of considering renal tubular disorders in patients with unexplained glucosuria and diabetes mellitus, especially if the latter is well-controlled. FRG usually presents with glucosuria but may be associated with generalized aminoaciduria and hyperuricosuria. Genetic analysis should be considered in patients with young-onset diabetes and glucosuria, particularly with a positive familial history.
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Keywords
Glucosuria, SGLT2 mutation, diabetes
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029

Severe first-trimester thyrotoxicosis in pregnancy: an underlying Graves' disease triggered by hCG?

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Introduction
Hyperthyroidism during pregnancy is uncommon, with an incidence of 0.1% to 0.4%, and is most commonly due to Graves' disease. Human chorionic gonadotropin (hCG) can transiently stimulate the thyroid during early pregnancy. Differentiating between gestational transient thyrotoxicosis and Graves' disease is crucial due to differing management strategies and associated maternal-fetal risks. We present a case of severe first-trimester thyrotoxicosis, likely triggered by hCG in the context of underlying Graves' disease, successfully managed with short-term Lugol's iodine in early gestation.
Case presentation
We report the clinical course of a 25-year-old pregnant woman presenting at 11 weeks of amenorrhea with intractable vomiting and severe thyrotoxicosis. Laboratory evaluation, thyroid ultrasound, and postpartum Tc99m scintigraphy were performed. Treatment included propylthiouracil (PTU) and Lugol's iodine initiated during the first trimester, with regular biochemical monitoring throughout pregnancy.
Results
TSH was undetectable and FT4 was >90 pmol/l. TSI was mildly elevated (1.9 IU/l) and became negative by 15 weeks. FT4 decreased to 72 pmol/l within 48 hours of treatment. Lugol's iodine was discontinued at Day 6, and PTU was continued, leading to normalization of thyroid hormones and liver enzymes. Delivery at 39 weeks was uneventful. Postpartum scintigraphy supported the diagnosis of Graves' disease.
Conclusion
This case illustrates the importance of recognizing Graves' disease in early pregnancy and demonstrates that short-term Lugol's iodine may be a safe and effective adjunct in first-trimester management when rapid hormonal control is needed. Early diagnosis and timely intervention are key to reducing maternal and fetal complications. Close postpartum follow-up is essential to monitor for relapse.
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Keywords
Graves' disease, pregnancy, thyrotoxicosis, Lugol's iodine
DOI: 10.1530/endoabs.112.029

030

Diagnosis of familial dysalbuminemic hyperthyroxinemia in a family initially suspected of thyroid hormone resistance beta

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Introduction
Isolated elevation of serum free thyroxine (FT4) with normal thyroid-stimulating hormone (TSH) may indicate several conditions such as thyroid hormone resistance beta (THRβ), TSH-secreting pituitary adenoma, assay interference, or familial dysalbuminemic hyperthyroxinemia (FDH). We report a case of FDH in a mother and son, both initially misdiagnosed with familial THRβ.
Methods
Targeted genetic analysis of the thyroid hormone receptor beta (*THRB*) and albumin (ALB) genes was conducted using whole-exome and confirmatory Sanger sequencing. Variant classification was performed according to ACMG guidelines.
Case presentation
A 7-year-old boy was referred for suspected THRβ following detection of elevated FT4 (25pmol/l) with normal TSH (4.08mU/l) on a Roche immunoassay, during evaluation for attention deficit disorder. He displayed no signs of thyrotoxicosis. Serum sex hormone-binding globulin (SHBG) and thyroglobulin (TG) concentrations were within normal range, while free triiodothyronine (FT3) was slightly increased (7.2pmol/l). His mother had previously been diagnosed with THRβ, despite negative *THRB* gene analysis, after presenting at age 38 with palpitations and mild exophthalmos. Genetic testing of the THRB gene revealed no variant in the mother. However, both mother and son carried the ALB gene variant NM_000477.7:c.725G>A (p.Arg242His), confirming FDH. This variant is the most prevalent FDH-causal variant (hotspot) in Western Europe and is associated with a mild hyperthyroxinemia phenotype. It is a missense variant that increases thyroxine binding affinity due to substitution of the bulky arginine with histidine, leading to artifactual FT4 elevation in one-step immunoassays.
Conclusion
FDH should be considered in THRB-negative patients with isolated hyperthyroxinemia, particularly when FT3 is normal or only mildly elevated. ALB gene analysis is essential for accurate diagnosis. This case highlights the risk of misdiagnosis with the Roche Cobas e601 platform, which overestimates FT4 in FDH.
Keywords
Hyperthyroxinemia, familial dysalbuminemic hyperthyroxinemia, ALB gene, immunoassay interference, thyroid hormone resistance
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031

