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001

The STE-20 kinase TAOK3 regulates obesity-associated metabolism and type 2 immunity in murine adipose tissue

Maes Bastiaan[1,2,3,4], Fayazpour Farzaneh[2,3], Catrysse Leen[5,6], Lornet Guillaume[1], Van De Velde Evelien[2,3], De Wolf Caroline[1,2], De Prijck Sofie[1,2], Van Moorleghem Justine[1,2], Vanheerswynghels Manon[1,2], Deswarte Kim[1,2], Descamps Benedicte[7], Vanhove Christian[7], Hammad Hamida[1,2], Janssens Sophie[1,2,3,*] & Lambrecht Bart N[1,2,9,*]
[1]Laboratory of Immunoregulation and Mucosal Immunology, VIB-UGent Center for Inflammation Research, Ghent 9052, Belgium; [2]Department of Internal Medicine and Pediatrics, Ghent University, Ghent 9000, Belgium; [3]Laboratory for Endoplasmic Reticulum Stress and Inflammation, VIB-UGent Center for Inflammation Research, Ghent 9052, Belgium; [4]Department of Endocrinology, Ghent University Hospital, Ghent 9000, Belgium; [5]Cellular and Molecular (Patho)Physiology, VIB-UGent Center for Inflammation Research, Ghent 9000, Belgium; [6]Department of Biomedical Molecular Biology, Ghent University, Ghent 9000, Belgium; [7]IBiTech-MEDISIP-Infinity Lab, Department of Electronics and Information Systems, Ghent University, Ghent 9000, Belgium; [8]Department of Endocrinology, Ghent University Hospital, Ghent 9000, Belgium; [9]Department of Pulmonary Medicine, Erasmus University Medical Center Rotterdam, Rotterdam 3015 GJ, the Netherlands; [*]These authors shared supervision of the work

Aim
Healthy adipose tissue contains numerous innate and adaptive immune cells that carry a type 2 cytokine immune signature, controlled by IL-33 and reflected by accumulation of $ST2^+$ T regulatory cells (Tregs), type 2 innate lymphoid cells (ILC2s), and alternatively activated macrophages. These type 2 responses are lost in mice or humans on high-caloric diets that lead to obesity. Understanding how type 2 immunity is regulated in adipose tissue could contribute to prevention and treatment of obesity. The STE-20 kinase Thousand and one amino acid kinase-3 (TAOK3) has been linked to immune regulation and obesity in mice and humans, but its precise function is unknown.
Methodology
We used whole-body $Taok3^{-/-}$ mice on a C57BL/6J background. Organs were harvested from 12 week old mice for processing to single cell suspensions, and then stained with fluorochrome labeled antibodies. Samples were analyzed on a BD LSRFortessa™. Next, mice were fed a high-fat diet (60% fat) for 15 weeks. Metabolic homeostasis was analyzed by performing intra-peritoneal glucose tolerance challenge and insulin tolerance challenge. Tissues were taken and analyzed as above. Gene expression was analyzed from RNA isolated from flow cytometry sorted Tregs.
Results
Here, we show that ST2-expressing Tregs are upregulated in diverse tissues of $Taok3^{-/-}$ mice, but particularly in epididymal visceral white adipose tissue (eWAT) of male $Taok3^{-/-}$ mice. Whereas $ST2^+$ Tregs disappeared from eWAT upon high-fat diet in wild-type mice, they were spared in obese $Taok3^{-/-}$ eWAT. Concomitantly, diet-induced metabolic dysfunction was attenuated in $Taok3^{-/-}$ mice. Mechanistically, adipose tissue $Taok3^{-/-}$ Tregs were more responsive to IL-33, through higher expression of ST2, and expressed more PPAR and type 2 cytokines.
Conclusion
Taken together, Taok3 regulates the homeostasis of $ST2^+$ Tregs in adipose tissue and contributes to metabolic dysfunction upon excessive caloric intake. Inhibiting Taok3 kinase activity might prove to be an interesting route in targeting immune dysregulation associated with obesity.

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002

Identification of myokines potentially involved in the improvement of glucose homeostasis induced by bariatric surgery

Orioli Laura[1,2], Derop Julien[3], Canouil Mickaël[5], Sawadogo Kiswendsida[4], Deldicque Louise[5], Lause Pascale[1], de Barsy Marie[2], Loumaye Audrey[1,2], Deswysen Yannick[6], Navez Benoit[6], Bonnefond Amélie[3] & Thissen Jean-Paul[1,2]
[1]Institute of Experimental and Clinical Research (IREC), Endocrinology, Diabetes and Nutrition (EDIN), Université Catholique de Louvain (UCLouvain), Brussels, Belgium; [2]Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [3]Inserm U1283, CNRS UMR 8199, European Genomic Institute for Diabetes, Institut Pasteur de Lille, Lille France; [4]Statistical Support Unit, King Albert II Cancer and Hematology Institute, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [5]Institute of NeuroScience (IONS), Université Catholique de Louvain (UCLouvain), 1348 Louvain-La-Neuve, Belgium; [6]Department of Oeso-gastro-duodenal and bariatric surgery, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background and aims
The contribution of myokines to improved glucose homeostasis induced by bariatric surgery is unknown. Our study aims to identify myokines potentially improving glucose homeostasis following bariatric surgery.
Patients and methods
Obese insulin-resistant patients were evaluated before and 3 months after bariatric surgery, i.e. a sleeve gastrectomy or a Roux-en-Y gastric bypass ($n62$). Muscle biopsies were taken from vastus lateralis ($n = 39$). Glucose homeostasis was evaluated using the HOMA test. Changes in muscle transcriptome were determined by RNA-Seq ($n12$). Genes encoding myokines were identified based on the prediction of a signal peptide and annotations. Changes in myokines expression identified by RNA-seq were replicated by RT-qPCR ($n39$).
Results
Thirty-six (58%) of the 62 patients included in the study were females and 39 (63%) underwent a sleeve gastrectomy. The mean age (±SD) was 44 (±11) years and the median pre-operative BMI [IQR] was 42.6 [40.7-44.4] kg/m^2. All the clinical and biological parameters were significantly improved after surgery except for HDL cholesterol. In particular, insulin sensitivity was significantly increased after surgery (HOMA-S +34.2%, $P < 0.0001$). The RNA-Seq study identified 1363 single genes whose expression was changed by surgery (FDR ≤ 0.10). Among those, 41 up-regulated (FC ≥ 1.3) and 56 down-regulated (FC ≤ 0.7) genes encoded myokines. Increased expression of CX3CL1 (+73%, $P < 0.0001$), ADAMTS9 (+35%, $P < 0.0001$), BDNF (+30%, p 0.006) and ANG (+29%, $P < 0.0001$) as well as decreased expression of MSTN (-45%, $P < 0.0001$) and FNDC5 (-25%, $P < 0.0001$), genes encoding myokines known to regulate glucose homeostasis, were confirmed by RT-qPCR. Increased expression of NTE5 (+28%, p 0.001), BMP8B (+67%, $P < 0.0001$), TNFRSF10B (+34%, $P < 0.0001$), SDC4 (+25, p 0.003), and KDR (+39%, $P < 0.0001$) as well as decreased expression of DLK1 (-32%, $P < 0.0001$), genes encoding myokines related to obesity and/or type 2 diabetes, were also confirmed. RT-qPCR analysis also showed a significantly reduced expression of MYH1 (-38%, p 0.002) and a significant increased expression of MYH2 (+21%, p 0.022).
Conclusions
Our study shows that bariatric surgery changes the muscle transcriptome and the expression of myokines, either known to regulate glucose homeostasis (fractalkine, ADAMTS9, BNDF, angiogenin, myostatin, irisin) or related to obesity/type 2 diabetes (NTE5, BMP8B, TNFRSF10B, SDC4, KDR, DLK1). The changes in the expression of myosin heavy chains suggest a less fast muscle phenotype after surgery. We are currently working at 1) measuring plasma levels of myostatin (MSTN) and fractalkine (CX3CL1), 2) identifying myokines potentially regulating glucose homeostasis using multivariate linear regression analysis, and 3) analyzing enriched pathways using Gene Set Enrichment Analysis.

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003

Gene expression signatures of target tissues in endocrine and non-endocrine autoimmune diseases. Présenté par Prof. Miriam Cnop

Szymczak F[1,2], Colli M. L.[1], Mamula M. J.[3], Evans-Molina C[4] & Eizirik D. L[1,5]
[1]ULB Center for Diabetes Research, Medical Faculty, Université Libre de Bruxelles (ULB), Brussels, Belgium; [2]Interuniversity Institute of Bioinformatics in Brussels, Université Libre de Bruxelles-Vrije Universiteit Brussel, Brussels, Belgium; [3]Section of Rheumatology, Yale University School of Medicine, New Haven, CT, USA; [4]Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN, USA; [5]Indiana Biosciences Research Institute (IBRI), Indianapolis, IN, USA

Objectives
Autoimmune diseases are typically studied with a focus on the immune system, and less attention is paid to responses of target tissues exposed to the immune assault. We aimed to evaluate, based on available bulk RNA sequencing data, whether inflammation induces similar molecular signatures in the target tissues of five autoimmune diseases, namely type 1 diabetes (T1D), Hashimoto's thyroiditis (HT), rheumatoid arthritis (RA), multiple sclerosis (MS) and systemic lupus erythematosus (SLE). Part of these data, related to T1D, RA, MS and SLE, but not HT, have been recently published (Szymczak et al, Sci Adv 2021). We next mined the datasets to discover similar and disease-specific gene signatures that could be targeted for therapy, including by repurposing drugs already in clinical use for other diseases.

Methods
We quantified the transcriptome from the target tissues of patients and healthy donors for each disease using our bioinformatics pipeline and performed differential gene expression analysis to capture their molecular footprints. Next, we compared the differential expression results of each tissue by Rank-Rank Hypergeometric Overlap (RRHO) to study commonly regulated genes and evaluated shared metabolic pathways. These pathways were then used to identify drugs that could be repurposed. We also performed bulk and single- cell RNA sequencing of induced pluripotent stem cell (iPSC) derived §-cells exposed to lFNo as biological confirmation to evaluate its impact in the different cell (sub) populations.
Results
There are important similarities among up-regulated, but not down-regulated genes, in the target tissues of the five autoimmune diseases studied; common findings include antigen presentation and interferon signatures. The two closest gene expression signatures were observed between T1D and HT. We selected type I lFNs for biological confirmation in human §-cells. Enrichment analysis of commonly up-regulated pathways between target tissues of T1D and HT identified neutrophil degranulation, signaling downstream of type I and type II lFNs, cytokine-cytokine receptor interactions, and cell adhesion molecules, among others. iPSC-derived §- cells exposed to IFNo showed enrichment of pathways related to interferon signaling and antigen presentation but also depletion of pathways related to citric acid cycle and electron transport chain. The effects of IFNo seem to be more marked in specific cell subpopulations. in *silico* comparison of the top 150 up-regulated genes overlapping between T1D and HT (from the RRHO) against drug-modified datasets highlighted bile acid-derived molecules (which may protect against ER stress) and dihydrofolate-reductase inhibitors as potential candidates to be repurposed.
Conclusions
These novel observations emphasize the role for lFNs in autoimmune diseases and point to novel therapeutic approaches to protect the target tissues of these diseases. Furthermore, our approach offers a method to screen and identify new drugs to be repurposed in a reduced bench-to-bedside timeframe.

