<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise as a non-pharmacological intervention to protect pancreatic beta cells in patients with type 1 and type 2 diabetes</td>
<td>001</td>
</tr>
<tr>
<td>Function and composition of pancreatic islet cell implants in omentum of type 1 diabetes patients</td>
<td>002</td>
</tr>
<tr>
<td>A plasma miR-193b-365 signature predicts non-responsiveness to Lactococcus lactis-based antigen-specific immunotherapy in new-onset type 1 diabetes</td>
<td>003</td>
</tr>
<tr>
<td>Understanding pathogenic mechanisms and identifying therapeutic avenues in MEHMO syndrome using patient’s induced pluripotent stem cells</td>
<td>004</td>
</tr>
<tr>
<td>Identification of myokines potentially involved in the improvement of glucose homeostasis after bariatric surgery</td>
<td>005</td>
</tr>
<tr>
<td>NET proteome and bioenergetic profile of PMA- and ionomycin-stimulated neutrophils from people with established type 1 diabetes</td>
<td>006</td>
</tr>
<tr>
<td>The impact of interferon-α on global gene expression in iPSC-derived β- and α-like cells</td>
<td>007</td>
</tr>
<tr>
<td>Glycemic control in patients diagnosed with renal cell carcinoma. A case series</td>
<td>008</td>
</tr>
<tr>
<td>The course and outcome of subacute thyroiditis: a retrospective analysis and predictive model</td>
<td>009</td>
</tr>
<tr>
<td>The Insulin Sensitivity Index Derived from Euglycemic Clamps Is Correlated to Liver Fat Content Determined by Magnetic Resonance Spectroscopy In Type 1 Diabetes*</td>
<td>010</td>
</tr>
<tr>
<td>Diagnosis and management of patients with primary hyperaldosteronism: a single-centre experience</td>
<td>011</td>
</tr>
<tr>
<td>Changes in serum androgen levels in transgender women with and without gonadectomy</td>
<td>012</td>
</tr>
<tr>
<td>TPO antibody status prior to first radioactive iodine therapy as a predictive parameter for hypothyroidism in Graves’ disease</td>
<td>013</td>
</tr>
<tr>
<td>Relationship of Time-Varying Parameters of Glycemic Control and Glycation with Arterial Stiffness in Patients with Type 1 Diabetes</td>
<td>014</td>
</tr>
<tr>
<td>Modest changes in sex hormones during early and middle adulthood affect bone mass and size in healthy men. A prospective cohort study</td>
<td>015</td>
</tr>
<tr>
<td>Mortality-related risk factors of inpatients with diabetes and COVID-19: a Multicentric Retrospective Study in Belgium</td>
<td>016</td>
</tr>
<tr>
<td>Prolactinomas: our experience in Liège</td>
<td>017</td>
</tr>
<tr>
<td>A rare cause of Cushing syndrome</td>
<td>018</td>
</tr>
<tr>
<td>A profound hypocalcaemia following parathyroidectomy. A case report</td>
<td>019</td>
</tr>
<tr>
<td>A rare etiology of primary amenorrhea in a 16-year-old girl</td>
<td>020</td>
</tr>
<tr>
<td>Chromosome 22q11.2 deletion syndrome revealed by severe hypocalcemia and pulseless electric activity: Untangling a conglomerate of potential primary etiologic factors</td>
<td>021</td>
</tr>
<tr>
<td>Rapid Growing Thyroid Nodule: The Good One In The Bad Clothes</td>
<td>022</td>
</tr>
<tr>
<td>Is this just vitiligo? Nelson is hiding</td>
<td>023</td>
</tr>
</tbody>
</table>
001
Exercise as a non-pharmacological intervention to protect pancreatic beta cells in patients with type 1 and type 2 diabetes
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Aim of the work
Diabetes is characterized by progressive loss of functional pancreatic beta cells. None of the therapeutic agents used to treat diabetes arrest this process and preventing beta cell loss remains a major unmet need. We have previously shown that serum from 8 young healthy males who exercised for 8 weeks protects human islets and human insulin-producing EndoC-bETA cells from apoptosis induced by pro-inflammatory cytokines or the endoplasmic reticulum (ER) stressor thapsigargin. Whether this protective effect is influenced by sex, age, training modality, ancestry and diabetes is unknown.

Methods
We enrolled 82 individuals, male or female, nondiabetic or diabetic, from different origins, in different supervised training protocols for 8-12 weeks (including training at home during the COVID-19 pandemic). EndoC-bETA cells were treated with “exercised” serum to ascertain cytoprotection from ER stress.

Results
The exercise interventions were effective and improved VO2 peak values in both younger and older, non-obese and obese, non-diabetic and diabetic participants. Serum obtained after training conferred significant beta cell protection from severe ER stress-induced apoptosis. Cytoprotection was not affected by the type of exercise training or participant age, sex, BMI or ancestry, and persisted for up to 2 months after the end of the training program. Serum from exercised patients with type 1 or type 2 diabetes was similarly protective.

Conclusions
These data uncover the unexpected potential to preserve beta cell health by exercise training or participant age, sex, BMI or ancestry, and persisted for up to 2 months after the end of the training program. Serum from exercised patients with type 1 or type 2 diabetes was similarly protective.

002
Function and composition of pancreatic islet cell implants in omentum of type 1 diabetes patients
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Introduction
Islet transplantation provides a promising treatment option for type 1 diabetes patients, but limitations raise the need for establishing a functional beta cell mass in omentum. The goal of this study is to characterize the function and composition of pancreatic islet cell implants in the omentum of type 1 diabetes patients.

Methods
This study reports the function and composition of omental (OM) implants after placement of islet cell grafts with similar beta cell mass as in our IP-protocol. Four of seven C-peptide-negative recipients achieved low beta cell function (hyperglycemic clamp [HGC] 2-8 percent of controls) until laparoscopy, 2-6 months later, for OM-biopsy and concomitant IP-transplant with similar beta cell dose. This IP-transplant increased HGC-values to 15-40 percent. OM-biopsies reflected the composition of initial grafts, exhibiting varying proportions of endemic- cell-enriched clusters with more beta than alpha cells and leucocyte pole, n endocrine cytokeratin-positive clusters surrounded by leukocytes, and scaffold remnants with foreign body reaction. OM-implants on a polyglactin-thrombin-fibrinogen-scaffold presented larger endocrine clusters with infiltrating endothelial cells and corresponded to the higher HGC-values. No activation of cellular immunity to GAD65 was measured post-OM-transplant.

Conclusion
Establishment of a metabolically adequate FBM in omentum may require a higher beta cell number in grafts but also elimination of their immunogenic non-endocrine components as well as local conditioning that favors endocrine cell engraftment and function.

