# Endocrine Abstracts

**November 2024** Volume 106
ISSN 1479-6848 (online)

## Belgian Endocrine Society 2024

belgian endocrine society

published by bioscientifica

Online version available at
**www.endocrine-abstracts.org**

# CONTENTS

***BES 2024***

***CLINICAL STUDIES***



***CLINICAL CASE REPORTS***

# Clinical Studies

## 001

**The potential use of targeted omics for the identification and monitoring of diabetic kidney disease**

N. Van Roy & M. Speeckaert
Department of Endocrinology, Ghent University Hospital, Belgium: Department of Nephrology, Ghent University Hospital, Belgium

Introduction
Diabetic kidney disease (DKD) is a prevalent microvascular complication of diabetes mellitus (DM), associated with significantly worse prognosis. If addressed in early stages, progression can be delayed or even arrested. In clinical practice, diagnosis is based on eGFR and uACR or albuminuria. However, given the limitations of these markers, especially in early stages of the disease, there is a need to identify novel biomarkers [1]. Omics are a new field of study, involving comprehensive analysis of various types of biological data. In DKD, they are utilized in scientific research, but have not yet been implemented in routine clinical practice [2]. The intent of this research was to give a concise overview of the currently available data on targeted omics in the context of DKD in patients with T1DM and T2DM.
Methods
A structured search in PUBMED and EMBASE was conducted, followed by a manual search in the reference list of the selected articles. Articles describing the use of non-targeted omics, were excluded.
Results
28 articles were withheld, describing 25 different (panels of) targeted omics, both in urine and in blood. They belonged exclusively to the group of the proteomics and the metabolomics. The most researched urinary proteomic marker is CKD273, a classifier consisting of 273 peptides, originally developed in the context of chronic kidney disease (CKD), with promise in DKD. It is suggested to be especially predictive in the early stages of DKD, up to 1.5 years before the occurrence of albuminuria [3], and that it could play a role in monitoring/predicting therapeutic response [4]. In plasma, the proteomics KIM-1 and TNFR-1 could serve as a marker for both diagnosis and therapeutic response, either alone or in combination with other markers. However, results are less consistent as compared to CKD273 [5–7]. Few clinical conclusions can be drawn regarding urinary and plasma metabolomics, as most studies have short follow up and consist of non-targeted analysis.
Discussion/Conclusion
Omics hold promise as potential markers in DKD, but further research is needed to evaluate their performance in routine clinical practice. Most studies have (self-reported) limited power, lack external validation, and are primarily post hoc analyses. In addition, ethical issues need to be considered. As it concerns high-end technology which is not widely available, the cost is higher than that of the currently used markers [8]. Future research should take the heterogeneity and complexity of DKD into account, but also look at different confounders (genetics, medication, age, diet, diurnal variations, and other environmental and demographic factors).
References
1. Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, t reatmentgoals and latest guidelines. Diabetes Obes Metab 2020;22 Suppl 1:3–15. https://doi.org/10.1111/DOM.14007.
2. Tofte N, Persson F, Rossing P. Omics research in diabetic kidney disease: new biomarker dimensionsand new understandings? J Nephrol 2020;33. https://doi.org/10.1007/s40620-020-00759-4.
3. Zürbig P, Jerums G, Hovind P, MacIsaac RJ, Mischak H, Nielsen SE, *et al*. Urinary proteomics for earlydiagnosis in diabetic nephropathy. Diabetes 2012;61:3304–13. https://doi.org/10.2337/db12-0348.
4. Siwy J, Klein T, Rosler M, von Eynatten M. Urinary Proteomics as a Tool to Identify Kidney Responders to Dipeptidyl Peptidase-4 Inhibition: A Hypothesis-Generating Analysis from the MARLINA-T2D Trial. Proteomics Clin Appl 2019;13. https://doi.org/10.1002/PRCA.201800144.
5. Colombo M, McGurnaghan SJ, Blackbourn LAK, Dalton RN, Dunger D, Bell S, *et al*. Comparison ofserum and urinary biomarker panels with albumin/creatinine ratio in the prediction of renal function decline in type 1 diabetes. Diabetologia 2020;63:788–98. https://doi.org/10.1007/S00125-019-05081-8.
6. Nowak N, Skupien J, Niewczas MA, Yamanouchi M, Major M, Croall S, *et al*. Increased plasma kidneyinjury molecule-1 suggests early progressive renal decline in non-proteinuric patients with type 1 diabetes. Kidney Int 2016;89:459–67. https://doi.org/10.1038/KI.2015.314.
7. Sen T, Li J, Neuen BL, Neal B, Arnott C, Parikh CR, *et al*. Effects of the SGLT2 inhibitor canagliflozinon plasma biomarkers TNFR-1, TNFR-2 and KIM-1 in the CANVAS trial. Diabetologia 2021;64:2147–58. https://doi.org/10.1007/S00125-021-05512-5.
8. Critselis E, Vlahou A, Stel VS, Morton RL. Cost-effectiveness of screening type 2 diabetes patientsfor chronic kidney disease progression with the CKD273 urinary peptide classifier as compared to urinary albumin excretion. Nephrology Dialysis Transplantation 2018;33. https://doi.org/10.1093/ndt/gfx068.

DOI: 10.1530/endoabs.106.001

## 002

**Verapamil in combination with low-dose anti-thymocyte globulin reverses hyperglycaemia in newly diagnosed diabetic NOD mice**

P.J. Martens, M. Viaene, L. Degroote, C. Mathieu & C. Gysemans
Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium

Background and aims
The initiation of verapamil, a calcium channel blocker with beta cell protective and T cell targeting properties, exhibits significant promise for the preservation of beta cell function at symptom onset in type 1 diabetes (T1D). Nonetheless, an immunogenic process leads to the progressive destruction of beta cells. Potent systemic immunomodulatory agents, like low-dose anti-thymocyte globulin (ATG), have shown promising effects as single agents at T1D onset. Our aim was to combine the beta cell protective properties of verapamil with the potent immunomodulatory effects of low-dose ATG to establish enduring immune tolerance and sustained T1D remission.
Materials and methods
We combined continuous administration of verapamil (1 mg/ml in drinking water) with low-dose murine (m)ATG (250 μg per day on day 0 and 3; i.v.) to study their efficacy in new-onset diabetic non-obese diabetic (NOD) mice.
Results
Verapamil stably reversed disease in 20% of mice ($n = 3/15$). Low-dose mATG reversed T1D in 39% of mice ($n = 7/18$) 7 days after therapy start, but the effect waned to 22% of mice ($n = 4/18$) by 8-weeks follow-up. Verapamil combined with low-dose mATG induced durable disease remission in 45% of mice ($n = 9/20$). Only combination therapy was able to preserve C-peptide levels and decrease insulitis severity compared to untreated mice. Mechanistically, either low-dose mATG-treated group induced lymphocyte and monocyte depletion 3 days after therapy start, recovering by day 14. Flowcytometry analysis revealed a decreased percentage of CD8+ T cells in the blood of either low-dose mATG-treated group at day 3, with a recuperation towards a CD8+ effector memory (CD44highCD62L-) phenotype by day 14. Moreover, all treated (verapamil, low-dose mATG or the combination) groups were associated with an increased frequency of FoxP3+(CD25+) regulatory T cells (Tregs) by day 3, that persisted until day 14 in the peripheral blood and pancreatic draining lymph nodes (PLN). Interestingly, while all low-dose mATG-treated groups were associated with an increased ratio of Tregs over activated (CD44high) CD8+ T cells in the peripheral blood by day 3, this effect did not persist until day 14. However, in the PLN, where an unbalanced immune state serves as one of the main drivers of T1D, only combination therapy resulted in an increased ratio of Tregs over activated (CD44high) CD8+ T cells that persisted until day 14.
Conclusion
Here we present the first evidence that continuous administration of verapamil in combination with a short course of low-dose mATG protected beta cells and induced a transient imbalance in immune cell frequency favouring Tregs, which may be sufficient to establish long-term tolerance and confer permanent T1D remission. This innovative approach shows significant therapeutic promise and represents a paradigm shift towards combination therapies in the future management of T1D.

DOI: 10.1530/endoabs.106.002

## 003

**Predictive factors of the response to intravenous glucocorticoids for active moderate-to-severe thyroid eye disease**

Natalia Baczewska, MD[1] & Maria-Cristina Burlacu, MD[1]
[1]Department of Endocrinology, Cliniques Universitaires Saint-Luc, Brussels, Belgium. Please send all correspondence to: N. Baczewska, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium, tel: +32 764 18 12, email: nataliabacz@gmail.com Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest

Objectives
To determine the predictive factors associated to the response to intravenous glucocorticoids (IVGC) administered in patients with active moderate-to-severe thyroid eye disease (TED).
Methods
We retrospectively studied 65 patients with active moderate-to-severe TED, with or without optic neuropathy (DON) treated between 2003 and 2023 at Cliniques Universitaires Saint-Luc in Brussels. The patients were treated either with three-days IVGC pulse therapy or 12 weeks IVGC EUGOGO (European Group on Graves Orbitopathy) schema. The response was evaluated at the end of the treatment with the revised EUGOGO 2021 composite index.

Results
Out of the 65 patients, 43 (66.2%) were responders. Responders were younger than non-responders at the start of treatment (51.49 ± 12.80 vs. 57.23 ± 12.82 years, $P = 0.092$) and had a female predominance (79.1% vs. 20.9%, $P = 0.089$). Non-responders had higher pre-IVGC triglyceride levels (145 ± [85178.75] vs. 106 ± [75.75-133.25] mg/dl, $P = 0.042$) without significant differences in statin use. There were no significant differences in smoking status, thyroid function and TSH receptor antibodies levels before IVCG between responders and non-responders. A pre-treatment CAS (clinical activity score) $> 4$ and DON were more frequently observed in non-responders (81.8% vs. 27.9%, $P = 0.002$ and 68.2% vs. 27.9%, $P = 0.008$ respectively). A post-treatment CAS $\geq 3$ was present in 77.2% of non-responders compared to 2.3% of responders ( $P < 0.05$). Non-responders more frequently required second-line treatments (36.4% vs. 7%, $P = 0.003$) and underwent active phase orbital decompression (59.1% vs. 9.3%, $P < 0.05$). Among the 49 patients treated according to the EUGOGO regimen, 35 (71.4%) were responders. DON, a pre-treatment CAS $> 4$ and a post-treatment CAS $\geq 3$ were more frequent in non-responders (50% vs. 11.4%, $P = 0.014$; 78.6% vs. 28.6%, $P = 0.006$ and 78.6% vs. no patient, $P < 0.05$ respectively). A posttreatment CAS $\geq 3$ was present in 78.6% of non-responders compared to 0% of responders ( $P < 0.05$).
Conclusion
DON and higher CAS before treatment are associated to poorer response to IVGC in patients with active moderate to severe TED.

DOI: 10.1530/endoabs.106.003

## 004

**Early phosphate changes as potential indicator of (un)readiness for artificial feeding: a secondary analysis of the EPaNIC RCT**

Lauwers C[1], Langouche L[1], Wouters P.J[1], Wilmer A[2], Van den Berghe G[1], Gunst J[1] & Casaer M.P.[1]
[1]Department of Cellular and Molecular Medicine, Department and Laboratory of Intensive Care Medicine, KU Leuven, Leuven, Belgium
[2]University Hospitals Leuven, Medical Intensive Care Unit, Department of General Internal Medicine, Leuven, Belgium

Purpose
Current international guidelines have not reached consensus on the optimal timing, dose and composition of artificial nutrition in critically ill patients, but several studies have showed harm with early enhanced feeding. Our group demonstrated earlier in the EPaNIC randomized controlled trial (RCT) that as compared to withholding parenteral nutrition (PN) until one week after intensive care unit (ICU) admission, supplementing insufficient enteral nutrition with PN prolonged ICU dependency.[1] Interestingly, the Refeeding RCT showed lower mortality by nutrient restriction in ICU patients developing hypophosphatemia upon the initiation of artificial nutrition.[2] We hypothesized that early phosphate changes in ICU may identify patients who are harmed by early feeding.
Methods
In this secondary analysis of the EPaNIC RCT, absolute hypophosphatemia (AHP) was defined as a phosphate $<0.65$ mmol/l on the second ICU-day, relative hypophosphatemia (RHP) as a decrease of $>0.16$ mmol/l between the first and second ICU- day, and combined hypophosphatemia (CHP) as the combination of AHP and RHP. We studied whether development of AHP/RHP/CHP interacted with the nutritional management (Early PN vs Late PN) for its impact on outcome through multivariable regression analysis.
Results
Of 3520 patients with available phosphate measurements, CHP developed in 5.3% ( $n = 187$), AHP in 9.1% ( $n = 321$) and RHP in 23.7% ( $n = 834$) of patients. There was an interaction between the development of RHP and the randomized nutritional intervention for its impact on outcome. Early PN associated with a lower likelihood of an earlier discharge alive from ICU in patients developing RHP (adjusted hazard ratio 0.76 (0.66-0.88)) as compared to Late PN, which was not observed in patients without RHP. Development of CHP or AHP did not associate with a differential impact of the randomized intervention.
Conclusion
RHP occurred in a significant proportion of critically ill patients and among these patients a higher caloric intake associated with a higher ICU dependency. The development of RHP may identify patients who are harmed by Early PN.
References
1. Casaer, M. P. *et al*. Early vs late parenteral nutrition in critically ill adults. N Engl J Med 365, 506-517 (2011). https://doi.org:10.1056/NEJMoa1102662.
2. Doig, G. S. *et al*. Restricted vs continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 3, 943-952 (2015). https://doi.org:10.1016/S2213-2600(15)00418-X

DOI: 10.1530/endoabs.106.004

## 005

**Unraveling the diagnostic conundrum of cyclical cushing's syndrome**

Buyse Stephanie Lapauw Bruno
Department of Endocrinology, Ghent University Hospital, Belgium