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Effect of glucocorticoid vs CRH treatment during sepsis on pituitary ACTH processing

Téblick Arno, De Bruyn Lauren, Vander Perre Sarah, Langouche Lies & Van den Berghe Greet
Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Herestraat 49, 2000 Leuven, Belgium

Purpose
Sepsis is hallmarked by high circulating glucocorticoids in face of low plasma adrenocorticotropic hormone (ACTH) (1). At the hypothalamic-pituitary level, ongoing stress-induced corticotropin-releasing hormone- (CRH) and arginine vasopressin- (AVP) driven expression of the ACTH-precursor POMC coincides with impaired proprotein convertase 1 (PC1/3)-mediated processing into ACTH, with ultimately leaching of unprocessed POMC into the circulation (2). Despite uncertainty of the effects on the hypothalamic-pituitary-adrenal axis, current guidelines continue to recommend glucocorticoid treatment in all patients with vasopressor-refractory septic shock. We hypothesized that further augmenting systemic glucocorticoid availability through exogenous administration of hydrocortisone would aggravate the sepsis-induced impairment in pituitary POMC processing, while infusion with CRH would restore it.
Methods
Male C57BL/6J mice (n48) were randomized to 4 groups: a healthy control group, a sepsis group treated with hydrocortisone (HC, continuous rate of 1.2 mg/day), with CRH (CRH, continuous rate of 1 µg/day) or with placebo (P, Plasmalyte). Sepsis was brought about by standardized cecal- ligation and puncture and mice were fluid-resuscitated, parenterally fed, opioid-analgesics and broad- spectrum antibiotics-treated. On day 7 of illness, mice were sacrificed and plasma concentrations of ACTH and POMC were quantified, as well as pituitary expression of POMC and ACTH, mediators of hypothalamic signaling (CRH-receptor, CRHR and AVP-receptor, AVPR), mediators of POMC processing into ACTH (PC1/3) and inflammatory markers (TNFα and IL1β).
Results
Sepsis-induced reduction of plasma ACTH was substantially further suppressed in HC-treated mice ($P \leq 0.0001$ in comparison with P-treated sepsis and healthy controls), coinciding with suppressed pituitary ACTH content ($P \leq 0.001$ vs. P-treated sepsis and vs. healthy). Plasma ACTH was normalized in CRH-treated sepsis ($P = 0.23$ vs. healthy). Pituitary gene expression and plasma POMC was always increased during sepsis, irrespective of treatment (all $P \leq 0.05$ vs. healthy). Pituitary gene expression of CRHR and AVPR was lower in HC-treated as compared with P-treated sepsis ($P \leq 0.01$). Pituitary protein expression of PC1/3 was suppressed in HC- and P-treated sepsis (both $P \leq 0.05$ vs. healthy), but not in CRH-treated sepsis ($P = 0.55$ vs. healthy). Pituitary gene expression of TNFα and IL1β was increased in, respectively, CRH-treated sepsis ($P \leq 0.05$ vs. healthy) and in HC- and CRH-treated sepsis (both $P \leq 0.05$ vs. healthy), but not in P-treated sepsis ($P > 0.05$ vs. healthy).
Conclusion
Increasing the systemic glucocorticoid availability in sepsis by continuous infusion of hydrocortisone further suppressed pituitary and plasma ACTH, suppressed pituitary CRHR and AVPR gene expression, but did not further suppress PC1/3 protein expression. In contrast, CRH infusion resulted in a normalization of plasma ACTH through restoration of PC1/3 protein expression. However, both therapies coincided with increased expression of inflammatory markers within the pituitary gland. The effects of the treatment-induced changes in plasma ACTH on adrenocortical steroidogenesis remain to be studied.
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005

Fragility fractures in postmenopausal women: development of 5-year prediction models using the FRISBEE study

Baleanu Felicia[1], Moreau Michel[2], Charles Alexia[3], Iconaru Laura[1], Karmali Rafik[1], Surquin Murielle[4], Benoit Florence[4], Mugisha Aude[4], Paesmans Marianne[2], Rubinstein Michel[5], Rozenberg Serge[6], Bergmann Pierre[3, 7] & Body Jean- Jacques [1,3]
[1]Department of Endocrinology, CHU Brugmann, Universite Libre de Bruxe lles, Brusse ls, Belgium; [2]Data Centre, Inst. J. Bordet, Universite Libre de Bruxelles, Brussels, Belgium; [3]Unite de Recherche Translationne lle, CHU Brugmann, Universite Libre de Bruxelles, Brussels, Belgium; [4]Department of Geria trics, CHU Brugmann, Universite Libre de Bruxelles, Brussels, Belgium; [5]Department of Nuclear Medicine, Ixelles Hospital, Universite Libre de Bruxelles, Brussels, Belgium; [6]Department of Gynecology, CHU St Pierre, Universite Libre de Bruxe lles, Brussels, Belgium; [7]Department of Nuclear Medicine, CHU Brugmann, Universite Libre de Bruxelles, Brussels, Belgium

Context
Individualized fracture risk may help to select patients requiring a pharmacological treatment for osteoporosis. FRAX and the Garvan fracture risk calculators are the most used tools, though their external validation has shown significant differences in their risk prediction ability.
Objective and Methods
Using data from the FRISBEE study, a cohort of 3560 post-menopausal women aged 60-85 years, we aimed to construct original 5-year fracture risk prediction models using validated clinical risk factors (CRFs). Three models of competing risk analysis were developed to predict major osteoporotic fractures (MOFs), all fractures and central fractures (femoral neck, shoulder, clinical spine, pelvis, ribs, scapula, clavicle, sternum).
Results
Age [sHR per year 1.05, 95% CI 1.04-1.06, $P < 0.0001$ (for MOFs); sHR per year 1.03, 95% CI 1.02- 1.04, $P < 0.0001$ (for all fractures); sHR per year 1.06, 95% CI 1.04-1.07, $P < 0.001$ (for central fractures)], a history of fracture [sHR 1.56, 95% CI 1.30-1.85, $P < 0.001$ (for MOFs); sHR 1.50, 95%CI 1.28-1.75, $P < 0.0001$ (for all fractures); sHR 1.47, 95% CI 1.22-1.77, $P < 0.001$ (for central fractures)] and total hip BMD [sHR 1.32, 95% CI 1.20-1.45, $P < 0.0001$ (for MOFs); sHR 1.36, 95%CI 1.28-1.46, $P < 0.0001$ (for all fractures); sHR 1.39, 95%CI 1.25-1.53, p < 0.0001 (for central fractures)] or spine BMD [sHR 1.10, 95% CI 1.03-1.19, $P = 0.01$ (for MOFs); sHR 1.08, 95%CI 1.004-1.66, $P = 0.04$ (for central fractures)] were predictors common to the three models . Excessive alcohol intake (sHR 1.39, 95% CI 1.01-1.90, $P = 0.04$), and the presence of comorbidities (sHR 1.27, 95% CI 1.00 -1.60, $P = 0.04$) were specific additional CRFs for MOFs, a history of fall (sHR 1.32, 95%CI 1.12-1.57, $P = 0.001$) for all fractures and rheumatoid arthritis (sHR 2.42 95%CI 1.33-4.39, $P = 0.004$) for central fractures. Our models predicted the fracture probability at 5-years with an acceptable precision (Brier scores ≤ 0.1) and had a good discrimination power (area under the receiver operating curve of 0.73 for MOFs and 0.72 for central fractures) when internally validated by bootstrap. Three simple nomograms, integrating significant CRFs and the mortality risk were constructed for different fracture sites. In **conclusion**, we derived three models predicting fractures with an acceptable accuracy, particularly for MOFs and central fractures. The models are

based on a limited number of CRFs and we constructed nomograms for use in clinical practice.

Keywords: osteoporosis, competing risk analysis, fracture, risk assessment, risk factors, BMD.

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006

The potential role of androgens as early determinants of body composition and metabolic health

Banica Thiberiu[1], Verroken Charlotte[1], Zmierczak Hans-Georg[1], Goemaere Stefan[1], T'Sjoen Guy[1], Fiers Tom[2], Kaufman Jean-Marc[1] & Lapauw Bruno[1]
[1]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; [2]Department of Clinical Chemistry, Ghent University Hospital, Ghent, Belgium

Introduction
Even in healthy men, androgen levels start decreasing from early adulthood and these decreases are more pronounced in men with an increasing body mass index (BMI). It is, however, unclear to what extent changes in other indices of body composition and metabolic health are associated with changes in sex steroid exposure in healthy men over time.
Objective
Investigating longitudinal changes in body composition and metabolic health in relation to sex steroid levels in young adult men.
Methods
Longitudinal, population-based, observational study: 999 healthy men aged 24-46 years of whom 691 were re-evaluated after 12 +/- 2 years. Serum sex hormone binding globulin (SHBG) and insulin levels were measured using immuno-assay, glucose by hexokinase method, testosterone (T) using LC-MS/MS, free T (cFT) and homeostasis model for insulin resistance (HOMA-IR) calculated. Body composition was determined using DXA (Hologic) at the whole body minus head. Fat (FM%) and lean mass (LM%) percentages were calculated. Linear mixed models were used for statistical analyses. All models were adjusted for baseline age.
Results
Baseline age was 34 ± 6 years. Mean BMI increased by 4.7% (25.1 kg/m^{2}vs 26.3 kg/m^2). Mean T levels decreased by 14.2% (20.8 nmol/l vs. 17.8 nmol/l), cFT by 19.1% (392 pmol/l vs. 317 pmol/l) and SHBG increased by 3.0% (39.8 nmol/l vs. 41.0 nmol/l) (all $P < 0.001$). FM% increased by 1.2% (19.6% vs 21.6%; $P < 0.001$), especially at the trunk (8.1 kg vs 9.6 kg; $P < 0.001$). LM% decreased by 1.8% (77.3% vs 75.4%; $P < 0.001$). HOMA-IR increased from 1.7 to 2.2 ($P < 0.001$). At baseline, total T, cFT and SHBG were inversely associated with truncal fat, FM% and HOMA-IR and positively associated with LM% (all $P < 0.001$). Longitudinally, changes in sex steroids were not associated with changes in either FM% and LM%. However, changes in total T, cFT and SHBG were inversely associated with changes in truncal fat and HOMA-IR (all $P < 0.018$).
Conclusion
In this population of healthy young men, adiposity and insulin resistance increased while LM% decreased over a period of 12 years. We found that a stronger decline in both total and free T levels was associated with stronger increases in truncal adiposity and insulin resistance. Whether our findings suggest a direct role of sex steroids as determinants of metabolic state, result from residual confounding or are mediated by the intriguing relationship between SHBG levels and metabolic health remains to be established. Moreover, the possibility of a reverse causality between androgen levels and metabolic state should be taken into account.

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007

Fasting plasma glucose level to determine the need for an OGTT to screen for gestational diabetes mellitus

Beunen Kaat, Neys Astrid[2], Van Crombrugge Paul[3], Moyson Carolien[1], Verhaeghe Johan[4], Vandeginste Sofie[5], Verlaenen Hilde[5], Vercammen Chris[6], Maes Toon[6], Dufraimont Els[7], De Block Christophe[8], Jacquemyn Yves[9], Mekahli Farah[10], De Clippel Katrien[11], Van Den Bruel Annick[12], Loccufier Anne[13], Laenen Annouschka[14], Devlieger Roland[4], Mathieu Chantal[1] & Benhalima Katrien[1]
[1]Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Belgium; [2]Medicine, KU Leuven, Belgium; [3]Department of Endocrinology, OLV ziekenhuis Aalst- Asse-Ninove, Belgium; [4]Department of Obstetrics & Gynecology, UZ Gasthuisberg, KU Leuven, Belgium; [5]Department of Obstetrics & Gynecology, OLV ziekenhuis Aalst-Asse-Ninove, Belgium; [6]Department of Endocrinology, Imelda ziekenhuis, Belgium; [7]Department of Obstetrics & Gynecology, Imelda ziekenhuis, Belgium; [8]Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Belgium; [9]Department of Obstetrics & Gynecology, Antwerp University Hospital, Belgium; [10]Department of Endocrinology, Kliniek St-Jan Brussel, Belgium; [11]Department of Obstetrics & Gynecology, Kliniek St-Jan Brussel, Belgium; [12]Department of Endocrinology, AZ St Jan Brugge, Belgium; [13]Department of Obstetrics & Gynecology, AZ St Jan Brugge, Belgium; [14]Center of Biostatics and Statistical bioinformatics, Leuven, Belgium

Aims
To determine the fasting plasma glucose (FPG) level at which an oral glucose tolerance test (OGTT) could be avoided to screen for gestational diabetes (GDM) and to evaluate the characteristics of women across this FPG threshold.
Methods
A multi-centric prospective cohort study (BEDIP-N) with 1843 women receiving screening for GDM with a 75g OGTT.
Results
A FPG < 78 mg/dl was the FPG cut-off with the best trade-off to limit the number of missed GDM cases [19.0% (44)] with a negative predictive value (NPV) of 97.3% (95% CI 96.5-98.0) for GDM, while avoiding 52.2% (1048) OGTT's. The area under thereceiver operating characteristic curve was 0.76 (95% CI 0.72-0.80) for FPG at the OGTT. Of all 231 (12.5%) women with GDM, 44 (19.0%) had FPG < 78 mg/dl, 112 (48.5%) had FPG 78-91 mg/dl and 75 (32.5%) FPG ≥92 mg/dl. GDM women with low FPG (< 78) had significantly lower BMI (early pregnancy: 24.7 ± 4.7 vs. 27.0 ± 5.4 Kg/m^2, $P = 0.007$; at OGTT: 27.1 ± 4.5 vs. 29.6 ± 5.2 Kg/m^2, $P = 0.003$), had lower insulin resistance (IR) [early pregnancy HOMA-IR: 8.2 (7.2-13.7) vs. 11.1 (8.5-17.6), $P = 0.020$; at OGTT: HOMA-IR 11.1 (8.2-15.0) vs. 19.0 (12.6-29.9), $P < 0.001$; Matsuda index 0.4 (0.4-0.7) vs. 0.3 (0.2- -cell function [ISSI-2 at OGTT: 0.13 (0.08-0.25) vs. 0.09 (0.04-0.15), $P = 0.004$] than GDM women with higher FPG (≥78). There were no differences in pregnancy outcomes and postpartum rate of glucose intolerance. Of the 1612 normal glucose tolerant (NGT) women, 766 had FPG < 78 mg/dl (47.5%) and 846 had FPG ≥78 mg/dl (52.5%). Compared to NGT women with higher FPG, those with low FPG had lower BMI (early pregnancy: 23.5 ± 3.9 vs. 25.2 ± 4.8 Kg/m^2, $P < 0.001$; at OGTT: 26.0 ± 3.9 vs. 27.8 ± 4.7 Kg/m^2, $P < 0.001$), lower blood pressure (BP) [early pregnancy: systolic BP (SBP) 114.1 ± 10.1 vs. 115.4 ± 10.6 mmHg, $P = 0.009$; diastolic BP (DBP) 69.7 ± 7.7 vs. 70.9 ± 8.3 mmHg, $P = 0.003$; at OGTT: SBP 112.6 ± 9.8 vs. 113.6 ± 10.3 mmHg, $P = 0.033$; DBP 66.3 ± 7.9 vs. 67.7 ± 7.9 mmHg, $P < 0.001$], less IR [early pregnancy HOMA-IR: 8.1 (5.9-11.5) vs. 10.1 (7.2-14.0), $P < 0.001$; at OGTT: HOMA-IR 9.6 (7.1-13.4) vs. 14.2 (10.6-19.9), $P < 0.001$; Matsuda 0.7 (0.5-0.9) vs. 0.5 (0.4- -cell function [ISSI-2 at OGTT: 0.17 (0.10-0.30) vs. 0.12 (0.07-0.21), $P < 0.001$]. Infants of NGT women with low FPG had less often macrosomia [6.8% (52) vs. 11.8% (99), $P < 0.001$] and were less often large-for- gestational age [9.2% (70) vs. 16.2% (136), $P < 0.001$] than infants of women with higher FPG. The rate of small-for-gestational age infants was similar between both groups.
Conclusions
FPG < 78 mg/dl has a high NPV for GDM and can be used to avoid OGTT's for GDM screening. In the GDM and NGT groups, women with low FPG had a better metabolic profile and in the NGT group also less fetal overgrowth.