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003
A plasma miR-193b-365 signature predicts non-responsiveness to Lactococcus lactis-based antigen-specific immunotherapy in new-onset type 1 diabetes
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Background and aims
Combining systemic immunomodulation with disease-relevant antigens could provide longer-term solutions for preventing and even reversing autoimmune type 1 diabetes (TID). Our team established that a combination therapy (CT), composed of a short-course low-dose anti-CD3 treatment with oral delivery of genetically-modified Lactococcus lactis (L. lactis) bacteria secreting full proinsulin plus the anti-inflammatory cytokine IL-10 (LL-PINS+IL-10), was effective in reversing TID in the non-obese diabetic (NOD) mouse model. Here, we aimed to identify robust peripheral biomarkers for prediction of CT response using circulating cell-free miRNAs (miRNAs). Furthermore, we exploited CITE-sequencing (CITE-seq), a multimodal phenotyping method that simultaneously measures RNA and cell surface proteins at single cell level to investigate the immune cell types as a possible source of the identified miRNA signature.

Materials and methods
New-onset diabetic NOD mice were injected intravenously with anti-CD3 (d0-5) and inoculated with LL-PINS+IL-10 for 6 weeks. TaqMan™ miRNA array followed by single-assay Q-PCR was performed on plasma samples taken from responder (R) and non-responder (NR) mice before CT initiation. CITE-seq was used to profile FACs-sorted circulating and pancreas-infiltrated CD45+ immune cells of new-onset diabetic NOD mice.

Results
Overall disease remission was 45% by the CT (n=110) compared to 0% in untreated controls (n=13; P<0.001) that remained hyperglycaemic. Using miRNA profiling, six miRNAs (miR-34a-5p, miR-125a-3p, miR-19b-3p, miR-328, miR-365-3p, and miR-671-3p) were identified as differentially expressed in plasma of R and NR mice at therapy initiation. CITE-seq analysis revealed a pro-inflammatory and activated phenotype in pancreas-infiltrated neutrophils and basophils. CITE-seq analysis revealed a pro-inflammatory and activated phenotype in pancreas-infiltrated neutrophils and basophils.

Conclusion
The miR-193b-365 signature could serve as a novel circulating prognostic biomarker for prospective personalization of L. lactis-based immunotherapy in human new-onset T1D.

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004 Understanding pathogenic mechanisms and identifying therapeutic avenues in MEHMO syndrome using patient’s induced pluripotent stem cells

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Background and aims
MEHMO is an X-linked syndrome comprising Mental retardation, Epilepsy, Hypogonitism, Microcephaly and Obesity. It is caused by a damaging p.Ile465SfSerfs mutation in EIF2S3 that encodes the β subunit of eukaryotic translation initiation factor 2 (eIF2), essential for protein synthesis and regulation of the integrated stress response. Patients with this EIF2S3 mutation also have neonatal hypoglycemia, early onset insulin-dependent diabetes and hypopituitarism. Here we investigated pathogenic mechanisms and potential treatments using patient’s induced pluripotent stem cell (iPSC)-derived pancreatic β-cells.

Materials and methods
Blood cells from a MEHMO patient with the p.Ile465SfSerfs mutation who developed diabetes at age 10 months were reprogrammed into iPSCs using the Yamanaka factors. iPSCs were differentiated in vitro into β-cells and exposed to endoplasmic reticulum (ER) stressors thapsigargin (1 mM) and brefeldin A (0.02 µg/ml). We investigated whether protection was conferred by exenatide (GLP-1 receptor agonist, 50 nM), forskolin (cAMP inducer, 10 µM) and ISRIB (integrated stress response inhibitor, 200 nM).

Results
Patient iPSCs showed morphological and developmental defects compared to control cells. Expression of crucial β-cell developmental markers NXK6.1 and PDX-1 was reduced compared to control cells (37.3% vs 62.2%, P< 0.0001), as was insulin content (11.2 vs 19.8 ng insulin/µg protein, P< 0.005, n=8). Basal β-cell death was not different (7.3% vs 8.4%, n=8), but the EIF2S3 mutation sensitized the cells to thapsigargin (24% vs 16%, P< 0.005) and brefeldin (36.7% vs 26.6%, P< 0.0001). ISRIB improved cell morphology and NXK6.1 and PDX-1 expression along the maturation but did not ameliorate β-cell survival. Exenatide and forskolin conferred protection against thapsigargin and brefeldin.

Conclusions
The diabetogenic EIF2S3 frameshift mutation alters patient’s iPSC-derived β-cell development and exacerbates ER stress-induced apoptosis. ISRIB rescues the developmental defect, and GLP-1 analogs protect from ER stress. This study points to an important role of EIF2S3 in β-cells and identifies novel therapeutic avenues for MEHMO syndrome. The patient iPSCs provide a powerful disease-in-a-dish model and can be used to study other clinical characteristics of MEHMO syndrome.

005 Identification of myokines potentially involved in the improvement of glucose homeostasis after bariatric surgery

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Purpose
Our study aims to identify myokines potentially involved in improved glucose homeostasis after bariatric surgery.

Methods
Obese patients were evaluated before and 3 months after bariatric surgery. Insulin resistance was assessed using the Homeostasis Model Assessment (HOMA) test. Muscle biopsies were taken from vastus lateralis. Genes encoding myokines involved in glucose homeostasis were identified using RNA-sequencing. Changes in myokines expression were confirmed by real-time quantitative PCR (RT-qPCR). Changes in myokines fractalkine and myostatin plasma levels were measured by ELISA. A linear regression analysis was used to predict changes in the HOMA test from changes in myokines expression or plasma levels.

Results
Insulin resistance was significantly improved (HOMA-IR, -53%, p < 0.001). Up-regulated genes included CX3CL1 (encoding fractalkine, +73%, p < 0.001) and BDNF (encoding Brain-Derived Neurotrophic Factor, +30%, p = 0.006) while MZV (encoding myostatin) was down-regulated (-45%, p < 0.001). Plasma levels of fractalkine and myostatin were, respectively, increased (+7%, p = 0.001) and decreased (-32%, p < 0.001). However, changes in insulin resistance were not correlated with changes in gene expression or plasma levels of fractalkine or myostatin. In contrast, increased expression of BDNF was significantly associated with decreased insulin resistance (HOMA-IR, adjusted estimate: -0.58 [-0.96, -0.19], p = 0.004).