Background
Cyclic Cushing Syndrome (CCS) is a condition characterized by at least two episodes hypercortisolism followed by episodes of normocortisolism or hypocortisolism. The clinical features are similar to those of non-cyclic Cushing Syndrome. However, the diagnosis is even more challenging than for its non-cyclic variant; various diagnostic modalities can yield false-negative results when performed during an episode without hypercortisolism. (1)
Objective
An extensive literature search was performed, using databases Embase and Medline in August, 2023. A combination of keywords (cyclic, periodic, intermittent, Cushing syndrome, hypercortisolism) and MeSH terms (Cushing's syndrome, pituitary ACTH secretion) was used. Relevant articles concerning non-pregnant, adult patients, published after 2003 were retained. Articles with unclear description or lack of cyclicity were excluded.
Results/discussion
Diagnostic tests for Cushing's Syndrome (CS) include 24-hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and the dexamethasone suppression test (DST). Unlike non-cyclic CS, DST can result in a paradoxical reaction with a significant increase in cortisol. DST is not advised when cyclicity is suspected. Even so, when a notable increase in cortisol is seen, cyclicity should be considered. UFC and LNSC are useful diagnostic tests, but repeated tests are necessary to identify cyclicity. Testing should ideally be conducted during periods of hypercortisolism. (1,2) An underemployed technique for detecting CCS involves measuring cortisol levels in hair, which can reflect cortisol levels over an extended period of time. However, standardized reference values for this method are currently unavailable. (3) The underlying etiology of CCS is similar to that of classic CS, including ACTH-dependent hypercortisolism due to a pituitary adenoma or ectopic ACTH production, and ACTH-independent hypercortisolism. Further differentiation is based on various tests: dynamic testing (CRH, desmopressin, high-dose DST), bilateral inferior petrosal sinus sampling (BIPSS), and imaging (pituitary MRI, FDG-PET, somatostatin analogs PET-CT). (2,4) The main difference from non-cyclic CS is that testing with desmopressin and BIPSS is unreliable during a trough phase. The high-dose dexamethasone test can, as in the DST, result in a paradoxical response. Regarding imaging, there is insufficient data to suggest that imaging in CCS differs from non-cyclic Cushing's. There is no clarity on the ideal sequence of investigations. In some cases, despite extensive investigations, the underlying etiology remains unclear. (4,5)
Conclusions
We conclude that additional research is necessary to obtain more information on this potentially notso-rare entity, given that there is no clear diagnostical pathway at this moment. Repeated testing is required, with attention to performing the tests at moments of hypercortisolism – given that false negative results are possible in trough phases. Emerging techniques like hair cortisol measurements show promise but need further investigation to develop standardized threshold values.
References:
1. Świątkowska-Stodulska R, Berlińska A, Stefańska K, Kłosowski P, Sworczak K. Cyclic Cushing's Syndrome – A Diagnostic Challenge. Front Endocrinol (Lausanne). 2021;12(April):1–7. doi:10.3389/fendo.2021.658429.
2. Nowak E, Vogel F, Albani A, *et al*. Diagnostic challenges in cyclic Cushing's syndrome: a systematicreview. Lancet Diabetes Endocrinol. 2023;11(8):593–606. doi:10.1016/S2213-8587(23)00150-X.
3. Manenschijn L, Koper JW, Van Den Akker ELT, *et al*. A novel tool in the diagnosis and follow-up of (cyclic) Cushing's syndrome: Measurement of long-term cortisol in scalp hair. J Clin Endocrinol Metab. 2012;97(10):1836–43. doi:10.1210/jc.2012-1852.
4. Cai Y, Ren L, Tan S, Liu X, Li C, Gang X, *et al*. Mechanism, diagnosis, and treatment of cyclic Cushing'ssyndrome: A review. Biomedicine and Pharmacotherapy [Internet]. 2022/06/20. 2022;153(June):113301. Available from: https://www.sciencedirect.com/science/article/pii/S0753332222006904?via%3Dihub.
5. Meinardi JR, Wolffenbuttel BHR, Dullaart RPF. Cyclic Cushing's syndrome: a clinicalchallenge. Eur J Endocrinol [Internet]. 2007 Sep;157(3):245–54. Available from: https://academic.oup.com/ejendo/article/157/3/245/6695913

DOI: 10.1530/endoabs.106.005

## 006

**Ga-68 DOTANOC incidentaloma; prevalence and clinical significance**

De Herdt Carlien[1], Naert Laura[1], Stroobants Sigrid[2,3] & De Block Christophe[1,3]
[1] Department of Endocrinology, Diabetology and Metabolism, University Hospital Antwerp, Edegem, Belgium.[2] Department of Nuclear medicine, University Hospital Antwerp, Edegem, Belgium.[3] University of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, Belgium

Introduction
Over the past years Ga-68 DOTANOC PET/CT is increasingly performed, which may lead to an increased finding of incidentaloma. In 2022, Bentestuen *et al*. published a systematic review concerning Ga-68 DOTA incidentaloma describing a prevalence of 4.5% with a malignancy rate of 13% (1). However, the rate of malignancy could have been overestimated because of publication bias.
Methodology
The results of Ga-68 DOTANOC PET/CT's performed between 2017 and 2022 in adult patients in the Antwerp University Hospital were retrospectively screened for the presence of incidentaloma. An incidentaloma was defined as an increased, non-physiological uptake of the DOTA-tracer, not related to the indication for imaging. Primary the prevalence of incidentaloma was analyzed and secondary the underlying cause of increased uptake was investigated.
Results
1240 Ga-68 DOTANOC PET/CT's performed in 804 subjects were analyzed. A total of 109 incidentaloma were described in 102 subjects with a mean age of 64 $\pm$ 13 years and F/M ratio of 63/39. The most frequently reported locations of incidentaloma were the thyroid ( $n = 24$), brain ( $n = 23$) and prostate ( $n = 21$) followed by the breast ( $n = 12$), stomach ( $n = 8$), vertebra ( $n = 7$), uterus ( $n = 4$), liver ( $n = 2$), pancreas ( $n = 2$), esophagus ( $n = 2$), kidney ( $n = 2$), ovarium ( $n = 1$) and mediastinum ( $n = 1$). The underlying cause of increased tracer uptake was investigated in 76 (70%) incidentaloma. The most frequent incidentaloma in the thyroid, brain and prostate were thyroid nodules (7/9, NR 15) , meningioma (15/18, NR 5), and benign prostate hypertrophy (8/13, NR 8), respectively. Rate of malignancy was 7.9% (6/76, NR 33) and consisted of 3 breast cancers, 2 renal cell carcinomas and 1 prostate cancer.
Conclusions
This is the largest single-center study describing the prevalence and underlying cause of Ga-68 DOTANOC incidentaloma to date. Evaluating the images of 804 subjects a prevalence of 13.6% was found which is higher than the prevalence of 4.5% previously described (1). This difference could be explained by the inclusion of studies only focusing on incidentaloma in one specific organ in the review of Bentestuen *et al*. Incidentaloma were most frequently encountered in the thyroid (22%), followed by the brain (21%) and prostate (19%). The rate of malignancy was low, 7.9%. This is lower compared to the rate of 13% previously described, which could be explained by the inclusion of case reports in the review of Bentestuen *et al* (publication bias). No thyroid cancer was diagnosed in this study population, however no work-up with ultrasound was performed in 67% of the thyroid incidentaloma. Malignancy rate of renal and breast incidentaloma were 100% and 25%, respectively. However this should be verified in a larger study population. With this abstract we want to stimulate other centers to publish/share their data of Ga-68 DOTA incidentaloma which can lead to a guidance in interpretation.
References:
1. Bentestuen M, *et al*. Prevalence and significance of incidental findings on 68 Ga-DOTA-conjugated somatostatine receptor-targeting PET/CT: a systematic review of the literature. Cancer Imaging. 2022; 22: 44.

DOI: 10.1530/endoabs.106.006

## 007

**Gender differences in acromegaly at diagnosis**

Denis C, Daly A, Natchev E, Maione L, Neggers SJCMM, Brue T, Colao A, Delemer B & Hulting AL
Hana V, Gatto F, Jaffrain-Réa ML, Stalla GK, Khyzhnyak O, Carvalho D, Fajardo-Montañana C, Beckers A and Petrossians P. The LAS study group. Service d'endocrinologie, Université de Liège, CHU du Sart Tilman, 4000, Liège

This study aims to identify sex differences and similarities in acromegaly and its comorbidities at diagnosis. Indeed, awareness regarding the sex related approach of acromegaly is increasing [1,2]. We used the LAS database [3], a relational database containing clinical data, comorbidities, and treatments of 3360 patients across 11 countries in Europe
The study population included more females (54.4%) than males (45.6%). Median age of diagnosis was earlier for men (43.6) than for women (46.3, $P < 0.001$). First symptoms appeared in average 2 years later for women (34.4) than for men (32.7, $P = 0.07$). Moreover, acromegaly progressed before diagnosis for a longer time in females (9 years) than in males (8 years, $P = 0.04$). With time, there was a progressive increase in the M/F sex ratio from 0.65 in the 70's to 1.1 in the 2010's. At diagnosis, tumors were bigger in males (15 mm) than in females (14mm, $P < 0.01$). There was no difference in the rate of chiasmatic compression. Cavernous sinus invasion seemed more frequent in males (41.2%) than in females (37.3%, $P = 0,05$). Signs and symptoms that led to diagnosis were not significantly different between the sexes. For both sex, in most cases, dysmorphic features were the first signs that led the physician to think about acromegaly. Carpal tunnel syndrome prevalence was close in females (20.1) and in men (19.7 %, $P = 0.55$), and was more frequent for patients who were older than 50. Likewise, thyroid nodules were significantly more common in females (39.9%) than in males (27.3%, $P < 0.001$). In contrast, colonic polyps were more frequent in males (16.8%) than females (9.3%, $P < 0.01$). Regarding cardiovascular comorbidities, there were no significant differences about hypertension, arrythmia, and ischemic cardiopathy between females and males. In contrast, history of myocardial infarction was more frequently observed in males (4.8%) than females (1.3%, $P < 0.001$). In conclusion, the various comorbidities observed in acromegaly differ depending on the sexes. Tumors were bigger in males than in females. Median age of diagnosis was earlier for males than for females and the delay of diagnosis was longer for females than for males. Thyroid nodules and carpal tunnel syndrome are more significantly common in females while colonic polyps and myocardial infarctions were more frequently observed in males. Certain comorbidities such as hypertension, arrythmia, and ischemic cardiopathy do not differ between the sexes.
References:
[1] MANAGEMENT OF ENDOCRINE DISEASE: Does gender matter in the management of acromegaly? Lexnders NF, McCormack AI, Ho KKY. Eur J Endocrinol. 2020 May;182(5):R67-R82.
[2] Sex difference in patients with controlled acromegaly-A multicentre survey. Dal *et al*. Clin Endocrinol(Oxf). 2023 Jan;98(1):74-81.
[3] Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. Petrossians P, Daly AF, Becker A *et al*. Endocr Relat Cancer. 2017 Oct;24(10):505-518.

DOI: 10.1530/endoabs.106.007

## 008

**Diabetes screening in dialysis populations with a glucose challenge test and continuous glucose monitoring: DIGEST study**

Depoorter Lore[1], Laghrib Yassine[2], Hellemans Rachel[2], De Fijter J.W[2] & De Block Christophe[1]
[1]Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital, Edegem, Belgium. [2]Department Nephrology, Antwerp University Hospital, Edegem, Belgium

Background
People on dialysis have an increased risk of developing diabetes mellitus. An oral glucose tolerance test (OGTT) is the most reliable method to identify dysglycemia, but it is cumbersome. We examined the effectiveness of the glucose challenge tests (GCT) in identifying people with dysglycemia who need further investigation with OGTT.
Methods
This single-center prospective cohort study included adults on dialysis at the University Hospital of Antwerp. Exclusion criteria were chronic infections, a history of diabetes and receiving glucose-lowering agents. The protocol involved a 50g-GCT followed by a 75g-OGTT 8-10 days later. Additionally, each participant was required to wear a blinded continuous glucose monitoring (CGM) sensor (DEXCOM® G6) during these ten days.
Results
Out of the 123 individuals screened, 50 met the eligibility criteria for the study. The primary reason for exclusion was a history of diabetes mellitus ( $n = 56$). Additionally, 27 individuals declined to participate, with 15 citing the extended duration of the OGTT. Ultimately, 23 individuals took part in the study, of whom 13 had dysglycemia, defined as a 2-hour glucose level after OGTT of $\geq$140 mg/dl. Individuals with dysglycemia exhibited higher BMI (26.2 $\pm$ 3.9 vs 22.8 $\pm$ 3.3 kg/m$^2$, $P = 0.039$), a longer dialysis vintage (4.5 $\pm$ 2.9 vs 1.6 $\pm$ 1.4 years, $P = 0.009$), and fewer listings for transplantation (8 of 13 vs 0 of 10, $P = 0.005$). In terms of CGM data, individuals with dysglycemia showed a lower time in range (95 $\pm$ 3% vs 98 $\pm$ 3%, $P = 0.020$) and a higher coefficient of variation (24% [IQR 20-29%] vs 16% [IQR 14-18%], $P < 0.001$). The participants with dysglycemia had a lower insulinogenic index (4.3 $\pm$ 2.1 vs 7.0 $\pm$ 3.6, $P = 0.04$) and similar HOMA-IR compared to those without dysglycemia. Interestingly, dysglycemia was more prevalent in individuals undergoing hemodialysis compared to peritoneal dialysis (12/14 vs 1/9, $P < 0.001$). Fasting glycemia levels were within the normal range and similar in both dialysis groups (85 $\pm$ 6 vs 85 $\pm$ 13

mg/dl, $P = 0.855$). CGM data showed a significantly lower coefficient of variation in peritoneal dialysis (23.6% vs 15.7%, $P = 0.002$). Importantly, the GCT had a sensitivity of 84% and specificity of 70% for detecting dysglycemia. Using a two-step approach, up to 40% of OGTTs could be avoided. Additionally, only 15% of individuals with dysglycemia would be missed.
Conclusion
Using a two-step approach of GCT and OGTT, up to 40% of OGTTs can be omitted, facilitating screening procedures for diabetes mellitus in people undergoing dialysis. This practical approach, should be further studied in order to help healthcare providers to identify and manage dysglycemia efficiently in this population.