Discovery of a novel form of neonatal diabetes caused by TMEM167A mutations that impair pancreatic β cell function and survival

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Background and Aims
Understanding the genetic causes of monogenic forms of diabetes affecting pancreatic β cells is essential for accurate diagnosis and treatment of these rare diseases. Mutations in genes involved in endoplasmic reticulum (ER) stress or in ER-to-Golgi protein trafficking cause neonatal diabetes, microcephaly and epilepsy syndrome. The aim of this study was to identify novel genetic causes of neonatal diabetes and study the pathogenic mechanisms.
Material and Methods
We performed genome sequencing in 2 individuals with neonatal diabetes, microcephaly and epilepsy. Replication studies were performed using next generation sequencing in 284 patients diagnosed with diabetes <6 months without a known genetic cause; 7 also had microcephaly. We inserted by CRISPRCas9 the TMEM167A V59E mutation in human induced pluripotent stem cells (iPSCs) and differentiated the iPSCs into βcells. βcell development was evaluated by immunocytochemistry, and proinsulin ER-to-Golgi trafficking by the Retention Using Selective Hooks assay. Insulin secretion was evaluated in vitro and in Rag2-/- mice transplanted with human iPSC-β cells by measuring human C-peptide levels during intraperitoneal glucose tolerance tests. βcell

apoptosis was assessed by Hoechst 33342 and propidium iodide staining, and ER stress markers by qPCR.
Results
We identified homozygous rare coding TMEM167A mutations in 2 probands and in 4 additional individuals in replication studies. All 6 patients with biallelic TMEM167A mutations were diagnosed with neonatal diabetes (median age at diagnosis 34 days, range 1 day - 22 weeks) and were insulin-treated from diagnosis (median insulin dose 1.13 U/kg/day, range 0.6 - 1.7). Four/6 individuals had low birth weight, all had severe microcephaly and 5/6 had epilepsy in the neonatal period. To study the impact of one of the mutations, iPSCs were edited to insert the homozygous TMEM167A V59E mutation, prior to differentiation into β cells. Mutant iPSC-β cells had impaired proinsulin trafficking from the ER to the Golgi. Mutant iPSC-βcells had a halved insulin content and blunted insulin secretion when stimulated by glucose, glucose plus the GLP-1 analogue exenatide and KCl. Upon exposure to ER stressors, mutant βcells had exacerbated ER stress and apoptosis, while treatment with exenatide, ISRIB and imeglimin improved βcell survival. After 4 months of *in vivo* maturation of iPSC-βcells transplanted into mice, human C-peptide was barely detectable in mice with mutant iPSC-βcells but present in those with healthy cells.
Conclusions
Recessive TMEM167A mutations are a novel cause of neonatal diabetes. The TMEM167A V59E mutation impacted proinsulin trafficking, markedly impaired insulin secretion and sensitized cells to ER stress. Exenatide, ISRIB and imeglimin hold therapeutic potential for ER stress-related diabetes. This disease highlights the crucial role of ER-to-Golgi trafficking and the ER stress response in βcells.
Keywords
TMEM167A, neonatal diabetes, ER stress, ER-to-Golgi protein trafficking
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032