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008

Fast-acting insulin aspart improves glucose control in a real-world setting: a 1-year multicenter study in people with type 1 diabetes using continuous glucose monitoring

Billion Lisa[1], Charleer Sara[2], Verbraeken Laurens[1], Sterckx Mira[1], Vangelabbeek Kato[1], De Block Nathalie[1], Janssen Charlien[2], Van Dessel Kristof[1], Dirinck Eveline[1], Peiffer Frida[1], Bolsens Nancy[1], Mathieu Chantal[2], Gillard Pieter[2] & De Block Christophe[1]
[1]Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital, and Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; [2]Department of Endocrinology, University Hospitals Leuven KU Leuven, Leuven, Belgium

Background and Aims
To evaluate whether switching from traditional mealtime insulin analogs to fast-acting insulin aspart (Fiasp) in routine clinical practice is efficacious and safe in adult people with type 1 diabetes (PWD1) using intermittent or real-time continuous glucose monitoring (iCGM or rtCGM).

Methods
Data from 438 adult PWD1 (60% men, age 44.6 ± 16.1 years, duration of diabetes 21.5 ± 14.0 years, iCGM/rtCGM: 391/47, injections/pump: 409/29), initiating Fiasp between January 2018 and May 2020 were retrospectively analyzed. Primary endpoint was the evolution of time in range (TIR:70-180 mg/dl) at 12 months. Secondary endpoints included change in Time < 70, Time < 54, Time > 180 and Time > 250 mg/dl, coefficient of variation (CV), standard deviation (SD), HbA1c, insulin doses, and composite endpoint of reaching TIR > 70% and Time < 70 mg/dl of < 4%.
Results
Time in range improved from 50.3 ± 15.6% to 55.5 ± 15.2% ($P < 0.0001$), corresponding to an increase of 75 minutes/day. Time < 70 mg/dl decreased from 7.4 ± 5.5% to 6.8 ± 5.5% ($P = 0.037$), Time < 54 mg/dl evolved from 3.1 ± 3.3% to 2.5 ± 3.0% ($P = 0.003$), Time > 180 mg/dl from 42.3 ± 16.7% to 37.7 ± 16.9% ($P < 0.0001$) and Time > 250 mg/dl decreased from 16.5 ± 12.8% to 13.1 ± 12.5% ($P < 0.0001$). Glucose variability also improved (CV from 41.9 ± 7.0% to 40.3 ± 6.9%, $P = 0.002$ and SD from 72.7 ± 18.0 to 65.8 ± 18.5 mg/dl, $P < 0.0001$). The number of people reaching the composite endpoint TIR > 70% and Time < 70 mg/dl of < 4% increased from 36.1% to 42.6% ($P = 0.047$). HbA1c (from 7.8 ± 1.1% to 7.7 ± 1.0%) and insulin doses (0.66 ± 0.24 to 0.62 ± 0.21 units/ kg body weight/day) remained stable.
Conclusions
Switching to Fiasp resulted in a 75 min/day increase in TIR, in combination with less time spent below range in a real-world study of adult PWD1.

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009

Lipohypertrophy monitoring study (LIMO): effect of injection site rotation and education on glycemic control

Bochanen N.[1], Decochez K.[2], Heleu E.[2], Cuypers J.[3], Vercammen C.[4], Coremans P.[5], Vanhaverbeke G.[6], Shadid S.[7], Keymeulen B.[8], Bolsens N.[1] & De Block C[1]
[1]University Hospital Antwerp, Endocrinology-diabetology-metabolism, Edegem, Belgium; [2]AZ Jan Portaels, Department of Endocrinology, Vilvoorde, Belgium; [3]AZ Turnhout, Department of Endocrinology, Turnhout, Belgium; [4]Imelda ziekenhuis, Department of Endocrinology, Bonheiden, Belgium; [5]AZ Nikolaas, Department of Endocrinology, Sint-Niklaas, Belgium; [6]AZ Groeninge, Department of Endocrinology, Kortrijk, Belgium; [7]Ghent University Hospital, Department of Endocrinology, Ghent, Belgium; [8]Academic Hospital and Diabetes Research Center Vrije Universiteit Brussel, Endocrinology, Brussels, Belgium

Background and Aims
Incorrect injection technique can cause lipohypertrophy resulting in unpredictable insulin release. We aimed to assess the impact of a correct injection technique and lipohypertrophy on HbA1c, hypoglycemia and glucose variability.
Methods
171 insulin-injecting people with diabetes were prospectively evaluated for 6 months. 146 subjects completed the study (75 type 1, 71 type 2). They were provided extensive education concerning injection technique via an online education platform (BD and MeTM) based on the international Forum for Injection Technique & Therapy Recommendations, encouraged to systematically use 4 mm needles and not reuse needles. Primary outcome parameter was the evolution between baseline and end-of-study percentage of needle re-use and injecting in a zone of lipohypertrophy vs glucometrics (HbA1c, hypoglycemia and glucose variability).
Results
At baseline, lipohypertrophy was present in 64%, 51% of patients injected in zones of lipohypertrophy, 37% rotated incorrectly and 96% reused needles. After the intervention, only 8% injected in a lipohypertrophy zone, 4% rotated incorrectly, and 21% reused needles. There was a significant reduction in severe hypoglycemia (from 15.8% to 4.1%, $P < 0.001$), number of unexplained hypoglycemias (from 47% to 16%, $P < 0.001$), and in the number of people with high glucose variability (from 64% to 30% $P < 0.001$). HbA1c (7.5 ± 1.2%) and total dialy insulin dose (62 ± 41 units) remained unchanged.
Conclusions
Online education on injection techniques focusing on avoidance of lipohypertrophy zones and reduction of needle re-use results in a significant reduction in severe hypoglycemic episodes, unexplained hypoglycemias and in the number of people with high glucose variability.

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010

Changes in androgen profile in transgender women with or without gonadectomy

Collet Sarah[1], de Meijer Delphine[1], Nobels Sarah[1], Kiyar Meltem[2] & T'Sjoen Guy[1]
[1]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; [2]Department of Experimental Clinical and Health Psychology, Ghent University, Belgium

Objectives
The European Network for the Investigation of Gender Incongruence (ENIGI) is a multicenter prospective cohort study. All participants receive a standardized gender affirming treatment protocol including regular follow-up visits. The current study compared the changes in androgens upon starting hormone treatment and during follow-up in transgender women (TW) with or without gonadectomy by investigating serum total (TT), calculated free testosterone (cFT), DHEA, DHEAS, androstenedione and SHBG.
Methods
This prospective cohort study was part of the ENIGI study. Sex steroids were assessed at baseline and at 12 and 24 months of follow-up using immuno-assay (SHBG, DHEAS) and LC-MS/MS (TT, DHEA, androstenedione). FT was calculated. Gender affirming hormones were initiated at baseline: estrogens (oral or transdermal) and anti-androgens (cyproterone acetate 25-50 mg/day). After orchiectomy the anti-androgen therapy was stopped and the estrogens were continued unchanged. Data from 113 TW with ≥ 2 years of follow-up at the Ghent, Belgium site were analyzed prospectively. Subgroup analyses were performed in TW who underwent orchiectomy (group A, $n = 59$) vs TW who did not (group B, $n = 54$), at baseline, pre-operatively vs at month 12, and post-operatively vs a month 24.
Results
In group A, serum TT levels decreased from 572.69 ± 11.76 ng/dl to 18.71 ± 11.91 ng/dl (baseline vs. pre-gonadectomy, $P < 0.001$) and cFT decreased from 11.34 ± 0.35 ng/dl to 0.26 ± 0.35 ng/dl (baseline vs. pre-gonadectomy, $P < 0.001$). No further effect of gonadectomy on serum TT and cFT levels could be shown, although a trend towards decrease was observed. SHBG increased post-gonadectomy ($P < 0.001$). Androstenedione, DHEA, DHEAS decreased from baseline to pre-gonadectomy ($P < 0001$), but remained stable afterwards. Similarly in group B, serum TT, cFT, androstenedione, DHEA and DHEAS decreased between baseline vs. 12 months ($P < 0.001$), while SHBG increased ($P < 0.001$); all variables remained stable afterwards. When comparing both groups after 24 months, no group differences in serum TT levels were found. However, SHBG was shown to be higher in group A vs. group B (73.2 ± 39.6 nmol/l vs. 57.2 ± 37.2 nmol/l respectively, $P = 0.004$), whereas cFT (0.18 ± 0.12 ng/dl vs. 0.26 ± 0.26 ng/dL, $P = 0.016$), androstenedione (71.0 ± 32.4 ng/dL vs. 85.3 ± 37.2 ng/dL, $P = 0.042$) and DHEA (4.99 ± 3.61 µg/L vs. 7.34 ± 4.62 µg/L, $P = 0.002$) were lower.
Conclusion
Serum TT and cFT levels remained unchanged post-orchiectomy compared to before, if low TT was confirmed when on hormonal treatment (including anti-androgens) reflecting patient compliance. At 24 months of follow-up TW who underwent orchiectomy had lower cFT, androstenedione and DHEA and higher SHBG, compared to those with a continued stable dose of anti-androgens.

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011

A cross-sectional analysis of the association between testosterone and biopsy-proven non-alcoholic fatty liver disease in 134 obese men

De Herdt C[1], De Block C[1,3], Verrijken A[1], Van Dessel K[1], Francque S[2,3], Van Gaal L[1,3] & Dirinck E[1,3]
[1]Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Antwerp, Belgium; [2]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium; [3]Universtity of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, Belgium

Background and aims
Low levels of testosterone and non-alcoholic fatty liver disease (NAFLD) in obese men are both linked to the metabolic syndrome, but the independent association between testosterone and NAFLD needs to be elucidated. In this cross-sectional analysis the association between total testosterone (total T) and calculated free testosterone (cFT) on the one hand and NAFLD, non-alcoholic steatohepatitis (NASH) and fibrosis on the other hand was investigated in obese men.
Methods
Data of 134 men of 18 years or older and a body mass index of at least 25 kg/m^2who underwent a liver biopsy after visiting the obesity clinic were collected. Liver biopsy was performed if there was suspicion of NAFLD.

Individuals were classified into 3 categories: no NAFLD, non-alcoholic fatty liver (NAFL) and NASH according to the Steatosis-Activity-Fibrosis score. Furthermore, the stage of fibrosis was evaluated. Because of an unequal distribution, the 5 stages were divided into stage 0-1 and stage 2-4. Free testosterone (cFT) was calculated by using the Vermeulen equation.
Results
Mean age was 45 ± 12 year, median BMI was 39.6 kg/m^2(range 25.0-64.9). Only 5.2% of the individuals had no NAFLD. Of the individuals with NAFLD, 15.7% had NAFL and 79.1% had NASH. Fibrosis stage 0 to 4 were present in respectively 47.8, 26.9, 17.2, 7.5 and 0.7%. CFT and total T were below the limit of normal in respectively 63% and 23% of individuals. One-way ANOVA showed no significant difference in the mean level of total T and cFT between men having no NAFLD, NAFL and NASH that persisted after controlling for covariables. Ordinal regression analysis did not show a significant effect of total T or cFT on the grade of NAFLD. One-way ANOVA showed a significant lower level of cFT in men having fibrosis stage 2-4 ($P = 0.013$) compared to men having fibrosis stage 0-1. After controlling for BMI, HDL-cholesterol, TSH, oestradiol and HOMA-IR, the significant difference in the level of cFT did not persist. No significant difference was seen in the level of total T. Ordinal regression analysis showed a decreasing level of cFT was associated with a higher stage of fibrosis ($P = 0.016$). This association did not persist after controlling for BMI, HDL-cholesterol, TSH, oestradiol and HOMA-IR. No significant effect of total T on the stage of fibrosis was seen.
Conclusion
To the best of our knowledge, this is until now the largest study investigating the association between sex steroid levels and biopsy-proven NAFLD. After controlling for covariables no association was found between the level of total T and cFT on the one hand and NAFLD, NASH or fibrosis on the other hand.