DOI: 10.1530/endoabs.106.008

## 009

**The value of liquid and solid mixed meal tests to diagnose postprandial reactive hypoglycaemic syndrome (PRHS)**

S. Desmedt, J. Marlier, F. Van de Velde, Y. Van Nieuwenhove, I. Matthys & B. Lapauw
Ghent University Hospital

Objectives
Precise diagnostics for postprandial reactive hypoglycaemic syndrome (PRHS) after gastric bypass surgery (GBS) are lacking. Oral glucose tolerance tests (OGTT) are advocated but might cause early dumping and lack specificity. In this observational study glycaemic responses during liquid and solid mixed meal tolerance tests (LMMTT and SMMTT) were evaluated.
Materials and methods
Twenty-two subjects at least one year after GBS, divided into PRHS and non-PRHS based on clinical assessment, and 14 control subjects (6 normal-weight, 8 with obesity) participated. All underwent a 3hour LMMTT and SMMTT during which glucometabolic responses as well as hypoglycaemic symptoms using the Edinburgh Hypoglycaemia Symptom Scale (EHSS) were assessed.
Results
During LMMTT, nadir glucose levels nor frequency of levels $<70$ mg/dl and $<$ 54 mg/dl did differ between the four groups. LMMTT could not differentiate between PRHS and non-PRHS in terms of total count of symptoms and the number of symptoms was not associated with low glycaemia. Remarkably, glycaemic values $<54$ mg/dl were only observed in the non-PRHS group. During SMMTT, glucometabolic responses were similar between PRHS and non-PRHS. There was no difference between PRHS and non-PRHS subjects in the incidence of glycaemia $<70$ mg/dl and the occurrence of glycaemia $<54$ mg/dl was extremely rare. Moreover, significantly low glycaemic levels $<54$ mg/dl were not found in healthy controls. Finally, significantly more hypoglycaemic symptoms were evocated in the PRHS group compared to non-PRHS during the second phase of SMMTT (from 75 to 120 minutes) with more neuroglycopenic and malaise symptoms in PRHS. Decrease rate of glucose was higher in PRHS subjects with malaise symptoms from 105-180 minutes compared to those without malaise.
Conclusion
Using a two-step approach of GCT and OGTT, up to 40% of OGTTs can be omitted, facilitating screening procedures for diabetes mellitus in people undergoing dialysis. This practical approach, should be further studied in order to help healthcare providers to identify and manage dysglycemia efficiently in this population.

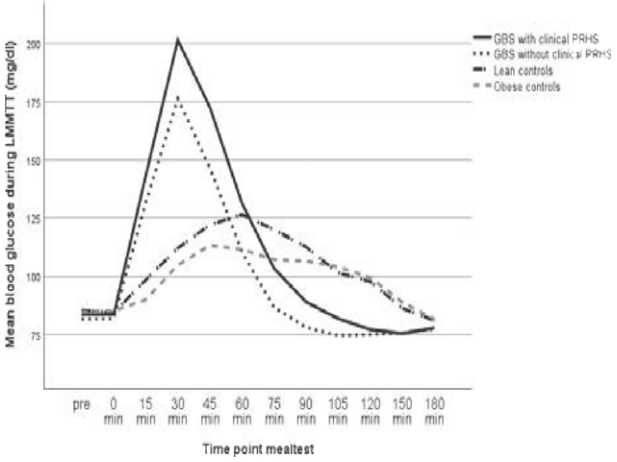


Figure 1. Mean glucose levels during LMMTT.

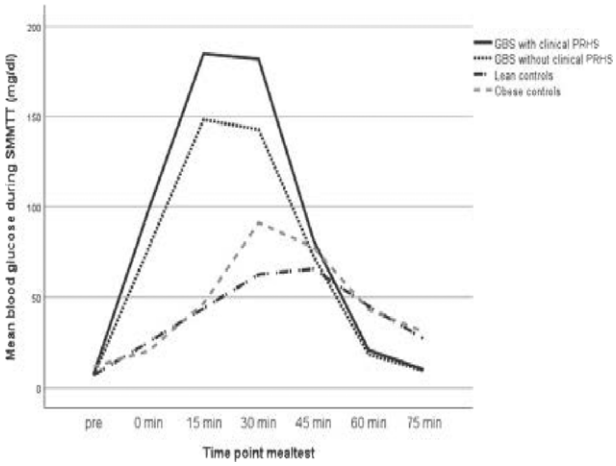


Figure 2. Mean glucose levels during SMTT.

DOI: 10.1530/endoabs.106.009

## 010

**The efficacy and safety of switching from rapid acting insulins to ultra rapid insulin l ispro (URLi) in people with type 1 diabetes using continuous glucose monitoring; a real world study**

Laura Naert [1] , Peter Coremans [2], Sabien Driessens [3], Annelies Van den Driessche [4], Kristof Van Dessel[1], An Verrijken[1], Nancy Bolsens[1] & Christophe De Block[1]
[1]Department of Endocrinology, Diabetology and Metabolism, University Hospital Antwerp, Edegem, Belgium. [2]Department of Endocrinology and Diabetes, VITAZ Hospital, Sint Niklaas, Belgium. [3]Department of Endocrinology, AZ Klina, Brasschaat, Belgium.[4]Department of Endocrinology, General Hospital Rivierenland, Campus Bornem, Belgium

Background and aims
To evaluate the efficacy and safety of switching from rapid acting insulins to ultra rapid insulin l ispro (URLi ) in a real world clinical practice in adult s with type 1 diabetes (T1D) using intermittently scanned or real time continuous glucose monitoring (isCGM or rtCGM respectively).
Materials and methods
In this real world, prospective, multicentre, 12 month study data from 22 patients with T1D (M/F 12/10; MDI/CSII 21/1; isCGM/rtCGM 19/ 3), who initiated URLi from January 2022 to January 2024, were analysed The primary objective was the evolution of time in range (70 180 mg/dl or 3.9 10.0 mmol/l) at 6 and 12 months. The secondary objectives included the change in HbA1c, time below range (TBR; $<$ 70 and $<$ 54 mg/dl), time above range (TAR; $>$ 180 and $>$ 250 mg/dl), number and timing of hypoglycaemic events, coefficient of variation (CV) of glycaemia and composite endpoints of reaching TIR $>$ 70% of time and TBR $<$ 70 mg/dl of $<$ 4% of time at 6 and 12 months.
Results
TIR evolved from 54.7 $\pm$ 13.8% to 56.4 $\pm$ 16.9% at 12 months ( $P = 0.304$). Time below 70 mg/dl (6.0 $\pm$ 5.2% at baseline) dropped significantly to 3.5 $\pm$ 2.5% and 3.3 $\pm$ 3.8% at 6 and 12 months ( $P = 0.009$). A significant decrease was also found for time below 54 mg/dl from 2.0 $\pm$ 2.2% to 0.6 $\pm$ 0.8% and 0.8 $\pm$ 1.8% at 6 and 12 months ( $P < 0.001$). Additionally, the number of hypoglycaemi c events dropped significantly from 27.0 $\pm$ 16.0 to 18.9 $\pm$ 9.5 and 19.4 $\pm$ 13.3 at 6 and 12 months ( $p = 0.019$). No significant difference s were observed for timing of hypoglycaemia, time above 180 mg/dl and 250 mg/dl, HbA1c and GMI. For the CV a significant decrease from 39. 5 $\pm$ 6.8 % to 9 $\pm$ 1 % at 12 months was seen ( $P =$ The number of people spending more than 70% of time in range increased from 13.6% to 27.3% ( $P = 0.174$) and those a chieving less than 4% of time below 70 mg/dl increased numerically from 50.0% to 72.7% ( $P = 0.150$).
Conclusion
We performed a 12 month, multicentre, prospective, real world study in which adults with T1D, using CGM, were switched from rapid acting insulins to URLi. Despite the small population and no significant improvement in TIR, a reduction in TBR ($<$ 70 mg/dl and $<$ 54 mg/dl) with 2.7% and 1.2% respectively,

corresponding to 39 and 17 minutes less time spent in hypoglycaemia, was observed. Also the number of hypoglycaemic events and glucose variability improved.

DOI: 10.1530/endoabs.106.010

## 011

**Sociodemographic, lifestyle and medical factors associated with calculated free testosterone concentrations in men: individual participant data meta-analyses (IPDMA)**

Nick Narinx MD[1], Ross J Marriott PhD[2], Kevin Murray PhD[2], Shalender Bhasin MD[3], Adrian S Dobs MD,MHS[4], Leon Flicker MBBS, PhD[5,6], Graeme J Hankey MBBS, MD[5,7], Robin Haring PhD[8,9], Alvin M Matsumoto MD[10,11], Eric S Orwoll MD[12], Gary A Wittert MBBCh, MD[13], Frederick C W Wu MBChB, MD[14], Leen Antonio MD, PhD[1], Dirk Vanderschueren MD, PhD[1*] & Bu B Yeap MBBS, PhD[11,15*]
* joint senior authors
[1]Laboratory of Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium. [2]School of Population and Global Health, University of Western Australia, Perth, Australia. [3]Brigham and Women's Hospital, Harvard Medical School, Boston, USA. [4]School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University, Baltimore, Maryland, USA.[5]Medical School, University of Western Australia, Perth, Australia. [6]Western Australian Centre for Healthy Ageing, University of Western Australia, Perth, Australia. [7]Perron Institute for Neurological and Translational Science, Perth, Australia. [8]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia. [9]European University of Applied Sciences, Faculty of Applied Public Health, Rostock, Germany. [10]Department of Medicine, University of Washington School of Medicine, Seattle, USA. [11]Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, USA. [12]Oregon Health and Science University, Portland, USA. [13]Freemasons Centre for Men's Health and Wellbeing, School of Medicine, University of Adelaide, Adelaide, Australia. [14]Division of Endocrinology, Diabetes & Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, UK. [15]Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Perth, Australia

Objective
Sociodemographic, lifestyle and medical variables influence total testosterone (T) and sex hormonebinding globulin (SHBG) concentrations. The relationship between these factors and "free" T remains unclear. We examined 21 sociodemographic, lifestyle and medical predictors influencing calculated free T (cFT) in community-dwelling men across ages.
Design
Cross-sectional analysis in 20,631 participants in the Androgens in Men Study.
Methods
Individual participant data (IPD) were provided by nine population cohorts. Total T was determined using mass spectrometry, SHBG using immunoassays and cFT using the Vermeulen formula. Associations were analysed using two-stage random effects IPD meta-analyses. Covariates including age, body mass index (BMI), marital status, and education were incorporated across all models. Additionally alcohol consumption, physical activity, and smoking were accounted for in models for lifestyle and medical variables.
Results
Cohort median ages ranged from 40 to 76 years and median cFT concentrations from 174.3 to 422.8 pmol/l. In men aged 17 - 99 years, there was a linear inverse association of cFT with age (-57.2 pmol/l [95% confidence interval, -69.4, -44.9] per 1-SD increase in age). cFT increased with increasing baseline BMI among men with BMI $< 23.6$ kg/m$^2$, but decreased among men with BMI $> 23.6$ kg/m$^2$ (-24.7 pmollL [95% CI, -29.1, -20.3] per 1-SD increase in the 25.4 - 29.6 kg/m$^2$ BMI range). cFT was lower in younger men, who were married or in a de facto relationship (-18.4 pmollL [95% CI, -27.6, -9.3]), and in men who; formerly smoked (-5.7 pmol/l [95% CI, -8.9, -2.6]); were in poor general health (-14.0 pmol/l [95% CI, 20.1,-7.8]); had diabetes (-19.6 pmol/l [95% CI, -23.0, -16.3]), cardiovascular disease (-5.8 pmol/l [95% CI, -8.3,-3.2]) or cancer (-19.2 pmol/l [95% CI, -24.4, -14.1]).
Conclusion
cFT was most prominently associated with age and BMI. The linear, inverse association with age, nonlinear association with BMI, and presence of diabetes, cancer and socio-demographic factors should be considered when interpreting cFT values.

DOI: 10.1530/endoabs.106.011

## 012

**Increase in testosterone measurements and doses of testosterone replacement therapy reimbursed by the belgian healthcare system between 2013 and 2022**

Jennifer Afrakoma Nyamaah, Nick Narinx, Joeri Walravens, Tom Fiers, Bruno Lapauw & Leen Antonio
Laboratory of Clinical and Experimental Endocrinology, KU Leuven, and Department of Endocrinology, Ghent University Hospital, Belgium

Objective
There are large regional and international differences in prescription patterns of testosterone replacement therapy (TRT) and testosterone measurements, with an increase in testosterone prescriptions reported in several countries. We investigated temporal changes in testosterone testing and reimbursed doses of TRT covered by the Belgian healthcare system.
Methods
Anonymous data on testosterone and sex hormone-binding globulin (SHBG) measurements (number of analyses and amount spent in euro) in men 17 years or older, were requested from the government (RIZIV) for 2012-2022. Data on TRT were requested from the government (Farmanet) from 1-2013 until 12-2022. This covers pharmaceutical preparations reimbursed in Belgium, prescribed by a physician and provided to the patient via public pharmacies. In Belgium, only Sustanon® is reimbursed, so this dataset does not contain data on transdermal preparations or testosterone undecanoate. Data are provided as number of delivered packages and amount spent. Since 2012, one package of Sustanon® on the Belgian market contains one dose of 250 mg testosterone esters.
Results
In 2013, total testosterone was measured 105.060 times in Belgian adult men. This increased to 149.602 in 2022 (+42% over a 10-year time period). The amount spent by the healthcare system for testosterone testing increased from €379.394 in 2013 to €551.759 in 2022 (+45%). SHBG was measured 48.442 times in Belgian adult men in 2013. This increased to 70.715 in 2022 (+46%). The amount spent by the healthcare system for SHBG testing increased from €155.547 in 2013 to €231.876 in 2022 (+49%). In 2013, 37.950 doses of Sustanon® were sold to adult men. In 2022, this increased to 76.189 doses (+101%), corresponding to a cost of €373.330 in 2013 and €675.042 in 2022 (+81%). To put these numbers into perspective, from 2013 till 2022, the number of Belgian adult men increased by 5.8%. Inflation was 28.5% over 10 years.
Conclusion
The number of testosterone measurements increased by 42% in Belgium between 2013 and 2022. Remarkably, the number of doses of the only reimbursed testosterone replacement therapy showed an increase of 101%, which is much larger compared to the number of testosterone measurements. These findings correspond to similar trends of prescription pattern increases reported in other European countries.