Main conclusions
Bariatric surgery is associated with both improved glucose homeostasis and changes in myokines involved in glucose homeostasis. Although gene expression and circulating levels of fractalkine and myostatin are changed by surgery, they do not correlate with changes in glucose homeostasis. In contrast, increased expression of BDNF is correlated with improved insulin resistance, suggesting its potential role in improved glucose homeostasis after bariatric surgery.

006 NET proteome and bioenergetic profile of PMA- and ionomycin-stimulated neutrophils from people with established type 1 diabetes

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Background and aims
Type 1 diabetes (T1D) is a chronic autoimmune disease, characterized by T-cell mediated destruction of the pancreatic insulin-producing beta-cells. Neutrophils, cells of the innate immune system, have been shown to infiltrate the pancreas and undergo neutrophil extracellular trap (NET) formation (NETosis). However, little is known about the involvement of neutrophils and specifically the role of NETosis in the pathophysiology of the disease. Our aim was to study the NET proteome and bio-energetic profile of neutrophils from people with established T1D in response to stimuli such as phorbol 12-myristate 13-acetate (PMA) and ionomycin.

Materials and methods
Peripheral blood neutrophils isolated from people with established T1D (14 ± 7 years at T1D onset; 12 ± 10 years disease duration; 133 ± 37 mg/dl random glycaemia) and sex- and age-matched healthy controls (HC) were stimulated with PMA (100 nM) or ionomycin (20 µM) for 3 hours. The NETomes were studied by LC-MS/MS analysis, while metabolic changes during NETosis were explored by Seahorse extracellular flux analysis.

Results
Levels of PMA- and ionomycin-stimulated NETosis were comparable in HC and T1D neutrophils (PMA: 85% vs 90%; ionomycin: 63% vs 77% respectively), as well as plasma levels of NET markers. However, the NETome of T1D neutrophils was dissimilar from that of HC subjects in response to PMA or ionomycin. Upon quantification with Progenesis QI software, a total of 44 proteins were differentially expressed in the NETomes of HC and T1D subjects when stimulated with PMA. Ionomycin-induced NETomes contained 27 differentially expressed proteins.
expressed proteins (1% FDR, P<0.05). Reactome analysis revealed that the proteins enriched in HC NETomes in PMA- and ionomycin-stimulated conditions were involved in neutrophil degranulation and innate immunity (i.e., neutrophil elastase [ELANE], azurocidin [AZU1]). In both stimulated conditions, proteins enriched in T1D NETomes were involved in glucose metabolism, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK1), fructose-bisphosphatase aldolase A (ALDOA), and UTP-glucose-1-phosphate uridyltransferase (UGP2). Interestingly, metabolic profiling revealed that the rate of extracellular acidification, an approximate measure for glycolysis, was similar between T1D and HC neutrophils, in response to both PMA and ionomycin. Lactate levels in cell supernatants of PMA- and ionomycin-stimulated neutrophils were also comparable in T1D and HC subjects. Despite a lack of response to ionomycin, PMA induced a comparable increase in mitochondrial respiration in T1D and HC subjects.

Conclusion
Our results showed that the T1D NET proteome was enriched in proteins involved in glucose and glycogen metabolism. Interestingly, T1D neutrophils did not have an aberrant bioenergetic profile as determined by Seahorse extracellular flux analysis compared to HC neutrophils. These results suggest that T1D neutrophils, when activated, may alter their NET proteome to avoid impaired glycolysis and dysfunctional NETosis.

007
The impact of interferon-κ on global gene expression in iPSC-derived β- and ζ-like cells
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Aim
IFNκ is a key regulator of the initial dialogue between pancreatic β-cells and the immune system in type 1 diabetes (T1D). IFNκ induces endoplasmic reticulum (ER) stress, insults and a massive HLA-ABC overexpression in human β-cells, three histological hallmarks of T1D. Against this background we investigated the global role of IFNκ on iPSC-derived islet-like cells, used here to mimic islet cells in the early neonatal period when autoimmunity against β-cells starts in many patients.

Methods
Human iPSC were differentiated to islet-like cells following a 7 stage protocol and then treated with 2000 U/ml of IFNκ for 24h (dose and timing selected based on time-course and dose-response studies). Bulk and single-cell (sc) RNA-seq were performed. In follow up experiments, dispersed islet-like cells were transfected with a siRNA control or a siRNA targeting NLRC5 and then exposed or not to IFNκ for 24h. Gene expression levels were measured by qPCR. NLRC5 protein expression was assessed by western blot. The HLA-ABC expression at the β-cell surface was measured by flow cytometry.

Results
At the end of the differentiation period (stage 7) there were around 50% insulin and 10% glucagon positive cells. Exposure to IFNκ induced a predominance of upregulated genes (761 upregulated vs 302 downregulated) as indicated by the bulk RNA-seq data. The upregulated pathways identified were antigen processing and presentation, JAK/STAT signaling and antiviral responses, scRNA-seq of the iPSC-derived islet-like cells identified β- and ζ-like cells based on their characteristic gene expression. β-like cells exposed to IFNκ had higher expression of the ER stress markers CHOP and XBPI, while ζ-like cells showed higher expression of the protective chaperone BiP, of the anti-apoptotic family member BCL2L1 (Bcl-xl) and of the viral sensor MDA5. However, the expression of HLA-ABC was similar in ζ-like cells exposed to IFNκ as compared to β-like cells, except for the protective HLA-E, which was higher in ζ-like cells. The transcriptional activator NLRC5 was up-regulated after IFNκ treatment in β- and ζ-like cells and silencing of NLRC5 in iPSC-derived islet-like cells decreased HLA-ABC (gene expression and protein expression at the surface), as well as genes related with antigen presentation such as TAP1 and B2M.

Conclusions
IFNκ induces a different response in β- and ζ-like cells. β-like cells have a more marked expression of ER stress-related genes while ζ-like cells have higher expression of anti-apoptotic genes, protective chaperones and antiviral mechanisms. These observations suggest that ζ-like cells can better endure viral infections and ER stress, which could improve their survival in the context to T1D when compared to β-like cells. On the other hand, IFNκ induces similar upregulation of HLA-ABC on β- and ζ-like cells, downstream of the transcriptional regulator NLRC5.

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008
Glycemic control in patients diagnosed with renal cell carcinoma. A case series
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Background
Few cases have been described with a new-onset or worsening of a pre-existing diabetes mellitus in patients diagnosed with a renal cell carcinoma and amelioration of their diabetes following tumour resection.

Methodology
This is a retrospective study (2003-2021) including adult cases who were diagnosed with a renal cell carcinoma, who underwent tumour resection and whom glycemic control was monitored. HbA1c was measured at 3 time intervals; 18 months pre-operative, 6 months pre-operative and 6 months postoperative. Furthermore BMI, antidiabetic treatment and tumour characteristics were collected. The Fuhrman grading system (FGS), ranging from 1 to 4, is the most widely used pathological classification and predictor of renal cell carcinoma progression. A difference in HbA1c of 0.3% was considered clinically significant.