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012

The impact of anti-androgen therapy on bone in men treated for paraphilia: a retrospective cohort study

De Landtsheer Anais, Bekaert Lieslinde, Antonio Leen & Vanderschueren Dirk
Department of Endocrinology, University Hospitals Leuven, 3000 Leuven, Belgium

Background
Guidelines suggest treating paraphilias with androgen-deprivation therapy (ADT). However little evidence is available about the long-term impact on bone and how to manage this adverse event.
Aim
The aim of this study is to assess the impact of ADT on bone mass and bone mineral density (BMD) in men treated for hypersexuality with cyproterone acetate (CPA) and GnRH agonists (GnRHa), and to evaluate the effect of treatment with bisphosphonates.
Methods
Baseline and follow-up DXA scan data (lumbar and femoral T-scores) were retrospectively extracted from electronic medical files of hypersexual men who received CPA and/or GnRHa.
Outcomes
Lumbar (-0.39 ± 0.17, Mean ± SEM, $P = 0.046$), femoral neck (-0.34 ± 0.09) and total femur (-0.33 ± 0.12, $P = 0.014$) T-scores decreased significantly in the CPA only group (n13) during a mean follow-up of 6.0 ± 5.3 years. In the GnRHa group (n29), T-scores of all sites decreased significantly over 6.6 ± 4.4 years; (lumbar:-0.55 ± 0.12, $P < 0.001$, femoral neck:-0.53 ± 0.09 and total femur: -0.44 ± 0.09, $P < 0.001$). There however was no significant T-score change in the group who received bisphosphonates (n11) (lumbar: -0.25 ± 0.14, $P = 0.106$, femoral neck -0.15 ± 0.17, $P = 0.402$ and total femur -0.25 ± 0.14, $P = 0.106$) during 5.0 ± 2.8 years of follow-up.
Clinical Implications
Patients with baseline T-scores in the osteopenic range may be at risk to fall in the osteoporotic range after more than 5 years of treatment with ADT. Treatment with bisphosphonates could prevent bone loss.
Strengths & Limitations
This study is the first to assess BMD loss over a long period in a large cohort of hypersexual men treated with ADT.
Conclusion
Following a mean duration of 6 years of ADT, a significant decline in BMD of approximately half a standard deviation in T-score at spine and femur was observed, which may be prevented by bisphosphonates.

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013

Let's go beyond: The relationship between arterial stiffness and CGM-derived glycemic control in patients with type 1 diabetes

Helleputte S.[1,2], Calders P.[1], Lapauw B.[3] & De Backer T.[4]
[1]Faculty of Medicine and Health Sciences, Ghent University, Belgium; [2]Fonds Wetenschappelijk Onderzoek (FWO) Vlaanderen; [3]PhD, MD, Department of Endocrinology, Ghent University Hospital, Belgium; [4]PhD, MD, Department of Cardiology, Ghent University Hospital, Belgium

Background
In patients with type 1 diabetes (T1D), arterial stiffness is a potential alternative biomarker for cardiovascular (CV) risk as it has recently shown important prognostic value in the development of CVD that is independent from traditional risk factors. Glycemic control by means of HbA1c is a main determinant of arterial stiffness progression, however the relationship with continuous glucose monitoring (CGM)-derived parameters such as time in range (TIR) has not been explored yet.
Aims
Evaluate arterial stiffness and its determinants in T1D patients who are still free from known CVD, and investigate its relationship with new CGM-derived parameters of glycemic control.
Methods
Cross-sectional study, in which adult T1D patients with a disease duration (DD) of at least 10 years and without known CVD were enrolled. The STENO T1D risk engine was used to estimate 10-years CV event risk, with 3 groups: low (< 10%), moderate (10-20%), and high CV event risk (20%). Current level and 10-years history of HbA1c was collected, as well as advanced glycation end products (AGEs; AGEreader). Patients were equipped with a CGM sensor (Dexcom G5) for 7 days, to determine TIR, time in hyper- and hypoglycaemia, and parameters of glycemic variability. Arterial stiffness was evaluated with carotid-femoral pulse wave velocity (cfPWV) (SphygmoCor). Ambulatory blood pressure monitoring, duplex carotid ultrasound and coronary artery calcium scoring was performed; and information on renal function and the presence of microvascular complications was also retrieved. Levels of physical activity (DynaPort MoveMonitor) and exercise capacity were evaluated as well. Pearson (r) and Spearman (rs) correlations, and multiple linear regression were used to investigate associations. Independent samples t-test and one-way ANOVA or their non-parametric alternatives were used to compare variables between two or more groups, respectively.
Results
54 patients (M/F: 32/22; age: 46 ± 9.5 yrs; DD: 27 ± 8.8 yrs; HbAc1: 7.8 ± 0.83%) were included. According to the STENO 10-year CV event risk score, 20 patients (37%) were at low, 20 patients (37%) at moderate, and 14 patients (26%) at high risk. Median cfPWV was 8.3 [6.8-10.1] m/s, with approximately 25% of patients showing increased aortic stiffness, i.e. cfPWV > 10 m/s or above the 90th percentile of age-and BP-matched reference values. cfPWV was strongly associated with the STENO score (r = +0.75), increasing in each higher STENO group ($P < 0.01$); and showed moderate to good individual correlations with the traditional risk factors age (rs = +0.69), disease duration (rs = +0.41) and 24-hour MAP (rs = +0.45). cfPWV was significantly associated with current HbA1c (rs = +0.28), mean 10-years HbA1c (rs = +0.36) and AGEs (+0.40), but not with any of the CGM-derived parameters. cfPWV was also negatively associated with VO2max and level of physical activity. Regressions models for cfPWV showed the following: (1) The STENO score explained 57% of variation ($R^2 = 0.566$, $P < 0.001$); (2) Sedentary time showed additional predictive value improving the fit of the model ($R^2 = 0.698$, $P < 0.05$); (3) Only one alternative model that did not include the STENO score achieved better fit ($R^2 = 0.675$, $P < 0.001$) including age, disease duration, mean 10-years HbA1c and 24 hours-MAP. CONCLUSION: This study demonstrates that a substantial proportion (~25%) of T1D patients who are still free from CVD show premature arterial stiffening, which was found to be highly associated with the STENO score. The present study also provides arguments that HbA1c should not be completely replaced by TIR, as long-term glycemic control reflected by HbA1c and AGEs was a main determinant of arterial stiffness, while no relationship was found with any of the CGM-derived parameters. Furthermore, physical inactivity showed an additional negative impact on arterial stiffness, while no relationship was found with any of the CGM-derived parameters. Furthermore, physical inactivity showed an additional negative impact on arterial stiffness. Future studies should investigate if evaluation of arterial stiffness could be implemented in clinical practice and which patients benefit the most from its assessment, so that adequate preventive measures can be taken.
Key words
Type 1 diabetes, Arterial stiffness, Glycemic control, Continuous glucose monitoring, Time in range.

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014

Estimated glucose disposal rate, non-alcoholic fatty liver disease and micro- and macrovascular complications in type 1 diabetes: Towards a new biomarker?

Mertens Jonathan[1,2,3], Weyler Jonas[3], Vonghia Luisa[2;3], Kwanten Wilhelmus[2,3], Dirinck Eveline[1,3], Francque Sven[2,3] & De Block Christophe[1,3]
[1]Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital, Edegem; [2]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem; [3]Laboratory of Experimental Medicine an Paediatrics (LEMP), University of Antwerp, Wilrijk

Background and aims
Insulin resistance is increasingly prevalent in patients with type 1 diabetes (T1D). Insulin resistance is associated with both cardiovascular complications and non-alcoholic fatty liver disease (NAFLD), but its assessment is challenging in T1D due to the technical difficulties of the euglycaemic clamp technique. The estimated glucose disposal rate (eGDR) is a validated alternative to quantify insulin resistance in T1D, but its role in clinical practice is largely unexplored. This study aims to explore the association between eGDR and micro- and macrovascular complications and NAFLD, compared to body mass index (BMI) or HbA1c alone.
Materials and methods
individuals with T1D were included in this cross-sectional study. eGDR was categorised in four groups ($\geq$ 8, 6-7.9, 4-5.9 and $<$ 4 mg/kg/min). NAFLD was determined by ultrasound combined with elastometry (Saverymuttu grade $\geq$ 1 and controlled attenuation parameter $\geq$ 248 dB/m). Microvascular complications were assessed with fundoscopy, microfilament test of the feet and 24-hour microalbuminuria. Macrovascular events were defined by clinical coronary, cerebrovascular or peripheral arterial events or significant stenosis requiring intervention. Multiple logistic regression was performed to identify independent associations with vascular complications and NAFLD, after adjusting for the most relevant confounders.
Results
A total of 510 individuals were consecutively included. NAFLD was present in 21.8% of cases. Median age was 48 [32-59] years with diabetes duration of 27 [15-36] years. An eGDR $<$ 4 was present in 7.8 % of cases, obesity prevalence was 19.1 %. Odds ratios (OR) for nephropathy and NAFLD in obese compared with normal weight individuals were 2.19 (95 % CI: 1.13-4.10; $P = 0.020$) and 10.32 (95 % CI: 5.73-18.60; $p < 0.001$). While the association with retinopathy was absent (OR 1.21 [95 % CI: 0.67-2.19; $P = 0.538$]), the association with macrovascular disease just barely failed to reach statistical significance (OR 2.47 [95 % CI: 0.92-6.65; $P = 0.074$]). Comparing individuals with eGDR $\geq$ 8 mg/kg/min, indicating high insulin sensitivity, to those with an eGDR $<$ 4 mg/kg/min indicating insulin resistance, showed significantly higher OR for nephropathy, NAFLD and macrovascular disease of 9.96 (95 % CI: 3.85-25.77; $p < 0.001$), 8.88 (95 % CI: 3.87-20.38; $p < 0.001$) and 6.06 (95 % CI: 1.60-22.73; $P = 0.007$), respectively in multivariable regression models including common risk factors. The association with retinopathy barely failed to reach a clinical and statistical significance (OR 2.11 [95 % CI: 0.91-4.93; $P = 0.083$].
Conclusion
Obesity, insulin resistance and NAFLD are prevalent in T1D and diabetes complications are not only related to BMI or metabolic control. Insulin resistance is associated with the presence of NAFLD and micro- and macrovascular complications. This work was presented orally at the 14th Advanced Technologies & Treatments for Diabetes (2021) conference and the 57th European Association for the Study of Diabetes (2021) conference.

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015

Factors associated with early postpartum weight retention in women with gestational diabetes

Minschart Caro[1], Snoeks Loran[2], Maes Toon[3], De Block Christophe[4], Van Pottelbergh Inge[5], Myngheer Nele[6], Abrams Pascale[7,8], Vinck Wouter[8], Leuridan Liesbeth[9], Mathieu Chantal[1,10], Billen Jaak[11], Matthys Christophe[1,9], Weyn Babs[12], Laenen Annouschka[13], Bogaerts Annick[14, 15] & Benhalima Katrien[1,10]
[1]Clinical and Experimental Endocrinology, Department of Chronic Diseases and Metabolism, KU Leuven, 3000 Leuven, Belgium; [2]Biomedical Sciences, KU Leuven, Belgium; [3]Department of Endocrinology, Imelda Hospital, 2820 Bonheiden, Belgium; [4]Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, 2650 Edegem, Belgium; [5]Department of Endocrinology, OLV Hospital Aalst, 9300 Aalst, Belgium; [6]Department of Endocrinology, General Hospital Groeninge, 8510 Kortrijk, Belgium; [7]Department of Endocrinology, GZA Hospital Sint-Vincentius, 2018 Antwerp, Belgium; [8]Department of Endocrinology, GZA Hospital Sint-Augustinus, 2610 Wilrijk, Belgium; [9]Department of Endocrinology, General Hospital Klina, 2930 Brasschaat, Belgium; [10]Department of Endocrinology, University Hospitals Leuven, 3000 Leuven, Belgium; [11]Department of Laboratory Medicine, University Hospitals Leuven, 3000 Leuven, Belgium; [12]Department of Electrical Engineering, Processing Speech and Images, KU Leuven, 3000 Leuven, Belgium; [13]Centre of Biostatics and Statistical Bioinformatics, KU Leuven, 3000 Leuven, Belgium; [14]Department of Development and Regeneration, KU Leuven, 3000 Leuven, Belgium; [15]Faculty of Medicine and Health Sciences, Centre for Research and Innovation in Care (CRIC), University of Antwerp, 2610 Wilrijk, Belgium