DOI: 10.1530/endoabs.106.012

## 013

**Ketosis-prone type 2 diabetes: phenotype and predictive factors of insulin independence**

Laura Orioli[1,2], Astrid Le Rigoleur[1] & Michel P. Hermans[1]
[1]Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, Brussels, Belgium. [2]Research Laboratory of Endocrinology, Diabetes, and Nutrition, Institute of Experimental and Clinical Research, UCLouvain, Brussels, Belgium

Background
Ketosis-prone type 2 diabetes (KPD) is characterized by diabetic ketoacidosis (DKA) or unprovoked ketosis without the typical phenotype of autoimmune type 1 diabetes.
Aims
To describe the phenotype of individuals presenting with inaugural DKA or ketosis without β-cell autoimmunity, and to identify predictors of insulin independence.
Methods
This single-center retrospective study included all inpatients aged $\geq$ 18 years, presenting with inaugural DKA or ketosis between 2010 and 2022. Demographic, clinical, and biological data were collected at baseline (during hospitalization) and last follow-up visit. Patients were classified into Aβ categories: presence (A+) or absence (A-) of β-cell autoimmunity and insulin dependence (β-) or independence (β+) at last follow-up visit. Predictors of insulin independence in the A- group were identified using backward multivariate logistic regression analysis, including all variables with $P < 0.200$ in univariate analysis. Data are reported as medians [P5-P95] or odds ratios (OR) with [95% confidence interval]. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal fasting C-peptide (CP) cutoff at baseline predicting for insulin independence.

Results
A total of 144 patients were included in the study, of whom 47% were in the A- group. Age and BMI at baseline were higher in the A- group compared to the A+ group (46 [26-68] vs. 30 [18-59] years, $P < 0.001$; 28.2 [18.4-38.2] vs. 22.0 [17.8-30.7] kg/m$^2$, respectively). Males and Sub-Saharan Africans represented 78% and 35% of the A- group, compared to 61% ( $P = 0.032$) and 9% ( $P = 0.001$) of the A+ group, respectively. At last follow-up visit, 39% of patients in the A- group were insulin independent (A-β+). No difference was found between the A-β+ and A-β- groups, except for fewer microvascular complications at baseline in the A-β+ group than in the A-β- group (0% vs. 18%, $P = 0.037$). Variables included in the multivariate model were overweight (OR 2.42 [0.79-7.48], $P = 0.122$), hypertension (OR 2.22 [0.77-6.42], $P = 0.140$), overall micro- and macrovascular complications (OR 7.12 [6.13-52.6], $P = 0.098$), and fasting CP level at baseline (OR 5.86 [0.79-43.4], $P = 0.084$). In the multivariate analysis, fasting CP level at baseline was predictive of insulin independence (OR 11.5 [1.02-131.0], $P = 0.048$). The fasting CP cutoff at baseline with best sensitivity (76%) and specificity (83%) for predicting insulin independence was 0.15 nmol/l.
Discussion
KPD is not uncommon among individuals presenting with inaugural DKA or ketosis at our center. Patients with KPD have a different phenotype from individuals with autoimmune diabetes. In our study, fasting CP level at baseline was an independent predictor of insulin independence in individuals with KPD.

DOI: 10.1530/endoabs.106.013

## 014

### Beyond the curve: predicting insulin therapy in gestational diabetes using OGTT results

Eugénie Van Mieghem[1], Niels Bochanen[1] & Christophe De Block[1,2]
[1] Department of Endocrinology, Diabetology and Metabolism, Faculty of Medicine, Antwerp University Hospital, Drie Eikenstraat 655 B⍰2650 Edegem, Belgium;[2]Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk B⍰2610, Belgium

Background and aims
Gestational diabetes (GDM) is defined as glucose intolerance resulting in hyperglycaemia with onset or first recognition during pregnancy and has a prevalence of 1-28% worldwide. Treatment consists of lifestyle and dietary measures. If this proves insufficient, insulin therapy is initiated. Adequate identification of patients requiring insulin therapy can help decide which patients require more intensive follow-up. The three measurements of the OGTT can be combined rather than being assessed individually. The area under the curve of the OGTT (AUC OGTT) provides an estimate of the overall glucose excursion following a 75g glucose load, while the profile of the OGTT illustrates the change in blood glucose over the course of the two hours following the glucose load.
Methodology
This is a retrospective monocentric study that examined whether the AUC OGTT and/or the profile of the OGTT can predict whether insulin therapy needs to be initiated in patients with GDM. The medical records of all patients with singleton pregnancy and with an abnormal OGTT between 03/2020 to 09/2023 were reviewed. Exclusion criteria were pre-existing diabetes, use of medication that may interfere with glucose metabolism and multiple pregnancy.
Results
A total of 235 patients with GDM were studied. They were on average 32.8 years old (±5.2), had a prepregnancy BMI of 27.1 kg/m$^2$ (±5.8), and had mean glycaemia of 89 (±13), 172 (±28), and 158 (±25) mg/dl during the 75g OGTT at 0, 60, and 120 minutes, respectively. Patients who required insulin therapy were older, had a higher weight and BMI before pregnancy, had higher glycaemias during the OGTT with also a higher AUC OGTT. They were also more likely to have an OGTT profile characterized by impaired fasting glycaemia. Insulin therapy had to be initiated in all patients with impaired fasting glucose on all three OGTT points. The predictive model using the profile of the OGTT was superior to the predictive model using the AUC OGTT. Additionally, the former could also differentiate between modality of insulin therapy (basal, prandial and/or basal/prandial) unlike the latter. Factors such as BMI, fasting glycaemia, AUC OGTT and OGTT profile, HbA1c, fructosamine and total daily dose of insulin predict abnormal postpartum OGTT results.
Conclusion
Worldwide, the number of women with gestational diabetes is increasing. Risk stratification is necessary to identify those who need more intensive follow-up. The AUC OGTT is a predictor of whether insulin therapy has to be initiated during pregnancy. However, the profile of the OGTT, especially profiles where fasting glycemia is impaired, seems to be a more important predictor for insulin therapy during GDM pregnancy.

DOI: 10.1530/endoabs.106.014

## 015

### Insulin resistance associates with slower age-related bone loss in otherwise healthy young men

Steven Van Offel[1,2], Charlotte Verroken[2], Hans-Georg Zmierczak[2], Stefan Goemaere[1,2] & Bruno Lapauw[1,2 1]
[1]Ghent University, Faculty of Medicine and Health Sciences, Department of Internal Medicine and Pediatrics, Unit of Endocrinology.[2]Ghent University Hospital, Department of Endocrinology

Background
It is now generally accepted that diabetes increases fracture risk, whereby in patients with type 1 diabetes areal bone mineral density (aBMD) is decreased while in type 2 diabetes (T2DM) it is preserved or even increased (1). In case of insulin resistance, being the precursor state of T2DM, large cross-sectional data could not find a significant correlation between insulin resistance and aBMD (2), but longitudinal studies are lacking.
Objective
To assess the impact of insulin resistance on the evolution of aBMD over time in young healthy men.
Methods
In 999 young healthy men aged 25-45, aBMD at the level of the femoral neck, total hip and lumbar spine was measured using dual energy x-ray absorptiometry (DXA) as part of the SIBLOS study. Insulin sensitivity was assessed using the calculation of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR, which is the product of fasting glucose with fasting insulin, divided by a constant). After an average period of 11.5±1.9 years, these measurements were repeated as part of the SIBLOS-extension (SIBEX) study in 670 participants. Annual percent changes (%/y) in aBMD were calculated to correct for the varying duration between the two time points. Univariate and multivariate analysis was performed using linear mixed effects modelling.
Results
Mean±SD aBMD decreased between SIBLOS and SIBEX at all three measurement sites, namely 0.45±0.52 %/y at the femoral neck, -0.23±0.41 %/y at the total hip and -0.13±0.46 %/y at the lumbar spine. This decrease was less pronounced in participants with higher levels of baseline HOMA-IR (i.e. higher level of insulin resistance; β=0.184 [0.110–0.257, $P < 0.001$], β=0.179 [0.106–0.253, $P < 0.001$] and β=0.155 [0.081–0.229, $P < 0.001$] respectively). After correction for baseline age, weight and height, these relationships maintained significance (β=0.150 [0.068–0.233, $P < 0.001$], β=0.143 [0.059–0.227, $P < 0.001$] and β=0.122 [0.037–0.208, $P = 0.005$] respectively). However, after additional correction for body composition (total body lean mass and fat mass), the association remained significant only at the femoral neck (β=0.090 [0.004–0.177], $P = 0.040$).
Conclusion
In a population of non-diabetic mid-adult men, higher HOMA-IR levels at baseline seem to protect against age-related aBMD loss, especially at the level of the femoral neck. This finding is consistent with insulin being considered a bone forming hormone. However, it is important to realize that bone strength depends on many other factors than aBMD alone.
References
1. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2007;18(4):427-44.
2. Verroken C, Zmierczak HG, Goemaere S, Kaufman JM, Lapauw B. Insulin Resistance Is Associated With Smaller Cortical Bone Size in Nondiabetic Men at the Age of Peak Bone Mass. J Clin Endocrinol Metab. 2017;102(6):1807-15.

DOI: 10.1530/endoabs.106.015

## 016

### Estradiol valerate pharmacokinetics in assigned-male-at-birth individuals: implications for gender-affirming care

Vervalcke J.[1], Marinelli L.[1,2], Van Den Eynde T.[1], Walravens J.[1] & T'Sjoen G.[1]
[1]Ghent University Hospital (Belgium), Dep. of Endocrinology and Metabolic Bone Diseases.[2]University of Turin (Italy), Dep. of Medical Sciences, Division of Endocrinology, Diabetology and Metabolism

Background
In people with gender incongruence, the assigned sex at birth and their own gender identity do not align. Some individuals decide to undergo gender-affirming hormone therapy (GAHT). In transgender individuals assigned-male-at-birth (t-AMAB) GAHT often consists of a combination of anti-androgens and a feminizing estrogen

treatment. However, feminizing hormone therapy target ranges are ill-defined. The Endocrine Society 2017 guideline [1] recommends not exceeding peak physiological estradiol (E2) levels of 100-200 ng/l. However, these hormonal targets are often misquoted. Most notably, the SOC8 [2] guideline erroneously recommends optimal E2 levels between 100 and 200 ng/l. Simultaneously, the pharmacokinetic (Pk) properties of estradiol valerate (EV) remain largely uninvestigated in t-AMAB individuals. Sexual dimorphism related to body composition, hepatic metabolism, circulating blood volume and renal function could alter the Pk profile of EV in t-AMAB individuals compared to cisgender women.

Objective

To describe Pk characteristics of EV in a cohort of t-AMAB-individuals using GAHT.

Methods

Participants were part of the European Network for the Investigation of Gender Incongruence (ENIGI) study. Self-reported time of drug administration and time of blood draw were recorded. All participants used Progynova (oral EV) 2 mg twice daily. The E2 levels were measured using liquid chromatography followed by tandem mass spectrometry (LC-MS/MS). Extreme outliers as defined by Tukey's rule were removed prior to data analysis. B-spline regression using RStudio ver. 2024.04.01 was performed to model E2 level evolution after 2 mg EV ingestion. Missing data was handled using spline interpolation. The model was then reinforced by adding data from individuals in which E2 levels were calculated using immunoassay (IA). Finally, the results were compared to historic Pk data retrieved after a scoping review of the literature in the Medline database [3].

Results

A total of 46 unique individuals with LC-MS/MS data, and 15 individuals with IA data were selected. Median age at start of GAHT was 23.7 years (range: 17.7-58.8 years). Median GAHT duration was 17 months (range: 2-40 months). A crude 24h Pk profile was generated. The 24h area under the curve (AUC) was 1684.1 ng/l*h. The median E2 level was 62.7 ng/l (range: 13.4-153.0 ng/l). A nearly horizontal trend line was observed, indicating minimal variation in E2 levels during the first 12 hours after drug administration. However, significant inter-individual variance was noted. The Pk profile of 2 mg oral EV in this cohort of t-AMAB individuals was comparable to historic Pk data of cisgender women.

Conclusion

The Pk model currently lacks robustness to formulate dosing recommendations. The preliminary data seem harmonious with the 2017 Endocrine Society guidelines, although standardized Pk studies in gender-diverse cohorts are needed to optimize endocrine care.

References

1. Hembree, *et al*. (2017). The Journal of clinical endocrinology and metabolism. https://doi.org/10.1210/jc.2017-01658.
2. Coleman, *et al*. (2022). International journal of transgender health, 23. https://doi.org/10.1080/26895269.2022.2100644.
3. Zimmerman, H. *et al*. (2000). Clinical drug investigation, 20(2), 123–134. https://doi.org/10.2165/00044011-200020020-00007.