Results
In total, 12 cases (83% men) with a mean age of 66±9 years were included. Two cases had metastases. Seven cases had a clear renal cell carcinoma. 4 a papillary renal cell carcinoma and 1 a chromophobe renal cell carcinoma. None of the cases had a new-onset diabetes. One case with a chromophobe renal cell carcinoma had type 1 diabetes and showed no worsening of the metabolic control despite having aggressive tumour characteristics (diameter 10 cm, FGS 3). Metabolic control stayed stable after nephrectomy, insulin doses were not reduced. Eight cases had type 2 diabetes. Five of the 8 cases had a worsening of glycemic control before diagnosis. All these cases had a clear cell carcinoma, besides 1 case with metastatic disease having a papillary renal cell carcinoma. This in contrast to the remaining 3 cases with type 2 diabetes without worsening of glycemic control having a papillary renal cell carcinoma. All the cases with a worsening of glycemic control pre-operatively showed a significant improvement after total tumour resection, as their BMI remained stable. In 1 case, insulin therapy was started before resection and could be reduced postoperatively. Three cases had no diabetes, however 1 case with a clear cell carcinoma revealed a clinically significant reduction of HbA1c postoperatively of whom BMI was unchanged. The FGS and tumour diameter were heterogeneously distributed between cases with or without deterioration of glycemic control.

Conclusion
We present the evolution of the glycemic control of 12 cases before and at diagnosis of renal cell carcinoma and after tumour resection. No case had a new-onset diabetes. The cases with a worsening of HbA1c pre- and postoperatively, respectively, were all clear cell carcinoma compared to the remaining cases having a papillary or chromophobe renal cell carcinoma. Literature describes clear cell renal carcinoma tends to be more aggressive. In this case series this carcinoma were also associated with a worsening of glycemic control.

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009
The course and outcome of subacute thyroiditis: a retrospective analysis and predictive model
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Background: Subacute thyroiditis (SAT) is a rare inflammatory disorder mainly affecting the thyroid gland. It is characterized by diffuse thyroid pain and tenderness, fever, and hyperthyroidism. The etiology is multifactorial and may include viral, autoimmune, or bacterial infections. The aim of this study was to perform a retrospective analysis of patients diagnosed with SAT in our institution and to develop a predictive model for the course and duration of the disease.

Methods: A retrospective analysis of medical records of patients diagnosed with SAT at our institution from 2003 to 2021 was performed. The following data were collected: demographic characteristics, medical history, and laboratory findings including thyroid function tests, antithyroid antibodies, and viral markers. The primary outcome was the duration of hyperthyroidism. A predictive model was developed using logistic regression analysis.

Results: A total of 12 cases (83% men) with a mean age of 66±9 years were included. Two cases had metastases. Seven cases had a clear renal cell carcinoma. 4 a papillary renal cell carcinoma and 1 a chromophobe renal cell carcinoma. None of the cases had a new-onset diabetes. One case with a chromophobe renal cell carcinoma had type 1 diabetes and showed no worsening of the metabolic control despite having aggressive tumour characteristics (diameter 10 cm, FGS 3). Metabolic control stayed stable after nephrectomy, insulin doses were not reduced. Eight cases had type 2 diabetes. Five of the 8 cases had a worsening of glycemic control before diagnosis. All these cases had a clear cell carcinoma, besides 1 case with metastatic disease having a papillary renal cell carcinoma. This in contrast to the remaining 3 cases with type 2 diabetes without worsening of glycemic control having a papillary renal cell carcinoma. All the cases with a worsening of glycemic control pre-operatively showed a significant improvement after total tumour resection, as their BMI remained stable. In 1 case, insulin therapy was started before resection and could be reduced postoperatively. Three cases had no diabetes, however 1 case with a clear cell carcinoma revealed a clinically significant reduction of HbA1c postoperatively of whom BMI was unchanged. The FGS and tumour diameter were heterogeneously distributed between cases with or without deterioration of glycemic control.

Conclusion
We present the evolution of the glycemic control of 12 cases before and at diagnosis of renal cell carcinoma and after tumour resection. No case had a new-onset diabetes. The cases with a worsening of HbA1c pre- and postoperatively, respectively, were all clear cell carcinoma compared to the remaining cases having a papillary or chromophobe renal cell carcinoma. Literature describes clear cell renal carcinoma tends to be more aggressive. In this case series this carcinoma were also associated with a worsening of glycemic control.

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Background
Subacute thyroiditis (SAT) is a destructive thyroiditis of probable viral origin. Thyroid dysfunction evolves through a set of stages (hyperthyroidism - hypothyroidism - euthyroidism) and is usually temporary, although some patients develop permanent hypothyroidism. The risk factors for permanent hypothyroidism remain largely unclear.

Methods
A retrospective analysis of patients with SAT at the University Hospital of Brussels from 2001-2020 was performed. Firstly, a description of the patient characteristics, inflammatory and thyroid parameters is provided. Secondly, a predictive model for the requirement to initiate thyroid hormone therapy (THT) is developed using logistic regression analysis. The optimal model configuration was selected by forward sequential analysis maximizing the classification accuracy while the prediction performance was validated by leave-one-out cross-validation.

Results
A total of 35 patients were included, with a female predominance (4:3). Thyrotroxinosis was detected in the majority of patients (91%), while hypothyroidism developed in 71% (of which 27% were subclinical). THT was initiated in half of the patients (18/35). The discontinuation of THT was attempted in 10/18 patients and was successful in most of these (8/10). The logistic regression model selected the predictors 'age', 'season' and 'treatment regimen', and demonstrated a maximum accuracy of 86%, classifying 30 of 35 patients correctly in the outcome measure.

Conclusion
THT was initiated for hypothyroidism in half of the patients, which is more than previously reported, although discontinuation of replacement therapy was successful in most patients in whom attempts were made. A scoring model was developed to identify patients who may benefit from THT in clinical practice.

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011
Diagnosis and management of patients with primary hyperaldosteronism: a single-centre experience
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Background
Primary hyperaldosteronism (PA) is a prevalent, but underreported syndrome. Diagnostic procedures and treatment options have been relatively constant since the development of the latest guideline of the Endocrine Society in 2016. Study objective
To clinically and biochemically describe subjects with PA who underwent a salt infusion test (SIT) or an adrenal venous sampling (AVS) in a tertiary hospital since 2009 and provide an overview of their treatment.