Aims
To identify factors associated with early postpartum weight retention (PPWR) in women with recent gestational diabetes mellitus (GDM).
Methods
Multicentric prospective study in women with a recent history of GDM based on the IADPSG criteria at the oral glucose tolerance test (OGTT) 6-16 weeks postpartum. Data obtained from electronic medical records, self-administered questionnaires, clinical examination and blood sample collection were used for the analysis. Early PPWR was defined as the difference between the maternal weight measured at the postpartum OGTT and the prepregnancy weight (kg).
Results
Of all 535 participants at the postpartum OGTT, 30.6% (164) had an impaired OGTT [28.8% (154) glucose intolerance and 1.9% (10) diabetes]. Of all women with an impaired OGTT, 32.9% (54) had impaired fasting glucose (IFG), 52.4% (86) impaired glucose tolerance (IGT) and 14.6% (24) had IFG and IGT combined. Weight retention (PPWR $>$ 0 kg) was observed in 53.8% (288) of all women, with 14.4% (77) retaining more than 5 kg. Women with PPWR $>$ 0 kg (288) had less often a higher education degree [65.4% (187) vs. 78.0% (191), $P = 0.015$], had more often a history of smoking [33.5% (90) vs. 23.2% (54), $P = 0.013$], lower prepregnancy BMI [24.9 kg/m^2(22.0-28.3) vs. 26.5 kg/m^2(23.3-30.7), $P < 0.001$] and more often excessive gestational weight gain (GWG) [28.7% (75) vs. 6.6% (15), $P < 0.001$] compared to women without PPWR (247). Babies born to mothers with PPWR $>$ 0 kg were more often small-for-gestational-age (SGA) [8.0% (23) vs. 2.8% (7) with an odds ratio (OR) adjusted for education, smoking history, prepregnancy BMI and GWG of 3.58 (95% CI 1.34-9.57), $P = 0.011$]. At the postpartum visit, women with PPWR $>$ 0 kg had a higher BMI [26.2 kg/m^2(23.1-29.9) vs. 25.3 kg/m^2(22.3-29.3), $P = 0.033$], higher fasting triglycerides [88.0 mg/dl (60.0-124.0) vs. 70.0 mg/dl (55.0-99.0), $P < 0.001$] and higher fasting plasma glucose (FPG) [90.0 mg/dl (84.5-96.5) vs. 88.0 mg/dl (83.0-95.0), $P = 0.016$] compared to women without PPWR. They gave less often breastfeeding [49.8% (143) vs. 65.0% (160), $P < 0.001$] and had a lower dietary quality index [77.5 (6.2-83.6) vs. 78.8 (72.1-84.2), $P = 0.041$].
Conclusions
Different factors such as education level, smoking status, excessive GWG and SGA are associated with PPWR at the postpartum OGTT in women with a recent history of GDM. Women with PPWR have a worse metabolic profile in early postpartum and give less often breastfeeding compared to women without PPWR.

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016

Characteristics, pregnancy outcomes and tolerance of screening tests according to the preference of women for the method of GDM screening

Raets Lore[1], Vandewinkel Marie[2], Van Crombrugge Paul[3], Moyson Carolien[1], Verhaeghe Johan[4], Vandeginste Sofie[5], Verlaenen Hilde[5], Vercammen Chris[6], Maes Toon[6], Dufraimont Els[7], De Block Christophe[8], Jacquemyn Yves[9], Mekahli Farah[10], De Clippel Katrien[11], Van Den Bruel Annick[12], Loccufier Anne[13], Laenen Annouschka[14], Devlieger Roland[4], Mathieu Chantal[1] & Benhalima Katrien[1]
[1]Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Belgium; [2]Medicine, KU Leuven, Belgium; [3]Department of Endocrinology, OLV ziekenhuis Aalst-Asse-Ninove, Belgium; [4]Department of Obstetrics & Gynecology, UZ Gasthuisberg, KU Leuven, Belgium; [5]Department of Obstetrics & Gynecology, OLV ziekenhuis Aalst-Asse-Ninove, Belgium; [6]Department of Endocrinology, Imelda ziekenhuis, Belgium; [7]Department

of Obstetrics & Gynecology, Imelda ziekenhuis, Belgium; [8]Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Belgium; [9]Department of Obstetrics & Gynecology, Antwerp University Hospital, Belgium; [10]Department of Endocrinology, Kliniek St-Jan Brussel, Belgium; [11]Department of Obstetrics & Gynecology, Kliniek St-Jan Brussel, Belgium; [12]Department of Endocrinology, AZ St Jan Brugge, Belgium; [13]Department of Obstetrics & Gynecology, AZ St Jan Brugge, Belgium; [14]Center of Biostatics and Statistical bioinformatics, Leuven, Belgium

Aims
To compare the characteristics, pregnancy outcomes and tolerance of screening tests between women who prefer a two-step screening strategy with a glucose challenge test (GCT), women who prefer an one-step screening strategy with an oral glucose tolerance test (OGTT) and women without clear preference for screening method for gestational diabetes mellitus (GDM).
Methods
1803 women from a Belgian multi-centric prospective cohort study (BEDIP-N study) received both a GCT and a 75g oral OGTT using the IADPSG criteria. Tolerance of screening tests and preference for screening strategy were evaluated by a self-designed questionnaire at the time of the GCT and OGTT.
Results
Of all women, 46.3% (834) preferred two-step screening, 26.2% (472) preferred an one-step screening strategy and 27.6% (497) had no clear preference. Women who preferred one-step screening had more often complaints from the GCT compared to women who preferred two-step screening [25.0% (114) vs. 18.0% (146), $P = 0.003$], while women who preferred two-step screening had more complaints from the OGTT compared to women who preferred the one-step strategy [50.4% (420) vs. 40.3% (190), $P < 0.001$] or women without preference [50.4% (420) vs. 34.9% (173), $P < 0.001$]. There was no difference in rate of parity between groups. Compared to women who preferred one-step screening, women who preferred two-step screening had less often an ethnic minority background [6.0% (50) vs. 10.7% (50), $P = 0.003$], had less often a low income [1.8% (15) vs. 5.0% (23), $P = 0.003$], had less often a first degree family history of GDM [3.8% (29) vs. 6.4% (28), $P = 0.039$] or a previous history of GDM [7.3% (29) vs. 13.8% (32), $P = 0.008$], had a lower BMI [23.9 $\pm$ 4.0 vs. 25.4 $\pm$ 5.3, $P < 0.001$), were less overweight or obese [respectively 23.1% (50) vs. 24.8% (116), $P < 0.001$ and 7.9% (66) vs. 18.2% (85), $P < 0.001$], and less insulin resistant in early pregnancy (HOMA-IR 8.9 (6.4-12.3) vs. 9.9 (7.2-14.2), $P < 0.001$]. Pregnancy outcomes were similar, except for a lower rate of labour inductions and emergency caesarean sections (CS) in the two-step screening group [respectively 26.6% (198) vs. 32.5% (137), $P = 0.031$ and 8.2% (68) vs. 13.0% (61), $P = 0.005$].
Conclusions
Women with a more adverse metabolic profile preferred one-step screening with OGTT while women who preferred two-step screening had a better metabolic profile, and more complaints of the OGTT.

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017

Prevalence of and risk factors for sexual dysfunctions in adults with type 1 or type 2 diabetes: Results from Diabetes MILES - Flanders

Van Cauwenberghe Jolijn[1,2], Enzlin Paul[3,4], Nefs Giesje[5,6,7], Ruige Johannes[1,8], Hendrieckx Christel[9,10], De Block Christophe[1,2] & Pouwer Frans[9,11,12]
[1]Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Edegem, Belgium; [2]Laboratorium of Experimental Medicine and Pediatrics, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; [3]Department of Neurosciences, Institute for Family and Sexuality Studies, KU Leuven, Leuven, Belgium; [4]Centre for Clinical Sexology and Sex Therapy, UPC KU Leuven, Leuven, Belgium; [5]Department of Medical Psychology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands; [6]Diabeter, National Treatment and Research Center for Children, Adolescents and Adults With Type1 Diabetes, Rotterdam, the Netherlands; [7]Department of Medical and Clinical Psychology, Center of Research on Psychological and Somatic disorders (CoRPS), Tilburg University, Tilburg, the Netherlands; [8]Centrum Diabeteszorg, AZ Nikolaas, Sint-Niklaas, Belgium; [9]School of Psychology, Deakin University, Geelong, Victoria, Australia; [10]The Australian Centre for Behavioural Research in Diabetes, Melbourne, Victoria, Australia; [11]Department of Psychology, University of Southern Denmark, Odense, Denmark; [12]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

Background and aims
The prevalence of sexual dysfunctions in people with diabetes is still debated and understudied in women. This study examines the prevalence of sexual dysfunction in men and women with type 1 or type 2 diabetes (T1D or T2D) and the associations with clinical and psychological variables.
Methods
Adults with diabetes (n756) completed an online survey including questions on sexual functioning (adapted Short Sexual Functional Scale), general emotional well-being (WHO-5), symptoms of anxiety (GAD-7), diabetes distress (PAID-20) and healthcare use.
Results
One third of participants reported a sexual dysfunction. Men reported erectile dysfunction (T1D:20%; T2D: 33%), and orgasmic dysfunction (T1D:22%; T2D:27%). In men, sexual dysfunction was independently associated with, older age (OR = 1.05, $P = 0.019$), higher waist circumference (OR = 1.04; $P = 0.001$) and longer duration of diabetes (OR = 1.04; $P = 0.007$). More men with sexual dysfunction reported diabetes distress (20% vs. 12%, $P = 0.026$). Women reported decreased desire (T1D:22%; T2D:15%) and decreased arousal (T1D:9%; T2D:11%). More women with sexual dysfunction reported diabetes distress (36% vs. 21%, $P = 0.003$), impaired emotional well-being (36% vs. 25%, $P = 0.036$) and anxiety symptoms (20% vs. 11%, $P = 0.026$).
Conclusion
Sexual dysfunctions are common in diabetes and differ between men and women. In men clinical factors are associated with sexual dysfunction. More women with sexual dysfunction had low well-being and anxiety symptoms compared to women without sexual dysfunction. For both men and women, sexual dysfunction was associated with diabetes distress.

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018

Risk for ketonaemia in type 1 diabetes pregnancies with sensor-augmented pump therapy with predictive low glucose suspend compared to low glucose suspend: an open-label crossover RCT

van Nes Falco[1], Mathieu Chantal[2], Laenen Annouschka[3], Gillard Pieter[2] & Benhalima Katrien[2]
[1]Master of Medicine, KU Leuven; [2]Department of Endocrinology, UZ Gasthuisberg, KU Leuven; [3]Leuven Biostatistics and Statistical Bioinformatics Center, KU Leuven

Background
Little is known about the influence of the Predictive Low Glucose suspend (PLGS) function of Sensor Augmented Pump therapy on ketone production in patients with type 1 diabetes mellitus (T1DM), compared to the Low Glucose Suspend function. To evaluate the effect, we compared the frequency of elevated ketone levels, the duration of insulin infusion suspension, the glycaemic control and patient satisfaction between the two settings.
Methodology
We carried out an open-label crossover RCT in 10 women with T1DM, aged 18 to 45, using the Medtronic 640G insulin pump. Gestational age at inclusion was 12 to 30 weeks. Patients were randomly assigned between 2 groups. Group 1 used the PLGS function for 2 weeks, followed by LGS for 2 weeks. Group 2 followed the schedule in reverse order. Ketone concentrations were measured 3 times daily (Fasted, 11h-13h, 21h-23h) using the Freestyle Abbott meter. CGM-data were collected to calculate Time in Range (TIR), Time above range (TAR) and Time in hypoglycaemia. Patients also completed 7 questionnaires on treatment satisfaction at baseline and at each study visit.
Results
Median age at inclusion was 31.50 years (24.0-33.0), gestational week was 12.50 weeks (12.0-15.0), TIR was 64.65% (55.6-68.7), BMI was 26.65 kg/m2 (24.5-31.8) and HbA1c was 5.95% (5.8-6.1). 9 patients were Caucasian, 1 had a Northern-African background. 8 women were nulliparous, 1 patient had diabetic retinopathy and 1 had microalbuminuria.
Conclusion
SAP therapy with PLGS mode is a safe alternative to LGS in pregnant T1DM patients, without increased risk for significant ketonaemia. Despite increased suspension time of insulin with PLGS, participants achieved similar glycaemic control, with less time in hypoglycaemia, and similar treatment satisfaction scores.