DOI: 10.1530/endoabs.106.016

## 017

### Age-stratified reference ranges for directly measured serum free testosterone in healthy men

Walravens Joeri[1], Snaterse Gido[1], Narinx Nick[2], Antonio Leen[2], Reyns Tim[3], Fiers Tom[3], Kaufman Jean-Marc[1] & Lapauw Bruno[1]

[1]Ghent University Hospital, Department of Endocrinology, Gent, Belgium. [2]Leuven University Hospital, Laboratory of Clinical and Experimental Endocrinology, Leuven, Belgium. [3]Ghent University Hospital, Department of Clinical Chemistry, Gent, Belgium

Introduction

Determination of serum (calculated) free testosterone (FT) in clinical practice has been suggested by several clinical guidelines for the diagnosis of male hypogonadism in men with borderline total T concentrations and in situations with altered sex hormone-binding globulin, as it correlates better with androgen exposure than total T. The gold-standard for the determination of FT levels is considered to be directly measured free testosterone (mFT) using equilibrium dialysis followed by mass spectrometry (ED LC-MS/MS). However, no widely accepted reference ranges are available for this clinical parameter. We established mFT reference ranges for healthy men aged 18 to 79 years.

Objective

To establish reference ranges for directly measured FT in serum of healthy adult men.

Methods

Reference ranges were determined following Clinical & Laboratory Standards Institute guideline C28A3c per age decade. Serum samples were analyzed from healthy men participating in the SIBLOS/SIBEX and EMAS studies, both population-based cohort studies. Additionally, healthy men between 18 to 24 years were recruited locally at UZ Gent. Exclusion criteria were medications or conditions that affect sex steroid metabolism or a BMI larger than 35 kg/m$^2$. mFT levels were measured in 996 men using ED LC- MS/MS as previously reported (1). Subsequently, 95% reference ranges were determined using the non-parametric method.

Results

We present age-stratified 95% mFT reference ranges. These reference ranges show an expected, decreasing trend of mFT with aging. Median mFT decreases at a remarkably stable rate of, on average, 14% per decade up into the 6th decade of life. The lower and upper limits decrease by, on average, 16% and 18% per decade, respectively.

**Table 1**

| Age category (years) | Median mFT (ng/dl) | 95% mFT reference range (ng/dl) |
|---|---|---|
| 18-29 ($n$ = 140) | 12,0 | 6,7 - 25,3 |
| 30-39 ($n$ = 252) | 9,8 | 4,9 - 18,5 |
| 40-49 ($n$ = 207) | 8,1 | 4,3 - 14,2 |
| 50-59 ($n$ = 146) | 7,1 | 3,8 - 12,8 |
| 60-69 ($n$ = 126) | 6,4 | 3,4 - 11,7 |
| 70-79 ($n$ = 125) | 5,6 | 2,7 - 8,7 |

Conclusion

We have determined mFT reference ranges in healthy men aged 18 to 79. These reference ranges are a first step to improving the framework for further development and integration of free testosterone measurements and calculations in clinical practice.

References

1. Fiers *et al*. (2018). Reassessing Free-Testosterone Calculation by Liquid Chromatography–Tandem Mass Spectrometry Direct Equilibrium Dialysis. J Clin Endocrinol Metab. 2018;103(6). doi:10.1210/jc.2017-02360.

DOI: 10.1530/endoabs.106.017

# Clinical Case Reports

## 018

### Neuroendocrine tumours in Lynch Syndrome: a case of an ACTH-producing atypical carcinoid lung tumour and literature review

Kevin Van Compernolle[1], Jacques Van Huysse[2], Marie Bex[3], Ellen Denayer[4], Lander Van Acker[5], Vincent De Wilde[6], Jan Lesaffer[7] & Annick Van den Bruel[8]
[1]Department of Internal Medicine, Leuven University, Leuven, Belgium. [2]Department of Pathology, AZ Sint-Jan AV, Bruges, Belgium. [3]Department of Endocrinology, UZ Leuven, Leuven, Belgium.[4]Department of Genetics, UZ Leuven, Leuven, Belgium.[5]Department of Pneumology, AZ Sint-Jan AV, Bruges, Belgium.[6]Department of Gastroenterology, AZ Sint-Jan AV, Bruges, Belgium.[7]Department of Thoracic Surgery, AZ Sint-Jan AV, Bruges, Belgium.[8]Department of Endocrinology, AZ Sint-Jan AV, Bruges, Belgium

Background
Lynch syndrome (LS), an autosomal dominant genetic cancer predisposition syndrome, is caused by mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 or PMS2. In autosomal dominant genetic cancer syndromes like LS, a germline mutation hits one MMR gene allele so that a somatic mutation in the wild-type allele of the same MMR gene will cause a complete loss of function. This results in hypermutability and microsatellite instability.1 LS gives rise to a broad spectrum of tumours, mainly colorectal and cervix carcinoma. We describe the first case of a neuro-endocrine lung tumour presenting as a Cushing syndrome in a LS patient.
Case presentation
A 49-year-old female LS patient (heterogenous for MLH1 mutation c.2103 + 3A > C) was diagnosed with Cushing syndrome after developing obesity WHO class 2, facial flushing, arterial hypertension and hypokalaemia. Serum, midnight salivary, and 24-hour urinary cortisol were markedly increased. ACTH was elevated at 148 pg/ml (normal range 7.2-63.3 pg/ml). A marked cortisol excess (urinary free cortisol 30 x ULN) and a normal pituitary MRI suggested an ectopic ACTH source. Chest/abdominal CT showed gross infracarinal lymph nodes (up to 51 mm) and a 15 mm-sized lung nodule, which was present and unaltered since 2016. The mediastinal lymph nodes exhibited increased somatostatin receptor (SSTR) expression on 68Gallium-DOTANOC-scan. The patient was started on spironolactone and octreotide in a dose elevation scheme till 1000 µg/24 h IV, quickly switched to ketoconazole 200 mg tid due to insufficient effect of octreotide on the cortisol levels. An endoscopic ultrasound-guided fine needle biopsy of the infracarinal lymph nodes confirmed the localization of a neuro-endocrine tumour with 10% cytoplasmatic ACTH expression. A robot-assisted thoracoscopic resection of the lymph nodes and a wedge resection of the lung nodule were performed. Ketoconazole could be ceased afterwards. Hydrocortisone was needed to counter postoperative adrenal insufficiency and was gradually tapered over a three-month period. Pathology of the lung nodule and lymph nodes proved an atypical carcinoid tumour, with tumour-free resection margins. On immunohistochemical analysis, a defect of MLH1/PMS2 was evident, consistent with the patient's germline mutation, and the tumour showed a microsatellite-high phenotype. Three months after surgery, a new 68Gallium-DOTANOC-scan suggested local tumour relapse in the mediastinal lymph nodes. Octreotide was started and the patient received concomitant chemoradiotherapy (cisplatin 25 mg/m$^2$-etoposide 100 mg/m$^2$ q3w); chemotherapy was ceased after 3 cycles due to intolerance (therapy-refractory vomiting) and severe grade 4 pancytopenia. Since then, she remains in sustained disease control, while continuing octreotide long-acting release 30 mg q4w.
Discussion
Cushing's syndrome in this patient with LS was at first suggestive of adrenocortical carcinoma, a known tumour type in the Lynch spectrum. 2 Nevertheless, the cortisol excess proved to be ACTH-dependent and the source of ACTH was an atypical lung carcinoid with mediastinal lymph node extension. A total of 28 cases of neuro-endocrine tumours in LS have been described in the literature so far. Twenty of the 26 tumours with a known origin were located in the gastrointestinal and gynaeco-urological tract; the other reported tumour types were pheochromocytoma and pituitary tumours. In the case presented, the tumour is most probably driven by LS and not merely a coincidentally occurring neoplasm in a LS patient. This is supported by the fact that the tumour is MSI-high, as it was suggested that it takes a sufficient amount of cell cycles before MSI occurs, which is unlikely in a coincidental tumour. 3 Also, immunohistochemical analysis of the tumour showed loss of MLH1/PMS2, consistent with the germline mutation of our patient. In conclusion, our case expands the neuroendocrine tumour spectrum in LS. Clinicians treating LS patients should be aware of atypical or rare tumour presentations.
References
1. Bengtsson, D. *et al*. Corticotroph pituitary carcinoma in a patient with Lynch Syndrome (LS) and pituitary tumors in a nationwide LS cohort. Journal of Clinical Endocrinology and Metabolism 102, 3928– 3932 (2017).
2. Kaur, R. J. *et al*. Adrenal cortical carcinoma associated with lynch syndrome: A case report and review of literature. Journal of the Endocrine Society 3, 784–790 (2019).
3. Karamurzin, Y. *et al*. Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: A reportof new cases and review of the literature. Hum Pathol 43, 1677–1687 (2012).
DOI: 10.1530/endoabs.106.018

## 019

### Case report: misleading increase in thyroid- stimulating hormone receptor antibodies during pregnancy in graves disease: value of functional, cell-based assays

Astrid Claessens[1,2], Katrien Clotman[1], Jan Monballyu[1] & Evy De Witte[3]
[1]Department of Endocrinology, AZ Klina, Brasschaat.[2]Faculty of Medicine, KU Leuven, Leuven.[3]Department of Clinical Biology, AZ Klina, Brasschaat

Introduction
Graves disease is an autoimmune endocrinopathy caused by thyroid-stimulating hormone receptor antibodies (TSH-R-Ab). Classically, this results in hyperthyroidism as thyroid-stimulating autoantibodies (TSAb) predominate. Within the spectrum of autoimmune thyroid disease, hypothyroidism in the context of thyroid-blocking autoantibodies (TBAb) is rare. In addition, TSH-RAb can also exhibit neutral activity[1]. The net activity of the antibodies determines the clinical presentation and approach. Specific consideration and monitoring in the context of pregnancy is suggested due to TSH-R-Ab's ability to migrate transplacentally and affect the fetus' thyroid gland. However, conventional thyroid receptor binding tests detect all types of thyroid hormone receptor antibodies and cannot differentiate between them. The value of functional, cell-based, assays in an atypical course of Graves disease is demonstrated in this case report.
Case report
A 36-year-old woman with Graves disease without ocular involvement was referred to us because of an increasing TSH-R-Ab titer and paradoxical evolution towards hypothyroidism during twinpregnancy (Table 1). She had been treated for 56-months with propylthiouracil (PTU) along with LT4replacement therapy according to the block-replacement-regimen. The TSH-R-Ab titer, measured with two different chemiluminescence immuonoassays during follow-up, remained persistently elevated. However, from the gestational age of 10 weeks, we noticed a tendency toward hypothyroidism and a remarkable increase in TSH-R-Ab titer, taking into account the difference in immunoassay. The quantity and functional properties of TSH-R-Ab can be altered during gestation due to immunological changes. In classical Graves caused by TSAb, these antibodies will usually decrease during pregnancy. However, the antibodies may become blocking[2] or neutral in rare cases. In consideration of hypothyroidism, the dose of PTU was reduced incrementally. L-T4 was associated given the low-tonormal T4-titer, where we aimed for higher values to sustain neurological fetal development. Ultimately, PTU was stopped and L-T4 progressively increased according to thyroid testing every two weeks. Development of both fetuses was normal with no evidence of hypo- or hyperthyroidism. Considering the appearance of TBAb would imply a risk of hypothyroidism in the fetuses, a functional TSH-receptor-antibody assay was requested to differentiate between all types of TSH-R-Ab[3]. This test was performed by Prof. Dr. Kahaly at Johannes Gutenberg University (Mainz, Germany). We concluded that neither thyroid-stimulating nor thyroid-blocking antibodies were present. Therefore, the measured antibodies were neutral. A favorable result given that these antibodies do not affect thyroid function, neither the mother's nor the fetuses'. Since this was a twin pregnancy complicated with atypical Graves hyperthyroidism, further multidisciplinary management and postpartum monitoring of the neonates' thyroid function is indicated.
Conclusion
When observing a switch between hyper- and hypothyroidism in patients with known Graves disease, it is important to screen for functional TSH-R-Abs. This distinction is important during pregnancy because inadequate maternal L-T4 levels could irreversibly impair fetal neurological development. Other indications for screening could include Graves disease with positive TSHR-A-bs persisting after 18 months of block-replacement therapy, before pregnancy when there is a known history of auto-immune thyroid disease addressed with thyroidectomy[4] or radioactive iodine and autoimmune thyroid dysfunction secondary to immune reconstitution therapy[5].

References
1. Antonelli A. Graves' disease: Clinical manifestations, immune pathogenesis (cytokines andchemokines) and therapy. Published online 2020. doi:10.1016/j.beem.2020.101388.
2. Kung AWC, Jones BM. A Change from Stimulatory to Blocking Antibody Activity in Graves' Disease during Pregnancy*. Published online 1998. Accessed February 11, 2024. https://academic.oup.com/jcem/article/83/2/514/2865426.

Attachment

Table 1. Overview of longitudinal maternal blood analysis and current treatment.

| Date | Gestational age, week | TSH level, mIU/L | FT4 level, pmol/L | TSH-R-Ab, IU/L | Dose PTU, mg/d | Dose L-T4, mcg/d |
|---|---|---|---|---|---|---|
| 23/02/2023 | -27 | 1.26 | 20.9 | 6.38¶ | 150 | 75 |
| 05/09/2023 | 1 | <0.01 | 37.3 | 4.17¶ | 150 | 87.5 |
| 02/10/2023 | 5 | - | - | 4.07¶ | 150 | - |
| 03/11/2023 | 9 | 7.48 | 7.5 | 30.90§ | 150 | - |
| 08/11/2023 | 10 | 7.89 | 7.8 | 33.40§ | 100 | - |
| 27/11/2023 | 13 | 6.14 | 7.26 | - | 50 | - |
| 11/12/2023 | 15 | 1.71 | 9.8 | 32.90§ | 25 | 25 |
| 02/01/2024 | 18 | 1.37 | 12.3 | 30.00§ | - | 50 |
| 15/01/2024 | 20 | 1.07 | 12.38 | 5.43¶ | - | 50 |
| 01/02/2024 | 22 | 0.674 | 12.09 | 4.49¶ | - | 75 |
| 16/02/2024 | 24 | 0.244 | 25.76 | 4.95¶ | - | 100 |

Legenda: TSH = thyroid-stimulating hormone; TSH-R-Ab = thyroid-stimulating hormone receptorantibody; PTU = propylthiouracil; L-T4 = L-thyroxine
† Reference range outside of pregnancy is 0.27–4.2 mIU/L. Reference range during pregnancy is 0-2.5mIU/L.
‡ Reference value of 12.4-20.4 pmol/L
* Reference value of 11.0-24.0 pmol/L.
§ Reference value of <0.55 IU/L. Results obtained by Siemens Immulite 2000 TSI assay (CLIA).
¶ Reference value of <1.75 IU/L. Results obtained by Roche Cobas e601 Elecsys TSI assay (ECLIA).