Results
A total of 59 subjects with a mean age of 53 ± 13 were diagnosed with PA. 19% of patients only underwent a SIT and 46% underwent AVS after their SIT. In total 80% of patients underwent a AVS. Reasons for screening for PA were: therapy resistant hypertension (59%), hypertension with an incidental mass (7%) and hypertension with hypokalaemia (56%). One subject without hypertension had a positive screening for PA in the hormonal work-up of an adrenal incidentaloma. Echocardiogram showed left ventricular hypertrophy in 23 patients (51%). Plasma aldosterone/ renin ratio (ARR) was above the threshold of 20 in 96% of subjects. With a mean plasma aldosterone (PA) of 349.4 ng/mL 81% had a PA level above 150 ng/mL. A combination of both an elevated PA and ARR above the previous established threshold was seen in 77% of the patients who underwent a SIT. 15% had a PA between 100 - 150 ng/mL and 2 patients (5%) had a PA between 50 – 100 ng/mL. Of 18 patients who received only a SIT, 75% had a positive SIT and except for 1 patient (11%), all were treated with medication. AVS was performed by the same experienced interventional radiologist. AVS showed unilateral aldosterone hypersecretion in 23 subjects and bilateral hypersecretion in 12 subjects. In 9 subjects the right adrenal vein was not reachable and in 3 subjects there were analytical problems. Of the 23 subjects with lateralization, 16 underwent a unilateral adrenalectomy of which 7 could stop all antihypertensive drugs. Of the 12 subjects with a non-diagnostic AVS, 6 underwent a unilateral adrenalectomy with the histological confirmation of an aldosterone producing adenoma and normal blood pressure was achieved in 3 of them.

Conclusion
Despite being a tertiary centre only 47 patients were referred since 2009 to undergo an AVS which suggests underdiagnosis of PA. Hypertension and hypokalaemia are not mandatory to screen for PA but were present in 63% and 56%, respectively. The number of patients with unilateral vs bilateral aldosterone hypersecretion was similar. The discrepancy between AVS and CT adrenals was 20%. Normal blood pressure was achieved in only 48% of patient who underwent a unilateral adrenalectomy after confirmation of lateralization, but the number of antihypertensive medication could be reduced in 92% subjects from an average of 5 to 1 or 2 pills.

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012
Changes in serum androgen levels in transgender women with and without gonadectomy
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Introduction
Transgender women on gender-affirming hormone therapy (GAHT) with estrogen and anti-androgens have low serum androgen levels. These low levels may be associated with clinical symptoms such as depressed mood, reduced sexual desire and tiredness. Whether androgen levels change over the course of anti-androgen use and after gonadectomy, in a context of unchanged estrogen treatment, remains to be elucidated.

Methods
This study is part of the European Network for the Investigation of Gender Incongruence (ENIGIC) and aimed to describe androgen profiles in transgender women in the years after initiation of GAHT and after gonadectomy. Transgender women who initiated estrogens and cyproterone acetate (CPA) had regular follow-up at the Ghent University Hospital and the Amsterdam University Medical Center, (Location VUMc) at baseline, three months, twelve months, after two to four years or after gonadectomy. Levels of total testosterone (TT) and androstenedione (A4) were determined using liquid chromatography tandem mass spectrometry (LC-MS/MS). Sex hormone binding globulin (SHBG) concentrations were obtained using immunoassay. Free testosterone (FT) was calculated according to Vermeulen. In Ghent, dehydroepiandrosterone (DHEA) and dehydroepiandrosteronesulfate (DHEAS) were additionally measured using LC-MS/MS and immunoassay respectively.

Results
In total, 309 transgender women were included. At three months of GAHT, mean TT and FT decreased by 18.4 nmol/L [95% CI -19.24, -17.63] and 0.4 nmol/L [95% CI -0.41, -0.38], respectively compared to baseline and remained stable thereafter. SHBG increased upon initiation of GAHT (mean Δ = 19.3 nmol/L [95% CI 13.32, 25.30]) and continued to increase in the first year (mean Δ = 6.8 nmol/L [95% CI 2.54, 11.07]), remaining stable afterwards. DHEAS and DHEA decreased by 1.8 umol/l [95% CI -2.17, -1.42] and 6.52 nmol/L [95% CI -9.06, -3.97] respectively after one year of GAHT and did not change afterwards. A4 had decreased by 1.2 nmol/L [95% CI -1.37, -1.00] after three month and remained stable afterwards. No differences in TT, FT, DHEAS, DHEA, A4 between groups were observed between women on anti-androgens and after gonadectomy.

Conclusion
In the first year after initiation of GAHT with estrogen and CPA, levels of TT, FT, DHEAS and DHEA and dehydroepiandrosteronesulfate (DHEAS) were additionally measured using LC-MS/MS and immunoassay respectively.

014
Relationship of time-varying parameters of glycemic control and glycation with arterial stiffness in patients with type 1 diabetes

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Objective
We investigated if a positive thyroid peroxidase antibody (TPO Ab) status before radioactive iodine (RAI) therapy in patients with Graves’ hyperthyroidism is a predictive parameter for developing hypothyroidism after RAI.

Methods
We performed a retrospective study of patients with Graves’ hyperthyroidism with a known TPO Ab status, receiving a first administration of RAI. Patients from four thyroid outpatient centres in Belgium receiving a first RAI therapy between the years 2011 and 2019 were studied. Clinical, laboratory, imaging, and treatment data were recorded from medical charts. Hyperthyroidism and cure (defined as combined hypothyroidism and cure) were evaluated in period 1 (≥ 2 and ≤ 50 months, closest to 6 months post RAI) and period 2 (> 9 months and ≤ 24 months post RAI, closest to 12 months post RAI).

Results
One hundred fifty-two patients were included of which 105 (69%) were TPO Ab positive. Compared to TPO Ab negative patients, TPO Ab positive patients were younger, had a larger thyroid gland, and had more previous episodes of hyperthyroidism. In period 1, 89% of the TPO Ab positive group developed hypothyroidism vs 72% in the TPO Ab negative group (P = 0.007). In period 2, the observation was similar: 88% vs. 72% (P = 0.019). In a multivariate logistic regression analysis, adjusting for age at diagnosis, FT4 at diagnosis, thyroid volume at diagnosis, ATD preceding RAI and RAI activity, the adjusted OR was 4.16 (95% CI: 1.0–18.83; P = 0.052) in period 1 and 4.78 (95% CI: 1.27–18.18; P = 0.024) in period 2.