	LGS	PLGS	p-value
Insulin suspension time per day (hours)	2.0 (1.3; 2.3)	3.5 (3.3; 5.0)	0.002
Insulin suspension time over 2 weeks (hours)	28.2 (17.9; 32.0)	48.8 (45.8; 70.0)	0.002
Total ketonaemia (mmol/l)	0.08 (0.06-0.1)	0.08 (0.07; 0.1)	0.084
Fasted ketonaemia (mmol/l)	0.08 (0.05; 0.10)	0.07 (0.06; 0.11)	0.432
Midday ketonaemia (mmol/l)	0.07 (0.04; 0.09)	0.09 (0.08; 0.10)	0.002
Evening ketonaemia (mmol/l)	0.08 (0.06; 0.11)	0.08 (0.06; 0.11)	1.000
Frequency of ketonaemia >0.6mmol/l (%)	0	0.5 (2)	1.000
Frequency of ketonaemia >1mmol/l (%)	0	0	
TIR (%)	64.7 (58.0; 68.8))	61.1 (56.5; 67.5)	0.492
Time >140mg/dl	30.1 (23.6; 35.2)	33.3 (28.6; 36.6)	0.193
Time >180mg/dl	10.4 (6.7; 13.7)	14.4 (10.5; 16.6)	0.275
Time <63mg/dl	7.5 (4.6; 8.3)	4.2 (2.4; 6.9)	0.014
Time <50mg/dl	2.1 (1.4; 2.7)	1.1 (0.8; 3.1)	0.232
Low blood glucose index	2.8 (1.8; 3.5)	1.9 (1.4-2.6)	0.019
Coefficient of variation (%)	37.3 (35.3; 39.7)	35.2 (32.9; 39.0)	0.310
Mean amplitude of glycaemic excursions (mg/dl)	121.0 (107.4; 135.6)	123.5 (114.6; 137.6)	1.000
DTSQs	31.0 (26.0; 34.0)	32.0 (27.0; 33.0)	0.656
HFS-B	19.0 (17.0; 22.0)	22.0 (19.0; 23.0)	0.547
PAID-5	2.0 (1.0; 5.0)	3.0 (1.0; 5.0)	1.000

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019

COVID-19 & Cushing's disease in a patient with ACTH-secreting pituitary carcinoma

de Filette Jeroen M.K.[1], Sol Bastiaan[1], Awada Gil[2], Andreescu Corina E.[1], Unuane David[1], Nguyen Duc Nam[3], Aspeslagh Sandrine[2], Poelaert Jan[3,4], Velkeniers Brigitte[1] & Bravenboer Bert[1]
[1]Department of Endocrinology; [2]Department of Medical Oncology; [3]Department of Critical Care Medicine and; [4]Department of Anesthesiology and Perioperative Medicine, University Hospital Brussels (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium

Background
The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of an unprecedented scale, with an ever-growing impact on healthcare systems. The clinical presentation of coronavirus disease 2019 (COVID-19) is diverse, ranging from asymptomatic illness to respiratory failure requiring admission to the intensive care unit (ICU). Risk factors for severe presentation include old age, male gender, underlying comorbidities such as metabolic syndrome, chronic lung diseases, heart-, liver- and kidney diseases, malignancy, immunodeficiency, and pregnancy (1). Little is known about the risk of COVID-19 in patients with rare endocrine malignancies, such as pituitary carcinoma.
Case presentation
We describe the case of a 43-year-old man with ACTH-secreting pituitary carcinoma (with cerebellar and cervical drop metastases) who experienced a severe COVID-19 pneumopathy. He had previously received multiple lines of treatment including surgery, radiotherapy, ketoconazole, pasireotide, cabergoline, bilateral (subtotal) adrenalectomy, and temozolomide chemotherapy, as described elsewhere (2). His most recent therapy was a combination of immune checkpoint inhibitors with ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) (anti-CTLA-4 and anti-PD-1, respectively) every 3 weeks for 4 cycles, after which maintenance therapy with nivolumab (240 mg) every 2 weeks was continued. Residual endogenous cortisol production was suppressed with ketoconazole 800mg daily. He had disease stabilisation with a decrease in 08:00h plasma ACTH, urinary free cortisol, and stable radiographic findings. Surgical resection of the left adrenal remnant was planned, but could not proceed due to the development of COVID-19 infection. In March 2021, he consulted our emergency department with respiratory exhaustion due to SARS-CoV-2 infection requiring urgent endotracheal intubation. He was commenced on high dose dexamethasone for 10 days together with broad-spectrum antibiotics for positive sputum cultures containing *Serratia*, methicillin-susceptible *S. aureus* and *H. Influenzae*. He developed multiple organ involvement, including metabolic acidosis, acute renal failure requiring continuous veno-venous hemofiltration, acute coronary syndrome type 2, septic thrombophlebitis of the right jugular vein, and critical illness polyneuropathy. He was readmitted twice to the ICU, for ventilator-associated pneumonia and central line-associated bloodstream infection respectively. He was eventually discharged from the hospital and able to continue his rehabilitation. Regarding his endocrine treatment, a "block-replace" regimen was adopted with the continuation of ketoconazole (restarted on day 11), and the supplementation of hydrocortisone at a dose depending on the current level of stress. The consecutive daily dose of hydrocortisone and ketoconazole is demonstrated in **Figure 1**.
Discussion
The learning points of this case are twofold. *Firstly*, this case illustrates the presence of many of the comorbidities for COVID-19 mortality in patients with Cushing's disease, such as the cardiovascular risk factors of obesity, arterial hypertension, impaired glucose metabolism, as well as increased thromboembolic risk and increased susceptibility to bacterial infections. Patients with endogenous glucocorticoid excess may therefore be particularly susceptible to severe COVID-19. Secondly, a « block-replace » therapy might be preferred in this patient population, to avoid adrenal insufficiency and reduce the need for biochemical monitoring (as suggested by Newell-Price et al.) (3).
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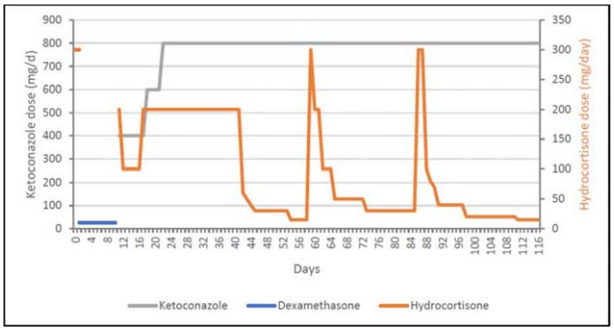

Figure 1. "Block-replace" therapy with ketoconazole and hydrocortisone/dexamethasone. Dexamethasone 10mg daily was initially started as COVID-19 treatment and as a stress regimen, followed by hydrocortisone at a dose consistent with current levels of stress. Ketoconazole was restarted on day 11 and titrated to a dose of 800mg daily to suppress endogenous glucocorticoid production.

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020

HLA-DR4/DR13 in a patient with durvalumab-induced thyroiditis

de Filette, Jeroen M.K[1], De Rop Jonas[1], André Stéphanie[2,3,4], De Mey Lynn[5], Aspeslagh Sandrine[6], Karmali Rafik[7], Van der Auwera Bart J[8] & Bravenboer Bert[1]
[1]Department of Endocrinology, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium; [2]Department of Pulmonary Medicine, Saint-Pierre University Hospital, Rue Haute 322, 1000, Brussels, Belgium; [3]Université Libre de Bruxelles, Brussels, Belgium; [4]Department of Pulmonary Medicine, Brugmann University Hospital, Brussels, Belgium; [5]Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium; [6]Department of Medical Oncology, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium; [7] Department of Endocrinology, CHU Brugmann Université Libre de Bruxelles, Brussels Belgium; [8] Diabetes Research Center, Vrije Universiteit, Brussel, Brussels, Belgium;

Background
Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 and its ligand (PD-1/PD-L1) are the current standard-of-care for many advanced cancers (1). This novel therapeutic approach comes with its costs in the form of immune-related adverse events (irAE). The underlying mechanisms are not yet fully understood. We explore the role of HLA in endocrinopathy related to ICI therapy using an interesting patient.

Case presentation
A 63-year-old woman was diagnosed in May 2019 with stage IIIB non-small cell lung carcinoma of the right superior lobe with PD-L1 expression > 50%. The patient had a partial therapeutic response on two cycles of radio-chemotherapy with carboplatin and vinorelbine, with persistence of mild hypermetabolism in pulmonary nodules. She was started on consolidation immunotherapy with durvalumab (anti-PD-L1), 10 mg/kg every two weeks, with the intended treatment duration of one year. A routine blood sampling performed before the first chemotherapy showed normal thyroid function with a TSH 1.37 mU/L (reference range: 0.27-4.20) and free T4 19.0 pmol/l (reference range: 12.0-22.0). The thyroid function was not rechecked before the first durvalumab dosing. In December 2019, after three cycles, the patient presented herself at the pneumology department with fatigue, weight loss (2 kg in two months) and increased shortness of breath. Laboratory analysis showed a mild hyperthyroidism with decreased TSH (0.23 mU/L) and increased free T4 (29.4 pmol/l). Approximately 6 weeks later, levothyroxine 50 mg daily was started because of an evolution towards hypothyroidism (with TSH 37.90 mU/L; free T4 5.8 pmol/l), as shown in **Figure 1**. Thyroperoxidase antibodies were positive (216 kUI/L, reference range: < 34), while the TSH receptor antibodies (TRAb, analysis of stimulating and blocking) were negative. Ultrasound examination of the thyroid was normal. Thyroid scintigraphy was not performed. HLA analysis showed A*02, -; B*15,*40; C*03,*07; the DR haplotypes: DRB1*04,*13, and the DQ haplotypes: DQB1*03,*06.
Discussion
This case report illustrates that more attention should be given to the immunogenetic background of oncology patients treated with immunotherapy (2). HLA polymorphisms have been implicated for 'conventional' autoimmune thyroid disease (AITD), such as DR4 (susceptible), DR7 and DR13 (protective) for Hashimoto, and DR3 (susceptible) for Graves' disease. Our patient has a mixed HLA susceptibility, with the presence of both HLA-DR4 (susceptible) and DR13 (protective). A variety fo other HLA associations have been described in patients with endocrinopathy related to immune therapy, such as DR4 in diabetes mellitus; DR4-DQ4 and DR9-DQ9 in diabetes mellitus of Asian origin (3); HLA-A2, A24, B7, DR1 and DR4 (lymphocytic hypophysitis) in two cases of nivolumab-induced hypophysitis, DRB1*04 : 05-DQA1*03 :03-DQB1*04 :01 (autoimmune polyglandular syndrome with pituitary disorder in a Japanese population) in a patient with isolated adrenocorticotropin deficiency by nivolumab-induced hypophysitis.
Conclusion
In summary, our case of patient with thyroiditis associated with the PD-L1 inhibitor durvalumab highlights not only the need for proactive monitoring of thyroid function, but also identifying biomarkers associated with an increased risk of ICI-induced side effects for better patient selection, optimal management and improved understanding of the mechanisms involved.
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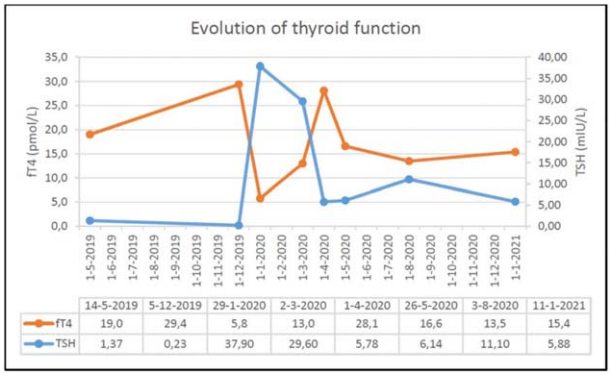

	14-5-2019	5-12-2019	29-1-2020	2-3-2020	1-4-2020	26-5-2020	3-8-2020	11-1-2021
fT4	19,0	29,4	5,8	13,0	28,1	16,6	13,5	15,4
TSH	1,37	0,23	37,90	29,60	5,78	6,14	11,10	5,88

Figure 1. Evolution fo thyroid function during durvalumab-associated thyroiditis.