3. Diana T, Li Y, Olivo PD, *et al*. Analytical Performance and Validation of a Bioassay for Thyroid-Blocking Antibodies. Thyroid. 2016;26(5):734-740. doi:10.1089/THY.2015.0447.
4. Dierickx I, Billen J, Vanhole C, *et al*. Journal of Obstetrics and Gynaecology Severe fetal andneonatal hyperthyroidism years after surgical treatment of maternal Graves' disease. Severe fetal and neonatal hyperthyroidism years after surgical treatment of maternal Graves ' disease. Published online 2014. doi:10.3109/01443615.2013.831044.
5. Muller I, Moran C, Lecumberri B, *et al*. 2019 European Thyroid Association Guidelines on the Management of Thyroid Dysfunction following Immune Reconstitution Thera

DOI: 10.1530/endoabs.106.019

## 020

### Radiofrequency ablation: an effective alternate treatment of ectopic ACTH syndrome secondary to a well-differentiated lung carcinoid tumor

Claire Barani[1], Jean François Goyers[2], Dominique Maiter[1] & Raluca Maria Furnica[1]
[1]Department of Endocrinology, Cliniques Universitaires Saint-Luc UCL, Bruxelles, Belgium. [2]Department of Radiology, Clinique CHC MontLégia, Liége, Belgium

Background
Ectopic ACTH syndrome (EAS) is a rare, severe condition covering a wide spectrum of tumors of different location and aggressiveness with a predominance of bronchial carcinoids and small-cell lung carcinomas. The usual poor prognosis of patients with EAS require prompt management of the disease. The ideal treatment is complete excision of the ACTH-secreting tumor, once hypercortisolemia is under control with medical therapy. We report a case of a patient with high surgical risk and intolerance to cortisol-lowering drug, in which hypercortisolemia has been successfully treated with radiofrequency ablation of a lung carcinoid tumor.
Case presentation
A 78-year-old woman was referred for a rapidly progressive ACTH-dependent Cushing syndrome (CS). Biological tests and mainly high urinary free cortisol excretion suggested the presence of Cushing's syndrome due to ectopic ACTH production. Imaging studies detected a pulmonary nodule of 11 mm in the left upper lobe. A CT-guided biopsy of the lesion was performed, confirming a well-differentiated carcinoid tumor with Ki67 index $< 10\%$. The patient started therapy with ketoconazole, but rapidly developed severe gastro-intestinal side effects with dehydration. Due to a very high surgical risk, lung resection was prohibited by the multidisciplinary team and a radiofrequency ablation of the lung carcinoid tumor was performed without major complication. The procedure allowed a rapid control of hypercortisolism and improvement of CS.
Conclusion
In conclusion, we show that radiofrequency ablation may be an efficient alternate treatment for the management of high surgical risk patients with ectopic ACTH syndrome secondary to a well-differentiated lung carcinoid tumor.

DOI: 10.1530/endoabs.106.020

## 021

### Arginine vasopressin deficiency associated with accelerated phase myeloproliferative neoplasm with monosomy 7

Mohamed Amine El Kesri [1], Raluca Maria Furnica [1], Martin Buysschaert [1], Violaine Havelange [2] & Stefan Matei Constantinescu[1]
[1]Department of Endocrinology and Hematology. [2]Cliniques Universitaires Saint-Luc, 10 Avenue Hippocrate, 1200, Brussels, Belgium

Introduction
Arginine vasopressin (AVP) deficiency is defined by the inability to concentrate urine, secondary to a deficiency in antidiuretic hormone (ADH) production by hypothalamic neurons. The onset of this syndrome should prompt an extensive work-up, with a particular focus in elderly patients on a tumoral etiology affecting the posterior pituitary[1].
Case report
An 81-year-old female patient was referred to our endocrinology clinic for the evaluation of polyuria/polydipsia (approximately 3L/day of urine along with increased thirst and dry mouth) that had abruptly developed and persisted for one month. She was undergoing regular hematological follow-up for a myeloproliferative neoplasm and oncological follow-up for a breast carcinoma, treated in 2015 with neo-adjuvant chemotherapy and trastuzumab, followed by surgery, radiotherapy and adjuvant tamoxifen. Initial analyses performed by her diabetologist suggested AVP deficiency or resistance. The patient presented with a fasting glycaemia of 103 mg /dl (normal $<$ 100 mg /dl) and HbA1c of 6.11% (normal 4-6%) high serum sodium levels of 144 and 147 mmol/l (normal 135-145 mmol/l) with normal serum osmolality of 287mOsm/kg (normal 275-295mOsm/kg) and low urinary osmolality of 191mOsm/kg (normal 300900mOsm/kg). The water deprivation test clearly indicated an AVP deficiency (Table 1). During the period of fluid restriction, the patient demonstrated a tendency towards hypernatremia and persistently low urinary osmolality, not reaching $>$600mOsm/kg as expected[1]. It was only after the administration of desmopressin that urine osmolality rose $>$50% and serum sodium normalized. Consequently, we initiated treatment with nasal desmopressin, which resulted in a good clinical response. Pituitary MRI revealed a slightly rightward-deviated pituitary stalk of normal thickness, a normal anterior pituitary and the absence of the spontaneous T1 hyperintensity of the posterior pituitary. $^{18}$F-FDG PET/CT did not show any suspicious hypermetabolic focus, and the pituitary gland did not exhibit increased uptake. A complete serological workup for autoimmune disease and germinoma was reassuring (including assessments of angiotensin converting enzyme, alpha-foetoprotein, human chorionic gonadotropin, complement, IgG4, and ANCA). Anterior pituitary function remained intact. Concurrently with the onset of her AVP deficiency, the patient developed bicytopenia with anemia at 8g/dL (normal 12-15g/dl) and thrombocytopenia at 90,000/mm$^3$ (normal 150-450 000/mm$^3$) along with 1% circulating blasts. A bone marrow biopsy revealed malignant transformation of her hematologic disorder into an accelerated phase myeloproliferative neoplasm with excess blasts at 12%, likely therapyrelated (epirubicin-cyclophosphamide chemotherapy in 2015). The blasts exhibited monosomy 7. Despite the poor prognosis, treatment with Azacitidine and Venetoclax was proposed, but the patient opted for supportive care only. Six months after diagnosis, she maintains normal sodium levels under desmopressin, a normal anterior pituitary function and receives bi-monthly hematology follow-up for iterative transfusions. Follow-up MRI after 6 months was proposed but cancelled at the patient's request. A pituitary biopsy, which could have provided a definitive diagnosis, was not performed due to her thrombocytopenia, the risk of postoperative pituitary hormone deficiency and the lack of potential therapeutic consequences.
Discussion
We report a case of AVP deficiency concomitant with accelerated phase myeloproliferative neoplasm with blast excess and monosomy 7. This clinical presentation, extremely rare, is known to occur in the context of myelodysplasia/acute myeloid leukemia with blasts harboring monosomy 7[2]. The mechanism of AVP deficiency and its relationship to this specific chromosomal aberration remains to be elucidated, with tumor infiltration of the posterior pituitary by the blasts and local hemorrhage being described in small histological series[3]. AVP deficiency in this context is associated with a worse hematological outcome but may recover after treatment of the underlying hematological disease by chemotherapy or bone marrow transplantation[3]. This case highlights the need of careful evaluation of elderly patients presenting with polyuria and polydipsia and of performing an extensive etiological work-up to exclude infiltrative and malignant disease.

**Table 1:**Evolution of clinical and biological parameters during the water deprivation test. The period of fluid restriction started at 00h and continued for 16h. IM: intramuscular

| | 8h | 10h | 12h | 14h | 16h 2mcg IM Desmopressin | 18h | 20h | 22h | 08h (Day 2) |
|---|---|---|---|---|---|---|---|---|---|
| Weight (kg) | 86 | 85.6 | 85 | 84.8 | 84.4 | / | 86.6 | / | 86 |
| Blood pressure (mmHg) | 105/66 | 136/76 | 145/70 | 141/77 | 150/74 | 131/70 | 126/70 | / | 129/55 |
| Heart rate (bpm) | 92 | 87 | 98 | 89 | 94 | 103 | 97 | / | 106 |
| Urinary output (ml) | / | 355 | 435 | 255 | 325 | 100 | 90 | / | / |
| Serum osmolality (mOsm/kg) | 298 | 298 | 300 | 299 | 300 | 289 | 285 | 284 | 283 |
| Serum sodium (mmol/l) | 147 | 150 | 149 | 149 | 151 | 143 | 141 | 140 | 140 |
| Urine osmolality (mOsm/kg) | 216 | 213 | 218 | 291 | 260 | 484 | 589 | 562 | / |

References
1. Tomkins M, Lawless S, Martin-Grace J, Sherlock M & Thompson CJ. Diagnosis and Management ofCentral Diabetes Insipidus in Adults. J Clin Endocrinol Metab 2022 107 2701-2715. doi:10.1210/clinem/dgac381.
2. de la Chapelle A & Lahtinen R. Monosomy 7 predisposes to diabetes insipidus in leukaemia andmyelodysplastic syndrome. Eur J Haematol 1987 39 404-411. doi:10.1111/j.1600-0609.1987.tb01447.x.
3. Muller CI, Engelhardt M, Laubenberger J, Kunzmann R, Engelhardt R & Lubbert M. Myelodysplastic syndrome in transformation to acute myeloid leukemia presenting with diabetes insipidus: due to pituitary infiltration association with abnormalities of chromosomes 3 and 7. Eur J Haematol 2002 69 115-119. doi:10.1034/j.1600-0609.2002.02763.x.

DOI: 10.1530/endoabs.106.021

## 022

### Management of a mixed ACTH and prolactin secreting pituitary adenoma during pregnancy

Astrid Le Rigoleur [1], Stefan Matei Constantinescu [1], Martin Lammens [2,5], Edward Fomekong [3], Frédéric Debiève [4], Dominique Maiter [5] & Orsalia Alexopoulou[1]
[1]Department of Endocrinology and Nutrition. [2]Neuropathology. [3]Neuro-surgery, and Obstetrics. [4]Cliniques Universitaires Saint-Luc, Brussels, Belgium. [5]Department of Pathology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium

Introduction
Mixed ACTH and prolactin secreting pituitary adenomas are extremely rare and can lead to both Cushing's syndrome (CS), and galactorrhea and/or oligo-amenorrhea. No cases have ever been reported during pregnancy. Diagnosis of CS during pregnancy is challenging due to the physiological activation of the hypothalamic-pituitary-adrenal axis[1], and it is associated with severe maternal and fetal complications[1]. Early diagnosis and treatment are therefore essential to improve feto-maternal outcomes. We describe the occurrence of a mixed pituitary macroadenoma secreting ACTH and prolactin successfully treated by transsphe-noidal surgery (TSS) during pregnancy.
Case report
A 26-year-old woman was diagnosed with a centimetric prolactin secreting pituitary adenoma after developing oligomenorrhea, galactorrhea, and headaches. Hormonal data at diagnosis are not available. Cabergoline was initiated and up-titrated to 1.5 mg per week. Her menstrual cycles regularized but there was no improvement of galactorrhea. One year after cabergoline initiation, MRI showed no decrease in adenoma size, and blood tests revealed persistent hyperprolactinemia at 74.4 µg/l (normal 5.0 -23.0 µg/l) and increased ACTH at 143 pg/mL (normal 5.0 – 49.0 pg/mL). Concurrently, she gained weight, developed prediabetes and high blood pressure. The low-dose dexamethasone suppression test (0.5 mg every 6h for 48h) successfully suppressed plasma cortisol to 26.6 nmol/l and urinary free cortisol (UFC) was normal (34 µg/24h, normal < 40µg/24h). Surgical management was suggested, but she did not have medical insurance and cabergoline was continued with close follow-up advised until administrative regularization. She was then lost to follow-up for over a year and was referred for the first time to our consultation because of an ongoing pregnancy and treatment resistant hypertension. She was 5 weeks pregnant, weighed 147 kg (BMI 52 kg/m$^2$), and blood pressure was 150/90 mmHg. On clinical examination, she presented with fine abdominal stretch marks, buffalo neck, galactorrhea and lower limbs oedema. Blood tests at 5 weeks gestation showed hyperprolactinemia at 73.3µg/l. Morning cortisol was 417.4 mmol/l, afternoon cortisol was 369 nmol/l, ACTH was increased to 187.5 pg/mL and UFC was moderately elevated at 81,3 µg/24h, suggesting ACTH dependent hypercortisolism. A pituitary MRI at 12 weeks of pregnancy, revealed overall stability of the adenoma, which was in centre of the sella without cavernous sinus invasion. Given the risk of feto-maternal morbidity and mortality associated with CS, and after discussion at a multidisciplinary meeting for pituitary tumors, she underwent TSS at 16 weeks of pregnancy without any complications. The postoperative blood test showed normalization of prolactin and corticotropic insufficiency for which hydrocortisone was started. Pathological examination showed a single adenoma with positive staining for both PRL/PIT1 and ACTH/TPIT (Figure 1) . Blood pressure rapidly normalized. We started insulin at 21 weeks of gestation for diabetes. A pituitary MRI at 27 weeks of pregnancy showed complete resection. A cesarean section was performed at 38 weeks and 6 days, after injection of 100 mg hydrocortisone IV, and a healthy boy of 3,25kg was born, with no maternal nor neonatal complications. Genetic testing is underway of inherited causes of pituitary adenomas.
Discussion
Only a few ACTH-PRL secreting adenomas have ever been reported [2,3]. This association of hormones is unusual because of the different transcription factors necessary for the differentiation of lactotroph (PIT1 dependent) and corticotroph cells (TPIT dependent). Cabergoline therapy is an option in such cases and has been described to decrease both PRL and ACTH levels [2,3]. This was not fully the case for our patient who showed resistance to cabergoline for both prolactin and ACTH. We hypothesize that the occurrence of pregnancy was possible because of the regularization of her menstrual cycles with cabergoline and because hypercortisolism was mild. This case highlights the importance of pre conceptional counselling and the safety and effectiveness of TSS for pregnant patients with Cushing's disease.