Conclusion
To date, the role of the TPO Ab status in patients with Graves’ hyperthyroidism has not been well studied as a predictive parameter for thyroid functional outcome after first administration of RAI. We show that TPO Ab-positive patients were more likely to develop early hypothyroidism after the first administration of RAI regardless of previously established factors associated with cure or treatment failure after RAI. Future studies investigating pre-treatment parameters affecting the outcome after RAI in patients with Graves’ disease should incorporate TPO Ab status as a variable.

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013
TPO antibody status prior to first radioactive iodine therapy as a predictive parameter for hyperthyroidism in Graves’ disease

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Objective
We investigated if a positive thyroid peroxidase antibody (TPO Ab) status before radioactive iodine (RAI) therapy in patients with Graves’ hyperthyroidism is a predictive parameter for developing hyperthyroidism after RAI.

Methods
We performed a retrospective study of patients with Graves’ hyperthyroidism with an unknown TPO Ab status, receiving a first administration of RAI. Patients from four thyroid outpatient centres in Belgium receiving a first RAI therapy between the years 2011 and 2019 were studied. Clinical, laboratory, imaging, and treatment data were recorded from medical charts. Hyperthyroidism and cure (defined as combined hypothyroidism and euthyroidism) were evaluated in period 1 (≥ 2 and ≤ 50 months, closest to 6 months post RAI) and period 2 (> 9 months and ≤ 24 months post RAI, closest to 12 months post RAI).

015
Modest changes in sex hormones during early and middle adulthood affect bone mass and size in healthy men.

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Aim
To investigate the relationship of arterial stiffness with short- and long-term parameters of glycemic control and glycation in patients with type 1 diabetes.

Methods
Cross-sectional study at a tertiary care centre including 54 patients with type 1 diabetes free from known CVD. Arterial stiffness was assessed with carotid-femoral pulse wave velocity (cf-PWV). Current level and 10-years history of HbA1c was evaluated, and skin advanced glycation end-products (AGEs), urinary AGEs, and serum AGE-receptor (sRAGE) concentrations. Continuous glucose monitoring (CGM) for 7 days was used to determine time in range, time in hyper- and hypoglycemia, and glycemic variability parameters.

Results
Clone-PWV was associated with current Hba1c (rs = +0.28), mean 10-years Hba1c (rs = +0.36), skin AGEs (rs = +0.40) and the skin AGEs-to-sRAGE ratio (rs = +0.40), but not with urinary AGE or serum sRAGE concentrations; and not with any of the CGM-parameters. Multiple linear regression for cf-PWV showed that the model with the best fit included age, type 1 diabetes duration, 24-hour mean arterial pressure and mean 10-years Hba1c (adjusted R2 = 0.645, P < 0.001).

Conclusion
Long-term glycemic exposure and glycation as reflected by mean 10-years Hba1c and skin AGEs, respectively, are key predictors of arterial stiffness in patients with type 1 diabetes, whereas no relationship was found with any of the short-term CGM-parameters. Our findings stress the importance of early and sustained good glycemic control to prevent premature CVD in patients with type 1 diabetes and suggest that Hba1c should continue to be used in the risk assessment for diabetic complications.

Keywords: Arterial Stiffness; Glycemic Control; Glycation; Hba1c; Type 1 Diabetes; Continuous Glucose Monitoring; Time In Range.

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The study included 375 patients. The median age was 73 [64-81] years and 93% factors for in-hospital death using multivariate analysis in both the total population. Survivors were compared to non-survivors in order to identify prognostic risk diagnosis was based on a positive polymerase chain reaction (PCR) test on diabetes and hospitalized due to confirmed COVID-19 were collected. COVID-19 We conducted a multicentre retrospective study during the first wave of the coronavirus disease 2019 (COVID-19) in Belgium. We describe the characteristics and prognosis of inpatients with diabetes and hospitalized due to confirmed COVID-19 in Belgium during the first wave of the pandemic. We also showed that metformin use before admission was associated with a significant reduction of COVID-19-related in-hospital mortality.

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017 Pro lactina tom as: our experi ence in Li ège

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Introduction

The prevalence of clinically relevant pituitary adenomas has been reevaluated at 1/1064 of the population (1). Among them, prolactinomas represent the majority with a prevalence of 1/2000. They occur usually in females, aged 20-50 Y.O., and 80% are microadenomas. Nearly 5% of prolactinomas appear in a familial or genetic setting (MEN-1 or PIPPA) (2). Cabergoline is proposed as the first line therapy and is usually efficient to normalize prolactin (PRL) levels, restore fertility and shrink tumor volume.

Patients and methods

We screened the patients followed for prolactinomas in our endocrinology department from 1980 to 2020. We looked for epidemiological and radiological data, prolactin (PRL) levels, treatments, a familial setting, cancer, associated endocrine problems and pregnancy follow-up.

Results

The study population consisted of 303 females (76%, median age: 34.5 Y.O.) and 97 males (24%, median age: 42.3 Y.O.). Tumors were mainly micro-adenomas in women and macro-adenomas in men. Median tumor size was 7 mm in females and 18 mm in males. PRL levels were lower in females (95.4 ng/ml vs 461.5 ng/ml) and correlated with tumor size. Main symptoms at diagnosis were amenorrhea and galactorrhea in women (80.1%). Men were complaining mainly of erectile dysfunction and/or loss of libido (44.3%) and headache (28.8%). A familial/gene-netic form was present in 16 patients (5%). These patients had bigger tumors. Overt or subclinical hypothyroidism occurred in 31.5% of our patients which is higher than the prevalence in comparable populations (3). Thyroid nodules were described in 22.5% of our patients. Breast cancer history was reported in 10 cases during follow up. Surgery was used in 38% of our patients, mainly before the year 2000; thereafter Cabergoline became the almost exclusive treatment. Under this medication, PRL levels were normalized in 80.6% of cases and a significant decrease of tumor size (> 50%) was noted in 67.2% of cases (4). 98 pregnancies occurred, 73 under cabergoline. The later was stopped at the discovery of pregnancy, but had to be restarted before delivery in 8 cases. No fetal complications were reported.

Conclusions

Prolactinomas are a frequent cause of infertility in young women. Cabergoline is now the first choice therapy due to its efficiency and tolerability. Our data show the presence of three different populations of patients, with different biological and radiological presentations: males, females and familial cases. Annamers should query for genetic forms due to the early onset and high prevalence of macroadenoma. The prevalence of overt or subacute hypothyroidism raises the question whether patients with prolactinomas need to be systematically screened for thyroid function abnormalities. Finally, we did not have complications during pregnancy, in line with other reports from the literature (5).