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021

Li-Fraumeni syndrome presenting as peripheral precocious puberty caused by a pure androgen-secreting adrenal adenoma

Ryckx Sofie, De Schepper Jean & Staels Willem
Division of Pediatric Endocrinology, Department of Pediatrics, KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Introduction
Precocious puberty in boys is the development of secondary sexual characteristics before 9 years of age. Peripheral precocious puberty (PPP), as opposed to central precocious puberty (CPP), is caused by autonomous secretion of androgens or human chorionic gonadotropin (hCG). Testicular volume, penis size, growth velocity, gonadotropin and androgen levels, and bone age readings aid in diagnosing precocious puberty and in identifying its cause. Distinguishing CPP from PPP is rather straightforward and based on the gonadotrophin levels, which are pubertal or prepubertal respectively. However, the differential diagnosis of PPP is challenging and includes several neoplastic causes, such as Leydig cell tumors, hCG-producing germ cell tumors, and androgen-secreting adrenocortical tumors (ACT) (1). ACT are rare in childhood with a reported annual incidence of 0.2-0.3 new cases per million per year. In children, as opposed to adults, most ACT are functioning and secrete cortisol, frequently in combination with androgens. Pure androgen-secreting adrenocortical tumors (PASACT) are extremely rare, they are usually sporadic and benign, but sometimes associated with tumor syndromes, such as Beckwith-Wiedemann syndrome and Li-Fraumeni syndrome (LFS) (2). We present a 2-year-old boy who presented with isosexual PPP due to a PASACT, as the first presentation of LFS. This case illustrates the differential diagnosis of PPP in young boys and highlights the importance of the histopathological and genetic analysis of PASACT.
Case report
A 2 ½ -year-old boy presented with a 6-month history of penile enlargement, pubic hair, frequent erections, and rapid linear growth. No exposure to exogenous testosterone was evident. The boy's personal and family history was unremarkable. On physical examination his weight was at +2.5 SD, and height at +1.7 SD. He was at Tanner stage Al P4 G3, penile length was 6.8 cm, and he had symmetrical prepubertal testes without palpable abnormalities. He had hypertension with repeated blood pressures above the 95th percentile. His skeletal maturation was advanced by 1 year. Serum gonadotrophin levels were prepubertal, while testosterone (9.9 µg/1) and dehydroepiandrosterone-sulphate (DHEA-S) levels (1.49 mg/1) were elevated. Serum electrolytes, 17-OH-progesterone, androstenedione, ACTH, renin, aldosterone, and cortisol levels were normal, as were 24-h urinary free cortisol excretion and urinary catecholamine levels. The testes were normal upon ultrasound examination, but in the left adrenal a hypo-echogenic lesion was found. Magnetic resonance imaging (MRI) confirmed a well-defined 26x23x3 lmm nodule with limited, but homogenous contrast accumulation, and no evidence of invasion into adjacent organs or vessels. Based on the hormonal findings and imaging features, we decided for tumor resection by laparoscopic adrenalectomy. The tumor was found to be benign based on its histological characteristics (Wieneke criteria, score: 0): tumor weight < 200g, no capsular invasion or tumor necrosis, mitotic activity < 15/20 HPF, and Ki67 index < 15%.Genetic tumor profiling included comparative genomic hybridization, which revealed complex chromosome rearrangements, and capture-based massively parallel sequencing, which identified a previously reported disease-causing variant of *TP53* (R158H). This variant was subsequently found as a heterozygous de novo germline missense mutation in a leukocyte sample, confirming the diagnosis ofLFS.
Discussion
Penile growth without testicular enlargement in boys under 9 years of age is a sign of PPP. The differential diagnosis of PPP in boys is broad and includes exposure to exogenous testosterone, testotoxicosis, genetic syndromes, and neoplastic causes. A detailed history and repeated physical examination are needed to document the stage and progression rate of puberty, and sometimes suffice to identify the cause of PPP. Initial screening should include bone age, measurement of gonadotropins, testosterone, hCG, DHEA-S, 17-0H-progesterone, cortisol, and aldosterone levels. PASACT is a rare neoplastic cause of PPP and represent a diagnostic challenge (3). We report on a boy presenting with isosexual PPP caused by a PASACT in the context of LFS. The selective secretion of testosterone and DHEA-S, the absence of invasion into adjacent tissues, and the small tumor size established by MRI were suggestive of an adrenocortical adenoma, as opposed to a carcinoma, and were decisive for a laparoscopic resection. Androgen secretion by ACTs is often accompanied by aldosterone secretion causing hypertension, but in this patient the hypertension was not related to an excess of aldosterone, cortisol, or catecholamines. Of note, blood pressures in children should always be measured using correct cuff sizes and interpreted using percentiles by age and height. The histology of PASACT is also challenging and a distinct scale, the Wieneke criteria, is used to grade pediatric ACT, as opposed to the Weiss criteria in adults (4). Germline *TP53* mutations causing LFS have been identified in more than half of children with ACT (5). Here, the absence of a positive family history of cancer is in line with the de novo nature of the *TP53* mutation. A high rate of de novo germline *TP53* mutations and a variable expression and penetrance make families with LFS prone be missed. The R158H

missense mutation reported here has previously been reported in children with ACT (5). This mutation hits the functional part of the DNA-binding domain of P53 and imparts a transcriptional activity comparable to null mutations. A strict surveillance protocol, including annual total body and brain MRI is therefore warranted in this patient and exposure to ionizing radiation should be minimized.

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022

Isomorphic (KOEBNER) phenomenon induced by insulin injections in psoriasis: a case report

Thijs Saartje[1], Degraeve Corinne[2] & Coremans Peter[1]
[1]Department of diabetes and endocrinology, AZ Nikolaas, Sint-Niklaas, Belgium; [2]Dermatology private clinic, Kruibeke, Belgium

Introduction

Lipohypertrophy is by far the most common skin-related complication of insulin therapy. Less common dermatological complications of insulin injections include lipoatrophy, localized allergic reaction, subcutaneous abscess, localized amyloidosis and hyperpigmentation of the skin at the site of injection. We describe the Koebner phenomenon in an insulin requiring type 2 diabetic patient during a psoriasis flare-up.

Case report

A 56-year old woman with type 2 diabetes for more than 30 years and treated with insulin since 3 years was evaluated at the diabetes clinic for routine follow-up. She also suffered from long standing severe psoriasis, for which she had been treated with methotrexate as well as a local treatment with calcipotriol 50 microgram/gram and betamethasone dipropionate 0.5 milligram/gram. 8 months earlier, the treatment with methotrexate was interrupted due to liver dysfunction. Concerning her diabetes, lispro was used as prandial and glargine as basal insulin. Her other medications were atorvastatin, aspirin and metformin. Hemoglobin A1c was 7.0 % and during the past months insulin need was stable. After withdrawal of methotrexate a serious psoriasis flare-up including involvement of her nails and her skin, localized at elbows, gluteal, lumbosacral and submammary regions was noticed. Also new sharply demarcated, erythematous, oval, red and scaly plaques that differ in size were observed at the insulin injection sites on the lower abdomen and the both anterior proximal thighs (figures 1 and 2). These plaques developed 48 to 72 hours after injection with both insulin lispro and glargine. They resolved with residual hyperpigmentation over a period of 2 to 3 weeks after once daily application with calcipotriol 50 microgram/gram and betamethasone dipropionate 0.5 milligram/gram. Psoriasis-associated Koebner phenomenon due to insulin injections was diagnosed. Ciclosporin was initiated, after 2 months no significant improvement was noticed. Six to eight weeks after initiating treatment with guselkumab (IL-23 inhibitor) all plaques, including those at the injection sites, resolved completely and no new lesions developed.

Discussion

Koebner phenomenon, also known as the isomorphic response, describes the appearance of new skin lesions of the same kind of a pre-existing skin disease along sites of cutaneous injury. This phenomenon is mostly observed in patients with psoriasis, although it can also be seen in vitiligo and lichen planus.[1]Psoriasis is a chronic inflammatory skin disease associated with multiple comorbiditie-s.[2]Observational studies established the association between psoriasis and the prevalence of diabetes. It has been proposed that the chronic systemic inflammation, seen in the psoriatic state, induces insulin resistance. The relative risk of developing diabetes in psoriasis is estimated to be 1.50.[3]To the best of our knowledge there are only 2 other cases describing the Koebner phenomenon response in patients with psoriasis induced by insulin injections.[4,5] Our case report is clearly different from the 2 other cases because these former reported patients used NPH insulin, whereas this case report describes a patient with koebnerization in psoriasis due to injections with insulin analogues.

Conclusion

Our case report confirms the possibility of inducing new psoriasis lesions at insulin injection sites, the so called Koebner phenomenon. Thus, clinicians should be aware of this possibility in insulin requiring diabetic patients with psoriasis. Therefore, we emphasize the importance of thoroughly inspection of all insulin injection sites and catheter insertion sites in insulin pump therapy, not only for excluding lipohypertrophy, but also for excluding other dermatological problems associated with insulin injections. We would not be surprised to the Koebner phenomenon emerging also in patients using flash glucose monitoring, continuous glucose monitoring or patch pumps in the future.

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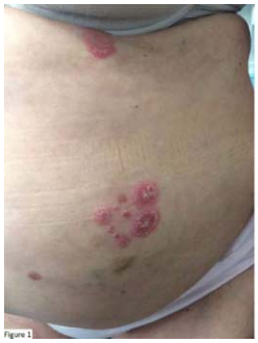

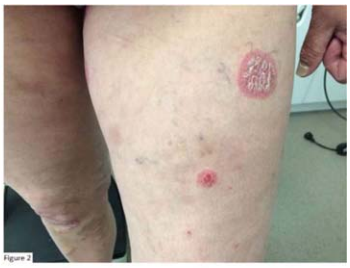

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023

Unusual cause of neonatal salt wasting syndrome in a female with subsequent primary amenorrhoea

Verdickt Sébastien & Bex Marie
Department of Endocrinology, University Hospitals Leuven, Belgium

Introduction

Congenital adrenal hyperplasia (CAH) is the most frequent cause of primary adrenal insufficiency (PAI) in infants and children. The list of genetic causes of PAI has grown extensively in recent years(1). Associated features can provide a clue to identify the underlying defect.

Case presentation

A 21-year-old female was referred for endocrinological advice about pregnancy. She had been diagnosed with isolated aldosteron deficiency at three weeks of age, presenting with failure to thrive, polyuria, renal salt loosing, hyponatraemia, hyperkalaemia, high plasma renin activity and low aldosteron. Cortisol was normal. During childhood and adolescence she was treated with fludrocortisone only. At age 14 she was diagnosed with late puberty. FSH was 15.1 U/L; LH 5.8 U/L and her karyotype 46,XX. Puberty was induced with ethinyloestradiol and was replaced later by oestroprogestogen contraception. Persistence of amenorrhea was confirmed at age 18, and birth control pills were resumed until her marriage 9 months before referral. A hormonal evaluation was performed in our clinic (table). Hypergonadotrophic hypogonadism and a partial cortisol deficiency with low adrenal androgens and moderately elevated ACTH were diagnosed. AMH was low. Hydrocortisone replacement therapy was added to fludrocortisone. She was referred to the fertility clinic and had one successful pregnancy using egg cell donation, giving birth to a daughter at age 25. Further attempts failed. In view of the combined deficiency of ovarian and adrenal steroids, including aldosterone, and a low 17-hydroxyprogesterone, a (partial) defect in the synthesis from cholesterol to pregnenolone was hypothesized.

Genetic screening for mutations leading to lipoid CAH was however negative: sequencing of 7 exons of the STAR gene (8p11.2) and 9 exons of CYP11A1-(P450 cholesterol cleaving enzyme 15q23-24) gene was normal. At age 32 a urinary steroid profile was obtained after withdrawal of adrenal hormone replacement for some days and of gonadal steroids for two months. She developed limited salt wasting, with mild but symptomatic hypotension. Only androgen- and progesterone metabolites were low. Plasma renin activity and ACTH were elevated, with low normal aldosteron en normal cortisol (table), indicating partial deficiency of mineralocorticoids and glucocorticoids at most. Hypogonadism persisted with mildly elevated LH and FSH. As the gonadal dysfunction predominated a mutation in the steroidogenic factor-1 (SF-1, NR5A1) was suspected[2]. A heterozygote missense variant was identified in exon 3 (c.104G> A, p.(Gly35Asp). This is located in the first zinc finger protein motif of the DNA binding domain. Her parents did not harbour the mutation, despite a history of premature menopause in the maternal family.

Discussion

Steroidogenic factor-1 (NR5A1) located on 9q33 is a nuclear receptor that regulates adrenal en reproductive development and function. It is also expressed in pituitary gonadotrophs, and the hypothalamus. Mostly heterozygous pathogenic variants are responsible for a wide spectrum of disorders of gonadal development. In 46,XY individuals phenotypes range from disorders of sex development (DSD) to oligo-azoospermia, and in 46, XX individuals from (familial) premature ovarian insufficiency to 46,XX ovotesticular DSD (p.R92 variants). Associated adrenal dysfunction is however rare less then 10 cases have been reported to date, mostly coupled to variants in p.G35 (heterozygous, like our patient) or in p.R92 (homozygous). SF-1 variants are an infrequent cause of unexplained childhood PAI, being identified in only 0.6% of 155 cases[3]. Our case illustrates that the adrenal dysfunction does not progress with time. It therefore is unlikely to identify this variant if the PAI is diagnosed at older age.