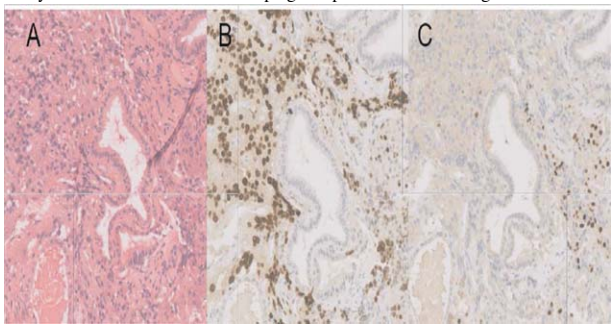



Figure 1: Pathological examinatio n showed a single adenoma with a m ixed PRL/PIT1 and ACTH/TPIT population. (A) Hematoxylin and eosin stain. (B) PIT1 staining. (C) TPIT staining. Immuno-histochemistry for prolactin and ACTH are not shown but matched the expected transcription factors

References
1. Hamblin R, Coulden A, Fountas A, Karavitaki N. The diagnosis and management of Cushing's syndrome in pregnancy. J Neuroendocrinol 2022; 34(8): e13118.
2. T'Sjoen G, Defeyter I, Van De Saffele J, Rubens R, Vandeweghe M. Macroprolactinoma associatedwith Cushing's disease, successfully treated with cabergoline. J Endocrinol Invest 2002; 25(2): 172-5.
3. Uraki S, Ariyasu H, Doi A, Furuta H, Nishi M, Usui T, Yamaue H, Akamizu T. Hypersecretion ofACTH and PRL from pituitary adenoma in MEN1, adequately managed by medical therapy. Endocrinol Diabetes Metab Case Rep. 2017 Apr 6;2017:17-0027.

DOI: 10.1530/endoabs.106.022

## 023

### Hyperthyroidism unmasked: thinking beyond the thyroid

Pieter-Jan Martens [1], Toon Van Gorp [2], Jaak Billen [3], Leen Antonio [4] & Marie Bex[1]
[1]Department of Endocrinology. [2]Department of Gynecologic Oncology. [3]Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium

Introduction
Thyrotoxicosis is usually caused by an overproduction of thyroid hormones due to conditions such as Graves' disease or thyroid nodules, or by an inflammation of the thyroid gland. We present a rare case in which both the pituitary and thyroid gland were intrinsically normal, yet endogenous severe hyperthyroidism ensued.
Case presentation
A 36-year-old female was referred by the gynecologist for evaluation of a worsening and unexplained thyrotoxicosis, diagnosed 11 weeks prior to her presentation to the emergency department with hematuria and urinary retention, caused by a pelvic mass. Her medical history is significant for endometriosis and a complete molar pregnancy, treated with two lines of chemotherapy (methotrexate and actinomycin D) eight years prior. Hormonal evaluation revealed a severe thyrotoxicosis (Table 1), previously not responding to a short course of

thyrostatics (methimazole 30 mg daily) and later to therapy with corticosteroids (methylprednisolone 32 mg daily, tapered to 12 mg over 4 weeks). This treatment had been instituted as initially the presentation with a sore throat suggested a diagnosis of viral thyroiditis, especially in the absence of TSH-receptor and thyroid peroxidase antibodies and a normal thyroid ultrasound. Nevertheless, as her condition deteriorated, additional scintigraphic imaging revealed a homogenous high technetium uptake, which shifted the diagnosis back to antibody-negative Graves' disease and methimazole was recommenced one week before referral. Further investigation identified the pelvic mass as malignant gestational trophoblastic disease (malignant GTD), characterized by high human chorionic gonadotropin (hCG) levels produced by syncytiotrophoblastic cells, that are monitored as key tumor marker to assess therapeutic efficacy. At high doses, hCG cross-reacts with the TSH receptor, causing hyperthyroidism with high isotope uptake, similar to Graves'. Initial hCG levels were only 6.769 IU/l, a level similar to those seen in the second month of pregnancy, but unexpectedly rose to > 1.000.000 IU/l upon initiating chemotherapy. This paradoxical increase could be attributed to the "high-dose hook" effect, a phenomenon where extremely high analyte levels saturate both capture and detection antibodies in immunoassays, leading to falsely low or undetectable results. Diluting the prechemotherapy sample confirmed that hCG levels at diagnosis were much higher (hCG 2.883.000 IU/l). As chemotherapy progressed, hCG levels decreased, accompanied by an improvement in thyroid function and resolution of thyrotoxicosis (Table 1).

Conclusion

This case highlights the impact of hCG on thyroid function, attributable to its structural similarities to TSH, allowing hCG to weakly bind to TSH receptors and stimulate thyroid activity if present in high levels. Although rare, it might be worthwhile measuring hCG in cases of unexplained thyrotoxicosis. Furthermore, even when using current hCG immunoassays, in situations of clinically expected extremely elevated hCG levels, the high-dose hook effect must be considered, as it can lead to falsely low results. This phenomenon is critical to recognize when interpreting immunoassay results in similar clinical contexts.

Table 1. Evolution of thyroid function tests over time (week 0 is at referral).

| Time (weeks) | TSH (mU/L) | Free T4 (pmol/L) | Free T3 (pmol/L) | HCG (IU/L) | MMI (mg) | Medrol (mg) |
|---|---|---|---|---|---|---|
| -11 | <0.01 | 28.3 | 12.3 | | Start 30 mg | |
| -9 | <0.01 | 26.8 | 8.3 | | 30 mg | |
| -7 | <0.01 | 36.9 | 14.9 | | 0 | |
| -5 | <0.01 | 51.5 | 19.6 | | 0 | Start 32 mg |
| -1 | <0.01 | 64.2 | 31.1 | | Start 10 mg | 12 mg |
| | | | | | | |
| **0** | **<0.01** | **45.7** | **17.4** | **[6769]** | **10 mg** | **4 mg** |
| | | | | 2 883 000* | → 30 mg | stop |
| 2 | <0.01 | 37.3 | 14.1 | 1 198 600 | 30 mg | |
| 3 | <0.01 | 26.4 | 5.8 | 761 590 | 30 mg | |
| 4 | <0.01 | 10.5 | 2.5 | 106 653 | 30 mg | |
| 5 | 0.99 | 6.8 | 2.4 | 8364 | 10 mg | |
| 7 | 1.14 | 8.0 | 4.2 | 690 | 0 | |
| 8 | 1.45 | 10.4 | | 246 | | |

As hCG levels decline, the thyroid function gradually improves so that ultimately methimazole can be discontinued while maintaining normalized thyroid function. Abbreviations: hCG: human chorionic gonadotropin. The initial undiluted hCG value (in parentheses) is affected by the high-dose hook effect; * same sample after dilution; Medrol: methylprednisolone; MMI: methimazole; T3: triiodothyronine (3.1-6.8); T4: thyroxine (11.9-21.6) ; TSH: thyroid-stimulating hormone (0.27-4.2) .

DOI: 10.1530/endoabs.106.023

## 024

**Primary aldosteronism diagnosed in pregnancy**

Laura Naert [1], Katrien Clotman [2], Dirk Ysebaert [3], Yves Jacquemyn [4], Christophe De Block [1] & Carlien DeHerdt[1]
[1]Department of Endocrinology, Diabetology and Metabolism, University Hospital Antwerp, Edegem, Belgium.[2]Department of Endocrinology, AZ Klina, Brasschaat; AZ Voorkempen, Malle.[3]Department of Hepatobiliary Surgery, University Hospital Antwerp, Edegem, Belgium.[4]Department of Obstetrics and Gynaecology, University Hospital Antwerp, Edegem, Belgium

Introduction

Despite being the most frequent cause of secondary hypertension, primary aldosteronism (PA) is only sporadically reported (< 80 case reports) in pregnancy (1). We present a case of a 29 year old woman in whom PA was diagnosed during pregnancy.

Case presentation

A 29 year old woman with an uncomplicated singleton pregnancy of a female foetus presented at the emergency department at 18 weeks of gestation (second trimester) with severe hypertension (200/126mmHG). Before pregnancy, she did not have hypertension. Blood sampling showed a normal kidney and liver function, but a severe hypokalaemia (2.5 mmol/l; reference range 3.5-5.1 mmol/l). Plasma aldosterone was elevated (1512 pmol/l) and direct renin concentration was suppressed (0.60 mIU/l) resulting in an aldosterone/ renin ratio of 2516.1 pmol/l/mIU/l. 24-hour urine cortisol, catecholamines and metanephrines were normal. Screening for hypertensive complications was negative. The tentative diagnosis of primary aldosteronism was made and patient was treated with intravenous potassium suppletion (80 meq KCl/ 24h) and 2 antihypertensives (Labetalol Methyldopa). In consult with the gynaecologist, Spironolactone at a dose of 50 mg BID was associated and the patient was referred to the Antwerp University Hospital at 19 weeks of gestation. Spironolactone was switched to Eplerenone because of limited more information regarding safety during pregnancy (1-6). The patient could be discharged on potassium gluconate 46 mEq daily, Eplerenone 25 mg once daily and 2 other antihypertensives (Labetalol, Nifedipine retard). However, the patient was readmitted after 2.5 weeks because of uncontrolled hypertension, oedemas and the development of mild proteinuria. The dose of Eplerenone was increased to 50 mg BID and MRI of the adrenals was performed, revealing an adenoma at the left adrenal (maximum diameter 1.9 cm). At 24 weeks of pregnancy, the patient underwent a laparoscopic left adrenalectomy. Pathology confirmed an adrenocortical adenoma. Post-operatively, potassium suppletion could be stopped and antihypertensive drugs could be tapered from 5 to 2 antihypertensives. Eplerenone was stopped. During further admission the patient was infected with COVID 19. Unfortunately, an urgent caesarean section was indicated at 24 weeks and 6 days of gestation because of foetal distress. The female neonate weighted 0.530 kg and was admitted to the neonatal intensive care unit (Apgar score 4-7-10).

Conclusion

We presented the case of a 29 year old female, who developed hypertension and hypokalaemia during the second trimester pregnancy and was diagnosed with PA. Blood pressure and potassium were not under control despite treatment with 5 antihypertensive drugs including Eplerenone 50 mg BID. At 24 weeks of pregnancy, she underwent a laparoscopic left adrenalectomy. The course was complicated with mild proteinuria and foetal distress necessitating caesarean section at 24 weeks of gestation. PA is a very rare etiology of secondary hypertension during pregnancy and is associated with increased maternal and foetal morbidity and mortality. Diagnosis is challenging due to the physiological changes during pregnancy with an increase of all the components of the renin angiotensin-aldosterone system. Suggestive features include hypertension before 20 weeks of gestation, worsening of hypertension as pregnancy progresses and hypokalaemia. Currently, no guidelines for the treatment of PA during pregnancy exist. The benefit of adrenalectomy is unclear and evidence supporting the choice of medical treatment with Eplerenone is anecdotal (1-6). A review of 13 cases with PA, diagnosed during pregnancy, revealed a poor outcome considering blood pressure was controlled in only 3 cases and 3 neonates deaths.

References

1. Forestiero V, Sconfienza E, Mulatero P, Monticone S. Primary aldosteronism in pregnancy. Rev Endocr Metab Disord. 2023;24(1):39 48.
2. Cabassi A, Rocco R, Berretta R, Regolisti G, Bacchi Modena A. Eplerenone use in primaryaldosteronism during pregnancy. Hypertension. 2012;59(2):e18 9.
3. Gunganah K, Carpenter R, Drake WM. Eplerenone use in primary aldosteronism duringpregnancy. Clin Case Rep. 2016;4(1):81 2.
4. Hutter DA, Berkowitz R, Davis SE, 3rd, Ashtyani H. Application of continuous positive airwaypressure in hypoxemic acute respiratory failure associated with diastolic dysfunction in pregnancy. Congest Heart Fail. 2006;12(3):174 5.
5. Morton A, Laurie J. Eplerenone in the management of resistant hypertension with obstructivesleep apnoea in pregnancy. Pregnancy Hypertens. 2017;7:54 5.
6. Morton A, Panitz B, Bush A. Eplerenone for gitelman syndrome in pregnancy. Nephrology(Carlton). 2011;16(3):

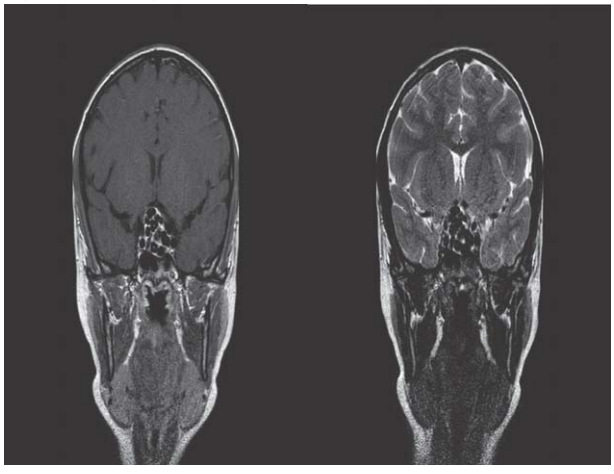
DOI: 10.1530/endoabs.106.024

## 025

**Are those teeth in your pituitary?**

Aurélien Schommers [1], Iulia Potorac [1], Gilles Reuter [2], Cécile Andris [3], Jean-François Bonneville [4] & Patrick Petrossians[1]
[1]Service d'Endocrinologie, CHU de Liège.[2]Service de Neurochirurgie, CHU de Liège.[3]Service d'Ophtalmologie, CHU de Liège.[4]Service d'Imagerie Médicale, CHU de Liège