References

A rare cause of Cushing syndrome
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Introduction
Diagnosis of Cushing syndrome (CS) is challenging due to its various non-specific symptoms, and multiple endogenous and exogenous causes. The incidence of endogenous CS is rare and estimated at 0.8 cases per million inhabitants per year in Europe (1). Primary bilateral macronodular adrenal hyperplasia (PMBAH) is an uncommon cause of endogenous ACTH-independent CS. It is a benign condition, characterized by the presence of bilateral macronodules (>1 cm), and autonomic hypersecretion of cortisol by the adrenal glands (2).

Case
A 64-year-old woman consulted our endocrinology clinic for persistent complaints of fatigue, depressed mood and reduced muscle strength. Her medical history consisted of chronic obstructive pulmonary disease, arterial hypertension, and paroxysmal atrial fibrillation. Physical examination showed a brittle skin with atrophy, and edema at the ankles. Proximal muscle wasting was present. The patient’s face was round, highly hyperemic with dorsocervical fat accumulation atrophy, and edema at the ankles. Proximal muscle wasting was present. The patient’s face was round, highly hyperemic with dorsocervical and facial fat deposition (Figure 1A). 24h urine collection showed an elevated urinary-free cortisol of 305.5 µg/dL (normal reference: 15.0 - 55.0 µg/dL) after overnight 1 mg dexamethasone suppression (normal reference: <12.0 µg/dL). Serum cortisol decreased insufficiently (30.6 µg/dL) after overnight 1 mg dexamethasone suppression (normal reference: <1.8 µg/dL). Morning blood analysis revealed a serum cortisol of 27.4 µg/dL (normal reference: 6.0 - 18.4 µg/dL), and a completely suppressed ACTH (<1.0 pg/mL) (normal reference: 7.20 - 63.30 pg/mL). Computed tomography (CT) and magnetic resonance imaging (MRI) of the adrenal glands showed bilateral hyperplastic adrenals sizing 58.9 by 29.7 mm on the right, and 55.6 by 42.6 mm on the left. With informed consent of the patient, bilateral adrenalectomy was performed with postoperative substitution of glucocorticoids (hydrocortisone 20 mg/day divided over 3 doses) and mineralocorticoids (fludrocortisone 100 µg once daily). Pathology report confirmed the diagnosis of PMBAH. At follow-up, a clear decrease of Cushing stigmata could be observed (Figure 1B). Genetic sequencing failed to reveal mutations in the ARMC5 gene.

Discussion
PMBAH is a rare cause of endogenous CS. Its exact prevalence is not established as its manifestation varies from subclinical, to severe and progressive forms (3). The pathophysiology of PMBAH is still under investigation. Although PMBAH is sporadic, ARMC5 germline mutations are described in up to 58% of patients, warranting pro-active analysis upon diagnosis (4). Although bilateral adrenalectomy with lifelong glucocorticoid and mineralocorticoid substitution remains the best treatment option, unilateral adrenalectomy may be considered in specific cases (2). Currently, no additive value is gained from adrenal vein sampling-based cortisol lateralization ratios in the guidance of unilateral adrenalectomy (5).

Conclusion
In patients with suspicious signs such as atrophy of the skin with ecchymosis, red to purple-colored stretch marks, proximal muscle weakness and/or a plethoric/moon face, presence of CS should be considered. After confirmation of endogenous CS, differentiation between ACTH-dependent and ACTH-independent disease is essential. PMBAH is a rare cause of endogenous ACTH-independent CS. Although bilateral adrenalectomy remains the best curative option, unilateral resection can be considered if significant differences in adrenal size are present.

References

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A profound hypocalcemia following parathyroidectomy. A case report

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Background
Hypocalcemia after parathyroidectomy is a relatively uncommon but serious complication in patients who underwent parathyroidectomy for primary hyperparathyroidism. The syndrome is described as a hypocalcemia (corrected serum calcium <2.1 mmol/L) lasting longer than four days after parathyroidectomy in the presence of a normal or elevated parathyroid hormone (PTH). Treatment is challenging and guidelines are based on clinical experience. To restore calcium levels high doses of calcium and active vitamin D are needed. Case Report

A 39-year-old woman with a medical history of kidney stones and osteoporosis was diagnosed with primary hyperparathyroidism. Corrected serum calcium was 2.72 mmol/L (2.15-2.50) in the presence of an elevated PTH (748 ng/L, 15-65). Further blood results showed a normal kidney function, a decreased phosphate (0.51 mmol/L, 0.61-1.45), an elevated alkaline phosphatase (276 U/L, 38-120) and a decreased level of 25-hydroxyvitamin D (18.2 ng/mL, 30-100) for which substitution with D-cure was started. Guided by the results of localization studies a selective parathyroidectomy of the left (1.3 x 0.7 cm) end right (1.8 x 1.0 cm) inferior parathyroid adenoma was performed together with a total thyroidecotomy because of bilateral thyroid nodules. Post-operatively PTH normalized to a level of 57 ng/ml (18.5-88). Postoperatively, 1.6 g elemental calcium supplementation (calcium carbonate 4 g) per day was started. Histology revealed both thyroid nodules and parathyroid adenomas were benign. At discharge, the patient had a low normal corrected calcium level (2.15 mmol/L, 2.18-2.60) with a normal PTH level (72 ng/L).

One and a half month postoperatively, she complained of paraesthesia and muscle cramps. Blood sample revealed a low corrected serum calcium of 1.61 mmol/L in combination with an unexpected elevated PTH of 210 ng/L. Other electrolytes (potassium, phosphate, magnesium) and thyroid function were normal. Calciuria was increased levels of PTH, increased alkaline phosphatase, depleted vitamin D status and osteoporosis (1). In this case report, the total daily dose of 9.2 g elemental calcium is within the range of 6-12 g to normalize calcium levels in HBS (1). Five months postoperatively, the patient still requires calcium and active vitamin D supplements. There are no data about the mean duration of hungry bone syndrome, but can last up to 12 months postoperatively. To decrease the risk of the hungry bone syndrome in a hyperparathyroid patient with bone disease the use of preoperative bisphosphonates is suggested but there is a lack of high quality randomized studies (2).

References

A rare etiology of primary amenorrhea in a 16-year-old girl

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Introduction
Premature ovarian insufficiency (POI) is a rare cause of primary amenorrhea (1). We report a 16-year-old girl with normal secondary sexual characteristics, but no menses due to an autoimmune POI and associated with autoimmune gastritis.

This is the first report of such constellation in an adolescent – both conditions separately already being rare in the pediatric population.