Familial hyperaldosteronism type I: contribution of long-read DNA sequencing

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Introduction
Primary aldosteronism (PA) is the most frequent cause (55%) of secondary arterial hypertension (HTN) in individuals under 40 years old. Hereditary forms, known as familial hyperaldosteronism (FH), should be considered in patients under 20 years of age, and in cases of a family history of early-onset HTN, PA, cerebral hemorrhage before the age of 40, or bilateral adrenal hyperplasia.
Case Report
We report the case of a 17-year-old asymptomatic patient with no personal medical history, referred for incidentally discovered HTN, secondary to PA (aldosterone 605ng/l, renin $<$2.1mU/l) with normal adrenal glands on abdominal CT-scan. The patient's father had a history of HTN diagnosed following a cerebral hemorrhage at the age of 26. No mutations associated with FH had been identified. Our patient's workup confirmed a glucocorticoid-remediable aldosteronism (aldosterone 47ng/l after Liddle's test). Long-read DNA sequencing using Oxford Nanopore Technologies revealed a pathogenic heterozygous CYP11B1-CYP11B2 chimeric gene (PMID 1472060), confirming a diagnosis of FH type 1 (FH-I). The patient's HTN has since been managed with Dexamethasone.
Discussion
FH-I accounts for 1% of PA cases and is caused by a chimeric gene resulting from the fusion of the *CYP11B1* promoter with the coding region of *CYP11B2*. This leads to ectopic ACTH-dependent aldosterone production in the zona fasciculata. Transmission is autosomal dominant. This case highlights the diagnostic value of long-read DNA sequencing in the molecular diagnosis of FH-I. This technique detects certain mutations, such as structural genetic rearrangements, which are often missed by conventional short-read sequencing methods. Accurate molecular diagnosis allows a targeted treatment and facilitates genetic family screening.
Keywords
Endocrine hypertension, familial hyperaldosteronism, genetic diagnosis
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033

Infected thyroid metastases revealing advanced metastatic pulmonary cancer: a case report

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Background
Acute Suppurative Thyroiditis (AST) is a rare condition due to the thyroid's intrinsic defense mechanisms (1). However, it can be severe or even life-threatening, requiring urgent and proactive management (1,2). We report the case of an immunocompetent middle-aged woman in whom infection of thyroid metastases led to a diagnosis of metastatic pulmonary cancer classified as non-small cell lung cancer – not otherwise specified (NSCLC-NOS group).
Case presentation
A 57-year-old woman presented to the emergency department with a painful cervical mass developed over the preceding days, without evidence of airway compromise. Cervical ultrasound performed by the radiologist revealed a multinodular goiter, while chest X-ray demonstrated a previously unknown right apical pulmonary mass, subsequently considered suspicious on computed tomography (CT) imaging. The patient was urgently referred for an endocrinological evaluation the following day. Thyroid ultrasound confirmed the presence of several hypoechoic, heterogeneous, partially cystic thyroid masses, with internal or peripheral vascularity, of up to 2cm. Fine-needle aspiration (FNA) of the two largest nodules was performed (Figure 1), yielding a purulent fluid. Unfortunately, a pathogen could not be identified, likely due to prior antibiotic treatment for a suspected pulmonary infection a few days earlier. Subsequently, despite broad-spectrum antibiotic coverage, a CT-guided biopsy of the apical pulmonary mass was performed for both histopathological and microbiological analysis. 16S rRNA PCR testing identified Porphyromonas endodontalis, which was considered the likely pathogen responsible for both the pulmonary and thyroid abscesses, particularly considering prior dental procedures. The staging workup revealed the presence of multiple metastatic lesions involving the kidneys, peritoneum, adrenal glands, thyroid and muscles. Follow-up thyroid ultrasound after completion of antibiotic therapy showed progression of the thyroid masses (Figure 1). This was attributed to oncologic treatment failure, with evidence of progression of the metastatic disease, leading to the patient's death within three months.
Discussion
Given a reported mortality rate ranging from 3.7 to 8.6% based on published reviews, AST requires a proactive management. Treatment combines drainage – either surgical or via FNA – with empirical antibiotic therapy, which generally includes penicillinase-resistant penicillin and β-lactamase inhibitors (2). Antifungal therapy should be considered in immunocompromised patients and antituberculosis treatment for patients from endemic areas (3). Although rare – accounting for 0.1-0.7% of thyroid pathologies (2-3) – AST should be suspected in cases of neck pain with fever, especially when local compressive symptoms are present and even more so in patients with predisposing factors such as immunosuppression, prior thyroid FNA, diabetes, pyriform sinus fistula,

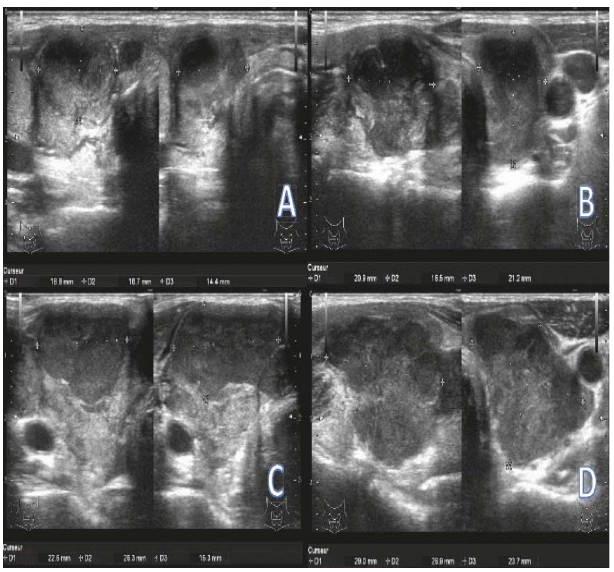

Figure 1: A and B: the two largest thyroid masses before FNA; C and D: progression of the same masses following antibiotic therapy, attributed to progression of the metastatic disease.