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Table: hormonal evaluation of gonadal and adrenal axis

Age	3 weeks	22 yrs[a]	32 yrs[b]	Unit	Normal range
LH		7.2-11.6	11.5	IU/L	2.4 – 12.6[c]
FSH		19.4-28.2	16.2	IU/L	3.5 – 12.5[c]
Oestradiol		3.3	< 1.5[d]	ng/L	25 – 195[c]
Progesterone		0.2	< 0.1	µg/L	0.2 – 1.5[c]
Testosterone		11.0	< 2.5	ng/dL	15.0 – 45.0
ACTH		167.2	244.3	ng/L	5.0 – 60.0
Cortisol		9.3	19.6	µg/L	6.2 – 18.0
Synacthen stimulated cortisol (60 min)		13.3		µg/L	> 18.0
Androstenedione		71	43.5[d]	ng/dL	100 – 200/30 – 200[d]
DHEAS		48.6	6.9	µg/L	80.0 – 350.0
17-hydroxyprogesterone (17-OHP)		0.05	0.09	µg/dL	0.01 – 0.11[c]
Synacthen stimulated 17-OHP (60 min)		0.09		µg/dL	
Plasma renin activity	172.6	2.2[a]	74.4	µg/L/h	0.4 – 2.8
Aldosteron	15.8	9.9[a]	14.6	ng/dL	10 – 33

[a] under treatment with fludrocortisone 150 µg od [c] follicular reference range [d] LC-MSMS
[b] gonadal steroid treatment withdrawn > 2 months and adrenal hormone replacement for 5 days

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024

Therapy-resistant hypocalcemia in auto-immune polyendocrine syndrome type 1

Verroken Charlotte[1], De Smet Stephanie[1], Kerrebrouck Marianne[1], Creytens David[2], T'Sjoen Guy[1] & Lapauw Bruno[1]
[1]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium; [2]Department of Pathology, Ghent University Hospital, Ghent, Belgium

A 22-year old female is followed at our department because of genetically confirmed autoimmune polyendocrine syndrome type 1 (APS-1). This was diagnosed at the age of 9 and in this patient characterized by autoimmune hypoparathyroidism, autoimmune hepatitis, autoimmune gastritis and premature ovarian insufficiency. Throughout childhood and puberty, the hypoparathyroidism was treated with moderate doses of calcium citrate (~3g/d) and calcitriol (~1.5µg/d), nevertheless resulting in rather poor disease control with fluctuating but mostly rather low calcium values and the development of basal ganglia calcifications (Figure 1A). The autoimmune hepatitis, vitamin B12 deficiency and ovarian insufficiency were treated with azathioprine and budesonide, vitamin B12 injections and a combined oral contraceptive pill, respectively. Because of persistently low calcemia, calcium citrate and calcitriol doses were gradually increased and calcitriol was replaced by alfacalcidol between 2017 and 2020. Nonetheless, despite intake of 7g of calcium citrate and 6µg of alfacalcidol daily, calcium levels continued to decrease and in April, 2020, the patient was hospitalized because of severe hypocalcemia (1.29 mmol/l; albumin-adjusted) with symptoms including paresthesia, muscle cramps and fatigue. Given the underlying autoimmune syndrome, a trial with systemic glucocorticoids (methylprednisolone up to 64mg/d) was initiated. After 1 week, calcium levels gradually increased towards low-normal values and the calcium citrate and alfacalcidol doses could slowly be tapered towards 4g/d and 2µg/d, respectively. Unfortunately, attempts to taper the dose of methylprednisolone again resulted in decreasing calcium levels, and calcium citrate and alfacalcidol doses had to be reincreased. An underlying autoimmune form of malabsorption was suspected given the relatively good response to systemic corticosteroid therapy. Moreover, in addition to severe hypocalcemia, the patient had mild but chronic deficiencies in iron, magnesium and zinc stores for which she intermittently took supplements. Upon work-up, there were no arguments for coeliac disease based on repeated negative biochemical screening as well as negative intestinal biopsy in 2015, nor for the presence of autoimmune pancreatic insufficiency based on normal fecal elastase and absence of pancreatic autoantibodies. Furthermore, esophagogastroduodenoscopy and colonoscopy showed no arguments for colonization with Giardia lamblia or Candida albicans. However, reassessment of duodenal biopsy tissue from 2015 as well as new gastric, duodenal, ileal and colonic biopsies showed a reduced number of neuro-endocrine and especially serotonin-positive cells in the stomach and duodenum, suggesting a diagnosis of APS-1-associated autoimmune enteropathy (Figure 1B). In addition to systemic glucocorticoids, immunosuppressive therapy with rapamycin was started in November, 2020. However, therapeutic monitoring showed highly variable blood levels ranging from undetectably low to therapeutic despite minimal dose adjustments, suggesting compromised absorption. Moreover, calcium levels further decreased and the autoimmune hepatitis that had long been controlled started to flare up again, probably due to interruption of azathioprine when rapamycin treatment was started. In May, 2021, the patient was hospitalized again for a short course of high-dose intravenous corticosteroids (methylprednisolone 125mg/d for 2 weeks while maintaining rapamycin at 4mg/d, calcium citrate at 6g/d and alfacalcidol at 6µg/d). Under this regimen, calcium levels gradually increased towards the low-normal range (~1.9 mmol/l, albumin-adjusted), rapamycin levels increased towards the therapeutic range and liver tests normalized. At discharge, intravenous corticosteroids were replaced by oral methylprednisolone starting at a dose of 128mg daily. Since June, 2021, methylprednisolone doses are being tapered very slowly with weekly follow-up. Currently, the patient has stable calcium values and therapeutic rapamycin levels under methylprednisolone 64mg/d, rapamycin 3mg/d, calcium citrate 6mg/d and alfacalcidol 4µg/d. In the following weeks, we hope to further taper and stop methylprednisolone treatment and, if possible, decrease the high maintenance doses of calcium citrate and alfacalcidol. In addition, we plan to perform new intestinal biopsies to reassess the number of neuroendocrine and serotonin-positive cells to confirm (or refute) successful immunosuppressive therapy.

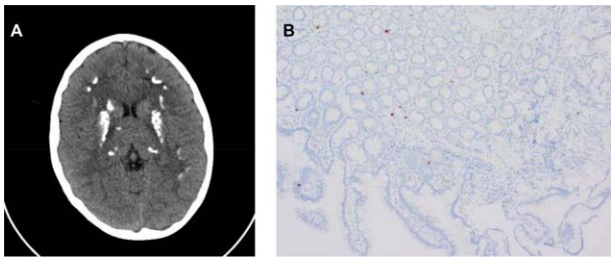

Figure 1. CT image of the patient showing extensive basal ganglia calcifications (A) and histology of duodenal tissue showing a reduced number of serotonin-positive cells on immunohistochemistry (B).

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025

Hypoglycemia after initiation of CFTR modulator therapy in a cystic fibrosis patient without diabetes

Vliebergh Joke[1], Bor Hakan[1,2], Marie Yskout[3], Dupont Lieven[3], Lorent Natalie[3], Van Bleyenbergh Pascal[3], Gillard Pieter[1], Van der Schueren Bart[1], Mertens Ann[1], Mathieu Chantal[1] & Vangoitsenhoven Roman[1]
[1]UZLeuven, Endocrinology; [2]Nutrition and dietetic, Gumushane University, Gumushane,Turkey; [3]UZLeuven, pneumology

Background
Cystic fibrosis (CF) is a genetic disorder in which a dysfunctional cystic fibrosis transmembrane regulator (CFTR) chloride channel can result in multimorbidity, including severe respiratory disease and reduced pancreatic exocrine secretion and diabetes. Recently, CFTR modulator therapy, has emerged with the potential of improving respiratory function and remission of diabetes. The effect of CFTR modulator therapy on pancreatic function in patients without preexisting diabetes remains unclear.
Case presentation
An 18-year old female with longstanding CF based on F508del/F508del genotype, was admitted for feeling generally unwell and recurring episodes of nausea, trembling and tinnitus usually 1 hour postprandially. She had been taking tezacaftor 50mg, ivacaftor 75mg, elaxacaftor 100mg daily for 6 months with a clear beneficial effect on respiratory symptoms. However, she associated the onset of neuroglycopenic symptoms with initiation of CFTR modulator therapy, and she had noted an increasing frequency of the episodes. A brief interruption of the tezacaftor-ivacaftor-elaxacaftor had not improved her complaints. Biochemical testing revealed a low venous blood level (63 mg/dl) at the time of nausea, in the presence of unadapted high insulin (141 pmol/l) and c-peptide (1.27 nmol/l) levels. Further clinical and biochemical evaluation did not show underlying infection nor any other significant alteration in comorbidities. The glycated hemoglobin level (HbA1c) had dropped from 6.2% before the initiation of tezacaftor-ivacaftor-elaxacaftor to 5.8 %, without the use of any exogenous insulin, nor any other glucose lowering therapy. The patient was advised to limit the intake of simple carbohydates and monitor the glycemia closely and symptoms improved.
Discussion
This case supports the preliminary notion that CFTR modulator therapy has the potential to affect glucose homeostasis in patients with CF. The underlying mechanism remains uncertain, as it could be that insulin resistance or beta-cell function or both might be affected. Indeed, relief of chronic inflammation, especially in the respiratory tract and the lungs might yield reduced insulin resistance and thus improved glucose homeostasis. But it is also possible that reduction of pancreatic inflammation directly affects the beta cells insulin secretory capacity. In the current case neuroglycopenic symptoms were present postprandially, resembling reactive hypoglycemia in patients with exaggerated insulin secretion in response to simple carbohydrates. This observation might indicate there is a (temporary) improvement in insulin secretion, and not only reduction of insulin resistance.
Conclusion
This case report describes recurrent hypoglycemic episodes after initiation of CFTR modulator therapy in the absence of prior antidiabetic medication use.

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026

Thinking beyond guidelines: an atypical case of adrenal incidentaloma

Vliebergh Joke[1], Van Cleynenbreugel Ben[2], Vermeer Sascha[3], Sciot Raf[4] & Bex Marie[1]
[1]Department of Endocrinology, University Hospitals Leuven, Belgium; [2]Department of Urology, University Hospitals Leuven, Belgium; [3]Department of Center for Human Genetics, University Hospitals Leuven, Belgium; [4]Department of Pathology, University Hospitals Leuven, Belgium;

Background
An adrenal incidentaloma is defined as an adrenal mass larger than 1 cm, detected on imaging performed for an indication other than evaluation of adrenal disease. Following the European Society of Endocrinology clinical practice guideline, assessment of malignancy by imaging and hormone excess should be done simultaneously(1). To investigate whether an adrenal mass is functionally active, a thorough clinical examination is required, extended with a 1mg overnight dexamethasone suppression test and measurement of plasma or urinary metanephrines to rule out autonomous cortisol secretion and pheochromocytoma respectively. Measurements of plasma-free or urinary fractionated metanephrines have an excellent sensitivity of 97% and specificity of 91% for the diagnosis of pheochromocytoma and are therefore recommended as initial screening tests(2). Chromogranin A (CgA) is also known as circulating marker of neuroendocrine tumors but is not routinely recommended to be measured.
Clinical Case
A 65-year-old man was referred by the urologist after detection of an adrenal incidentaloma on CT abdomen performed in the work-up for recurrent prostatitis. His medical history further included discus herniation, hypercholesterolemia treated with a statin and arterial hypertension which was well controlled on triple therapy with an ACE-inhibitor, calcium-channel blocker and beta blocker. On examination he had a normal BMI and systolic arterial hypertension grade I. The mass was localized in the left adrenal gland, measured approximately 50 x 70 x 78 mm, had regular borders but a heterogeneous composition with a density of $>$ 10 Hounsfield Units, central necrosis and focal calcification and was highly vascularized (figure). Based on these imaging features, adrenocortical carcinoma or pheochromocytoma was suspected. Initial hormonal work-up showed no arguments for autonomous cortisol secretion nor increased levels of sex or precursor steroids and an increased renin activity due to ACE inhibition. Serum CgA was also measured and was markedly elevated (1203 µg/L), favoring a diagnosis of pheochromocytoma, as the gastrin level was normal. Surprisingly, the urinary excretion of catecholamines and fractionated metanephrines was normal on repeat testing, resulting in the diagnosis not being biochemically confirmed. However, an additional Ga^{68}-dotate PET-CT scan showed increased expression of somatostatin receptors in the left adrenal mass only, which excluded other neuroendocrine tumors that could explain the elevated CgA. Preoperative alpha adrenergic receptor blockade was started and an open left adrenalectomy performed. Pathological examination confirmed the diagnosis of a pheochromocytoma 50 x 74 x 73 mm with positive staining for CgA and synaptophysin, and some adjacent normal adrenal parenchyma. Genetic screening with a pheo panel including RET, VHL and SDH genes detected a class 5 heterozygous nonsense mutation c.508C$>$ T (p.Gln170*) in the SDHA gene, causing a premature stop codon.
Conclusion
Strict following of the clinical practice guidelines would have missed the preoperative diagnosis of this rare non-secreting pheochromocytoma because of the lack of hypersecretion of urinary metanephrines, which is advised as the only screening test. When suspicion is high, measurement of CgA can be a useful additional marker for pheochromocytoma. Secondly, genetic analysis revealed a mutation in the SDHA gene, which is only since the last decade known as an additional susceptibility gene for mainly paraganglioma and pheochromocytoma. To our knowledge, this is the first report of a non-secreting pheochromocytoma associated with an SDHA gene mutation(3). The question rises whether this SDHA gene mutation could be the explanation for the rare biochemically silent character of this pheochromocytoma?
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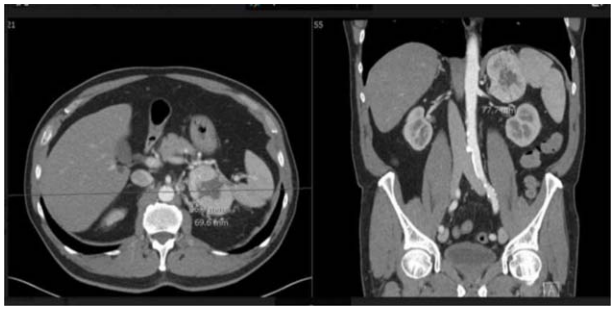

Figure. CT imaging showing a heterogeneous mass (> 10 HU) in the left adrenal gland with regular borders, central necrosis, a calcification and strong vascularization

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