Background
Pituitary teratomas are exceptional, with very few cases reported in the literature. Due to their rarity, it is difficult to establish a consensus for their management. We report the case of a young patient who was diagnosed with a non-symptomatic pituitary teratoma containing well-differentiated teeth. No specific treatment was dispensed, but the tumor benefits from a regular follow-up and shows no long-term progression.
Case presentation
An eleven-year-old boy was referred to pediatrics for a brachiocephalic myoclonus occurring for six months. The patient did not present headaches, visual complaints or signs of intracranial hypertension. The physical examination was unremarkable. MRI of the brain was performed and fortuitously revealed a 27 mm pituitary mass with suprasellar extension and the presence of multiple T1 and T2 hypointense images. The optic chiasm showed signs of compression (Figure 1) . The hormonal workup did not reveal any hormonal deficiency. Ophthalmologic examination showed no visual field defect. A germinoma was suspected. Thus, the patient benefited from chemotherapy. A follow-up MRI indicated no sign of tumor response which caused the diagnosis to be reconsidered. A biopsy of the mass was performed, with the removal of four teeth. No epithelial or cellular structure was identified microscopically. The diagnosis of mature teratoma was established. As the patient seemed to show no symptoms related to the teratoma, further surgical removal of the pituitary mass was not performed, and a close follow-up was decided. For the ten following years, subsequent MRIs have shown no sign of tumor progression. Currently, the patient remains asymptomatic.
Discussion
Intracranial teratomas represent 0,5% of all intracranial tumors. They mostly occur during the first two decades of life [1]. They belong to central nervous system germ cell tumors (GCTs), which are classified in three different subclasses: germinomas, non-germinomatous tumors (teratomas, embryonic carcinomas, endodermal sinus tumors, choriocarcinomas), and mixed GCT. The most frequent clinical manifestations include neurological deficits, diabetes insipidus and hypopituitarism [2]. Neuroimaging can help the differential diagnosis, but there is an overlap in the imaging features of GCTs [3]. In fact, non-germinomatous tumors appear heterogenous. Mature teratomas can contain fat, calcifications, cystic and solid components. Histologically, we identify three subtypes of teratomas: mature, immature, and teratomas with a malignant transformation. Mature teratomas are mainly composed of well-differentiated tissue with low mitotic activity, while immature teratomas contain poorly-differentiated fetal tissue. Teratomas with malignant transformation are exceptional and contain malignant somatic tissue [3]. Most of the reported tumors contain tissue issued from the three germ cell layers present in normal organogenesis (endoderm, mesoderm, and ectoderm). However, they may sometimes develop from a single germ cell layer if they show a histologically divergent differentiation [3]. The origin of teratomas is unclear. The most common explanation given is that teratomas originate from totipotent primordial germ cells. They develop from the endoderm in the yolk sac and migrate to the gonadal ridges during weeks 4 and 5 of gestation, but some cells seem to miss their target [4]. Currently, there is no consensus for teratoma management. Surgery is generally recommended [5]. Since any residual portion of a diagnosed mature teratoma may also contain a small part of immature or malignant tissue, recurrence after its partial removal has previously been reported [5]. Surprisingly, in our case, despise the fact that the tumor was not removed, the follow-up has so far shown no sign of progression.
Conclusion
Pituitary teratomas' management is still debated. Surgery is generally recommended, as all subtypes may include immature or malignant elements. Our case suggests that some of them might show a very low aggressive profile, implying that a simple close follow-up can also be an option. Figure 1.



References
1. Martha L. Tena Suck, Alma Ortiz Plata, Sergio Moreno Jimenez, Luis A. Tirado García: Pituitary Teratoma: A Case Series of Three Cases. Cureus. 2023 May 8;15(5):e38729. doi:10.7759/cureus.38729. PMID: 37292527; PMCID: PMC10246926.
2. Chiloiro, S., Giampietro, A., Bianchi, A. *et al.* Clinical management of teratoma, a rare hypothalamic-pituitary neoplasia. Endocrine 53, 636–642 (2016). https://doi.org/10.1007/s12020-015-0814-4.
3. Yang M, Wang J, Zhang L, Liu J. Update on MRI in pediatric intracranial germ cell tumors The clinical and radiological features. Front Pediatr. 2023 May 4;11:1141397. doi:10.3389/fped.2023.1141397. PMID: 37215600; PMCID: PMC10192609.
4. Keene DJ, Craigie RJ, Shabani A, Batra G, Hennayake S. Bipartite anterior extraperitoneal teratoma: evidence for the embryological origins of teratomas? Case Rep Med. 2011;2011:208940. doi:10.1155/2011/208940. Epub 2011 Aug 28. PMID: 21949666; PMCID: PMC3163403.
5. Glass T, Cochrane DD, Rassekh SR, Goddard K, Hukin J. Growing teratoma syndrome in intracranial non-germinomatous germ cell tumors (iNGGCTs): a risk for secondary malignant transformation—a report of two cases. Childs Nerv Syst. 2014 May;30(5):953-7. doi:10.1007/s00381-013-2295-1. PMID: 24122016.

DOI: 10.1530/endoabs.106.025

## 026

### Hypercalcemia following discontinuation of Denosumab in adults: a case report

Tondeur C. & Gombeir Y.
Department of Internal Medicine, Centre Hospitalier EpiCURA, Hornu, Belgium

Hypercalcemia following discontinuation of Denosumab in adults is described in the literature but remains a rare diagnosis. While pediatric cases receiving Denosumab for conditions like giant cell tumor of bone, fibrous dysplasia, osteogenesis imperfecta, central giant cell granuloma, and aneurysmal bone cyst have been discussed extensively, limited information exists regarding this phenomenon in adults. In this context, we present the case of a 77-year-old woman who was admitted to our hospital with hypercalcemia (3.5 mmol/l), confirmed by an ionized calcemia of 1.92 mmol/l. Diagnostic investigations showed normal albumin and phosphorus levels. Parathyroid hormone (PTH) level was normal at 17.9 ng/l (normal values 13.6-85). Further tests showed normal PTH-related protein (PTHrp), vitamin D (25-OH-D), TSH, CEA, and NSE levels. Protein electrophoresis was also normal. A thoraco-abdominal scan revealed a known pseudonodular formation with ground-glass appearance and a non-contrast-taking nodule in a PET-SCAN. The patient was treated with hyperhydration and pamidronate, normalizing her calcemia. However, a month later, calcemia rose to 3.05 mmol/l, necessitating readmission. Further tests to exclude granulomatosis included 1-25-OH-D and angiotensin convertase, both normal. Additional history-taking revealed that the patient had been receiving Denosumab injections every six months for osteoporosis but had missed her last injection, having not received it in the past 10 months. After resuming Denosumab and receiving hyperhydration, her calcemia stabilized. Denosumab, a human monoclonal antibody, inhibits osteoclast activity by targeting RANK ligand (RANKL)[1]. It is used to treat conditions like osteoporosis and various bone tumors. Osteoclast activity, essential for bone resorption, is countered by osteoblasts under normal conditions. Denosumab helps restore this balance by preventing bone resorption. Discontinuing Denosumab can lead to rebound hypercalcemia due in part to resumed osteoclast activity. A systematic review by H. Keisuke *et al.*[2] (2021) highlighted three adult cases treated for osteoporosis among others, showing treatments for rebound hypercalcemia including rehydration, diuretics, corticoids, and calcitonin. In some cases, bisphosphonates or Denosumab were re-administered. Prophylactic strategies include gradually reducing Denosumab or replacing it with bisphosphonates. This case represents the fourth documented instance of Denosumab cessation-induced hypercalcemia rebound in an adult treated for osteoporosis. It emphasizes considering Denosumab discontinuation in differential diagnoses of hypercalcemia, given its widespread use. Further research is needed to confirm the link between bone resorption and hypercalcemia, using bone resorption markers[3] and additional adult cases to improve management strategies for Denosumab discontinuation.

References
1. Rachner T.D., Khosla S., Hofbauer L.C., 2011. Osteoporosis: now and the future. Lancet 377 (9773), 1276–1287.
2. Keisuke H, Eisuke K, Tsukasa M, Michiro S, Kazuhiro C. Hypercalcemia following discontinuation ofdenosumab therapy: a systematic review. Bone Rep. 2021 November;15:1-6. doi:10.1016/j.bonr.2021.101148.
3. Deodati A., Fintini D., Levtchenko E., Rossi M., Ubertin,G., Segers H., Battafarano G., Cappa M., Del Fattore A., 2021. Mechanisms of acute

hypercalcemia in pediatric patients following the interruption of denosumab. J. Endocrinol. Investig. https://doi.org/10.1007/s40618-021-01630-4.

DOI: 10.1530/endoabs.106.026

## 027

### Neuroendocrine tumours in Lynch Syndrome: a case of an ACTH-producing atypical carcinoid lung tumour and literature review

Kevin Van Compernolle [1], Jacques Van Huysse [2], Marie Bex [3], Lander Van Acker [4], Vincent De Wilde [5], Jan Lesaffer [6] & Annick Van den Bruel [7]
[1]Department of Internal Medicine, Leuven University, Leuven, Belgium.[2-]Department of Pathology, AZ Sint-Jan AV, Bruges, Belgium.[3]Department of Endocrinology, UZ Leuven, Leuven, Belgium.[4]Department of Pneumology, AZ Sint-Jan AV, Bruges, Belgium.[5]Department of Gastroenterology, AZ Sint-Jan AV, Bruges, Belgium.[6]Department of Thoracic Surgery, AZ Sint-Jan AV, Bruges, Belgium.[7]Department of Endocrinology, AZ Sint-Jan AV, Bruges, Belgium

Background
Lynch syndrome (LS), an autosomal dominant genetic cancer predisposition syndrome, is caused by mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 or PMS2. In autosomal dominant genetic cancer syndromes like LS, a germline mutation hits one MMR gene allele so that a somatic mutation in the wild-type allele of the same MMR gene will cause a complete loss of function. This results in hypermutability and microsatellite instability.1 LS gives rise to a broad spectrum of tumours, mainly colorectal and cervix carcinoma. We describe the first case of a neuro-endocrine lung tumour presenting as a Cushing syndrome in a LS patient.
Case presentation
A 49-year-old female LS patient (heterogenous for MLH1 mutation c.2103 + 3A > C) was diagnosed with Cushing syndrome after developing obesity WHO class 2, facial flushing, arterial hypertension and hypokalaemia. Serum, midnight salivary, and 24-hour urinary cortisol were markedly increased. ACTH was elevated at 148 pg/ml (normal range 7.2-63.3 pg/ml). A marked cortisol excess (urinary free cortisol 30 x ULN) and a normal pituitary MRI suggested an ectopic ACTH source. Chest/abdominal CT showed gross infracarinal lymph nodes (up to 51 mm) and a 15 mm-sized lung nodule, which was present and unaltered since 2016. The mediastinal lymph nodes exhibited increased somatostatin receptor (SSTR) expression on 68Gallium-DOTANOC-scan. The patient was started on spironolactone and octreotide in a dose elevation scheme till 1000 μg/24 h IV, quickly switched to ketoconazole 200 mg tid due to insufficient effect of octreotide on the cortisol levels. An endoscopic ultrasound-guided fine needle biopsy of the infracarinal lymph nodes confirmed the localization of a neuro-endocrine tumour with 10% cytoplasmatic ACTH expression. A robot-assisted thoracoscopic resection of the lymph nodes and a wedge resection of the lung nodule were performed. Ketoconazole could be ceased afterwards. Hydrocortisone was needed to counter postoperative adrenal insufficiency and was gradually tapered over a three-month period. Pathology of the lung nodule and lymph nodes proved an atypical carcinoid tumour, with tumour-free resection margins. On immunohistochemical analysis, a defect of MLH1/PMS2 was evident, consistent with the patient's germline mutation, and the tumour showed a microsatellite-high phenotype. Three months after surgery, a new 68Gallium-DOTANOC-scan suggested local tumour relapse in the mediastinal lymph nodes. Octreotide was started and the patient received concomitant chemoradiotherapy (cisplatin 25 mg/m$^2$-etoposide 100 mg/m$^2$ q3w); chemotherapy was ceased after 3 cycles due to intolerance (therapy-refractory vomiting) and severe grade 4 pancytopenia. Since then, she remains in sustained disease control, while continuing octreotide long-acting release 30 mg q4w.
Discussion
Cushing's syndrome in this patient with LS was at first suggestive of adrenocortical carcinoma, a known tumour type in the Lynch spectrum.2 Nevertheless, the cortisol excess proved to be ACTH-dependent and the source of ACTH was an atypical lung carcinoid with mediastinal lymph node extension. A total of 28 cases of neuro-endocrine tumours in LS have been described in the literature so far. Twenty of the 26 tumours with a known origin were located in the gastrointestinal and gynaeco-urological tract; the other reported tumour types were pheochromocytoma and pituitary tumours. In the case presented, the tumour is most probably driven by LS and not merely a coincidentally occurring neoplasm in a LS patient. This is supported by the fact that the tumour is MSI-high, as it was suggested that it takes a sufficient amount of cell cycles before MSI occurs, which is unlikely in a coincidental tumour.3 Also, immunohistochemical analysis of the tumour showed loss of MLH1/PMS2, consistent with the germline mutation of our patient. In conclusion, our case expands the neuroendocrine tumour spectrum in LS. Clinicians treating LS patients should be aware of atypical or rare tumour presentations.
References
1. Bengtsson, D. *et al*. Corticotroph pituitary carcinoma in a patient with Lynch Syndrome (LS) and pituitary tumors in a nationwide LS cohort. Journal of Clinical Endocrinology and Metabolism 102, 3928–3932 (2017).
2. Kaur, R. J. *et al*. Adrenal cortical carcinoma associated with lynch syndrome: A case report and review of literature. Journal of the Endocrine Society 3, 784–790 (2019).
3. Karamurzin, Y. *et al*. Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: A report of new cases and review of the literature. Hum Pathol 43, 1677–1687 (2012).

DOI: 10.1530/endoabs.106.027