bacteremia, etc. (3) Much more rarely, AST has been reported in the context of underlying primary thyroid cancer, likely related to structural gland modifications (1,2). Regarding AST associated with thyroid metastases, only one case has been documented in which diagnosis of the primary cancer was suspected based on FNA of the thyroid mass (4). Destructive thyroiditis causing hyperthyroidism may be observed in AST, with variable frequency according to the literature. This can lead to diagnostic confusion, particularly with subacute thyroiditis, which represents one of the main differential diagnoses. Other differentials include infected thyroglossal duct cyst, lymphoma, deep vein thrombosis, abscess of adjacent neck tissue, etc. (3) Ultrasound performed by an experienced clinician remains the preferred initial diagnostic tool, typically revealing a heterogeneous iso- or hypoechoic mass, as observed in our case (Figure 1).

Conclusion

AST is a rare and potentially life-threatening thyroid condition. Infection of a primary neoplastic thyroid lesion is exceptional, whereas infection of a metastatic lesion within the thyroid gland has, to our knowledge, only once been reported in the literature as such.

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034

Thyroid involvement in marginal zone lymphoma: a case report

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Background

Thyroid lymphoma accounts for approximately 2-8% of malignant thyroid masses. Two types are recognized: primary thyroid lymphoma, originating in the thyroid and representing 1-2% of extranodal lymphomas, and secondary thyroid involvement, occurring in 11-27% of cases.

Case presentation

We report the case of a 69-year-old woman referred for dysphagia and anterior cervical discomfort. She reported a palpable left inguinal lymphadenopathy identified four months prior to her presentation. We performed a cervical ultrasound, identifying a partially cystic nodule in the right thyroid lobe, a 10mm hypoechoic isthmic nodule with peripheral vascularity, a 23 mm irregular hypoechoic mass in the left lobe with central vascularity, and multiple left jugulo-carotid lymph nodes (Figure 1.A.). Technetium-99m thyroid scintigraphy showed a nearly absent uptake of the left lobe, corresponding to a hyper-metabolic area on the FDG PET-CT. Fine-needle aspiration (FNA) of the left thyroid nodule revealed inflammatory and hemorrhagic cytology, while biopsy of the inguinal lymph node confirmed the diagnosis of marginal zone lymphoma. PET-CT staging established a stage IVB marginal zone lymphoma. Due to the disseminated disease and clinical symptoms, treatment with Rituximab and Bendamustine was initiated. After four cycles, follow-up thyroid ultrasound no longer revealed the isthmic and the left hypoechoic thyroid masses (Figure 1.B.). The patient also reported clinical improvement including of dysphagia.

Discussion

The thyroid gland is an uncommon metastatic site for nodal or extranodal lymphomas (1). Hashimoto's thyroiditis has been linked to an increased risk of primary thyroid lymphoma through chronic lymphocytic stimulation, though this association is less obvious in secondary forms (5). Our patient had a history of Hashimoto's thyroiditis. Clinically, symptoms related to thyroid infiltration-such as hoarseness or dysphagia-are less frequently observed in secondary thyroid lymphoma (2), which was the case in our patient. Thyroid ultrasound is the first-line imaging tool. Primary lymphoma usually appears as a diffuse hypoechoic area with septations, whereas secondary lymphoma may mimic anaplastic thyroid carcinoma, presenting as a solid hypoechoic mass (3). Internal vascularity and lack of calcification may help differentiate lymphoma from anaplastic thyroid carcinoma; both are often hypermetabolic on FDG PETCT (3). Fine-needle aspiration cytology (FNAC) may be performed, but is often insufficient for diagnosis due to limited sample size and inability to perform immunohistochemistry. Core needle or surgical biopsy is preferred as they preserve tissue architecture (3). Secondary thyroid lymphoma is typically disseminated at diagnosis, in contrast to primary thyroid lymphoma, which tends to remain localized and is associated with a more favorable prognosis (4). Treatment strategy depends on staging; disseminated cases typically require systemic chemotherapy combined with Rituximab (5).

Conclusion

Thyroid involvement in marginal zone lymphoma is rare, but should be considered in patients with thyroid nodules and generalized lymphadenopathy. PET-CT and histopathological confirmation are crucial for accurate diagnosis, staging, and treatment planning. Biopsy is recommended in order to allow immunohistochemical analysis and to preserve tissue architecture, essential for proper classification.

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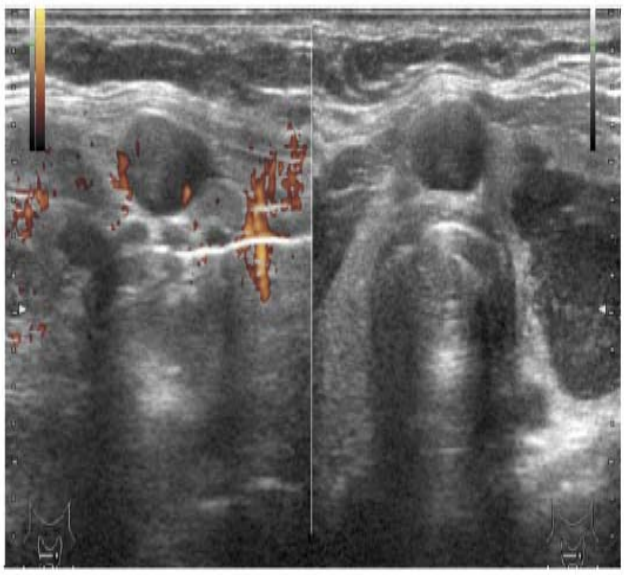

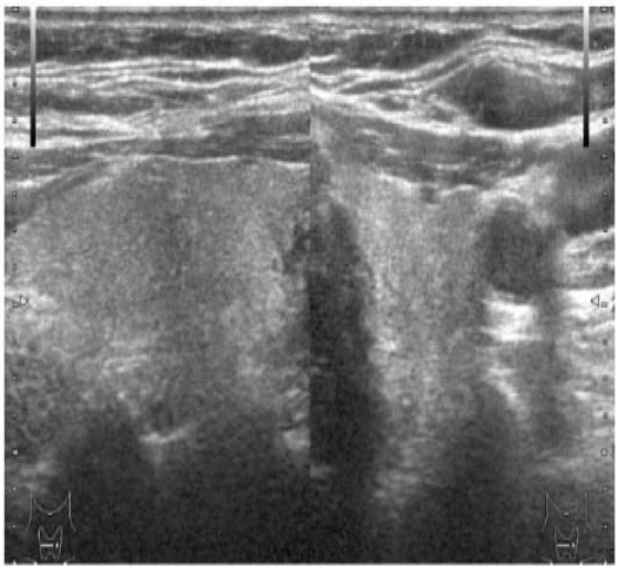

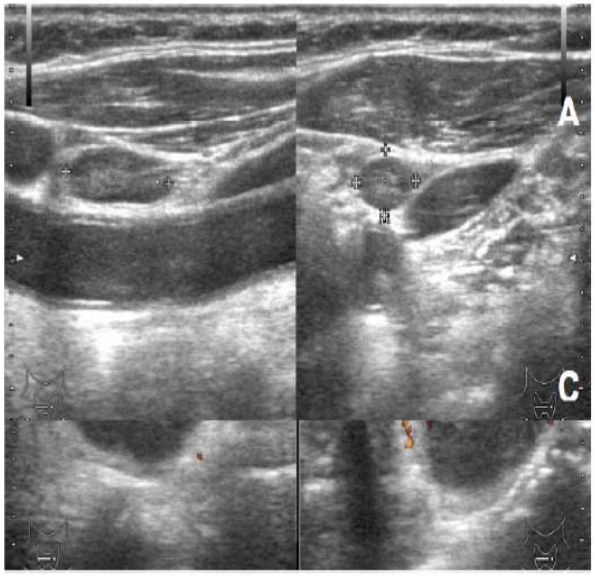

Figure 1: (A) Hypoechoic isthmic nodule.(B) Hypoechoic mass in the left lobe of the thyroid gland.(C) One of the jugulocarotid lymph nodes.(D) Left thyroid lobe after four cycles of Rituximab and Bendamustine.

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