Case presentation
A 16-year-old girl was referred to our department with primary amenorrhea and hyperprolactinemia. She had breast development for 2 years. She had no other complaints, i.e. no galactorrhoea, bursitism, hot flushes or mood changes. No recent weight loss, excessive weight gain or monthly abdominal pains were noted. Her medical history was unremarkable and she took no drugs or food supplements. There was no family history of autoimmune or endocrine diseases, early menopause, or fragile X syndrome. At physical examination, her weight was 50 kg (Z score −0.84), height 171 cm (Z score 0.67), and blood pressure 130/84 mmHg. She was at Tanner IV for breast and pubic hair development. Thyroid palpation was normal. Skin pigmentation and nails were normal. No dysmorphic features were noted. Hormonal analysis one month before referral showed elevated prolactin (56.2 µg/L), levels high normal FSH (23.2 mIU/L), normal LH (13.6 mIU/L), normal estradiol (32.6 ng/mL), and normal thyroid function. Repeat laboratory investigations confirmed a lower but still elevated prolactin of 48.1 µg/L (ref 3.71 - 23.12 µg/L) with a normal monomeric recovery, and elevated morning cortisol (312 µg/L), a high FSH (97.6 µIU/L), a high normal LH (56.7 µIU/L) and SHBG (98.9 nmol/L) with unmeasurable estradiol and AMH, suggesting an incipient POI. Genetic investigations including karyotype, CGH-microarray, and FISH of chromosome X were normal. FMRI triple repeat analysis showed a heterozygous intermediate expansion allele with 52 repeats. Screening for anti-ovarian, anti-adrenocortical, and anti-21-hydroxylase antibodies was repeatedly negative, but anti-TPO antibodies and anti-parietal cell antibodies consistently elevated. Abdominal ultrasound showed normal-sized ovaries without follicles and a uterus with an endometrial thickness of 5 mm. Pelvic MRI confirmed normal ovarian size and revealed only one follicle cyst in the right ovary (9 mm in diameter). By brain MRI a hypointense lesion (2.8 mm in diameter) was found in the posterior part of the anterior pituitary. Spinal bone mineral density was normal (DEXA, Z-score of −0.2). Hematology tests showed a normal erythrocyte sedimentation rate and white blood cell count but revealed an iron deficiency anemia. Serum gastrin was elevated while tissue transglutaminase IgA and fecal occult blood tests were negative. Endoscopic-histologic evaluation confirmed the presence of atrophic gastritis.

Discussion
We report on an adolescent girl with autoimmune POI associated with autoimmune gastritis. The initial transient ovarian failure during immune attacks complicated the diagnosis of autoimmune POI and in this case probably explains the absence of hot flashes, the initially normal estradiol levels, and the normal bone mineralization (3). Furthermore, diagnosing autoimmune POI is also difficult due to low sensitivity and specificity of anti-ovarian antibody testing - frequently false negative as seen in our patient (3). In this girl, the diagnosis was further complicated by elevated prolactin and cortisol levels, which were likely related to stress or transient FSH induced hyperprolactinemia. The diagnosis of atrophic gastritis and thyroid autoimmunity and the exclusion of other diagnoses allowed us to diagnose autoimmune POI. Diagnosing autoimmune forms of POI is important in view of the incipient risk of autoimmune adrenal insufficiency and need for follow-up (4).

Conclusion
Autoimmune POI can present with primary amenorrhea in adolescent women. Thorough immune evaluation is needed to diagnose autoimmune POI when anti-ovarian antibodies are negative. Full autoimmune screening, including not only anti-ovarian and anti-adrenocortical antibodies but also anti-parietal cell antibodies should be done in unexplained POI, especially when iron deficiency is present.

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Case report

A 28-year-old man, known with autism spectrum disorder (ASD), presented at the emergency department (ED) for muscle cramps. Medical history included the myelodysplasia treated with tyrosine kinase inhibitor (TKI) the last 10 years, gastric bypass and recurrent fractures due to osteoporosis managed by alendronate. Four months prior to the admission, alendronate was switched to zoledronate because of digestive adverse effects. Under zoledronate, there was exacerbation of the muscle cramps. At the ED, temperature was 36.5°C, respiratory rate 22 cycles/min, heart rate 110 beats/min and upper limbs spams (Trousseau sign) hindered blood pressure measurement. Shortly after arrival at the ED, the patient suddenly developed pulseless electric activity, requiring advanced cardiopulmonary resuscitation including endotracheal intubation followed by admission to the intensive care unit. Investigations revealed a long QTc at 513 msec, severe hypocalcemia (Ca 1.32 mmol/L [range 2.12-2.60], ionized Ca 0.66 mmol/L [range 1.17-1.33]), normal magnesium (0.68 mmol/L [0.74-0.90]), hypophosphatemia (phosphorus 0.49 mmol/L [0.78-1.42]), normal vitamin D 53 ng/mL and inadequate low parathyroid hormone (PTH) level (38 ng/L [range 7-70]). Management included parenteral magnesium, calcium and oral calcitriol. Amiodarone was temporarily administered for sustained ventricular tachycardia. TKI and bisphosphonate were interrupted. The medical records showed low calcium level immediately after initiation of TKI ruling out gastric bypass and bisphosphonate as primary etiologic factors. Genetic testing was requested based on low calcium level, inadequately low PTH and atypical facial features (asymmetric crying facies, malar flatness and hooded eyelids). This identified deletion of chromosome 22q11.2 spanning the region of catechol-O-methyltransferase (COMT) and T-box transcription factor 1 (TBX1) genes. Upon discharge, oral substitution of calcium, magnesium and calcitriol was continued.

Discussion

Severe hypocalcemia can represent a life-threatening condition. Etiologies of hypocalcemia are divided into PTH and non-PTH mediated causes.4 In our patient this could be due to TKI, malabsorption following gastric bypass, bisphosphonate initiation and, besides his psychiatric past medical history, the patient’s phenotype suggested a congenital disorder. Identification of chromosome 22q11.2 deletion confirmed a constitutional defect in calcium metabolism which might have been sequentially exacerbated by initiation of TKI, gastric bypass and bisphosphonate. Hypocalcemia in chromosome 22q11.2 deletion syndrome results from hypoparathyroidism and occurs not only in the neonatal period, but also in adulthood.2 Other clinical characteristics encompass cardiac defects, abnormal facies, thymic hypoplasia, cleft palate (and hypocalcemia) defined by the acronym CATCH-22. The disease spectrum is heterogeneous. In our patient, structural cardiac defects and immune deficiency have been excluded. While ascertainment of TBX1 deletion relates to the clinical presentation encompassing hypoparathyroidism that of COMT gene could be associated with autism spectrum disorder.3,5 Indeed, TBX1 gene has been reported to influence cell proliferation and differentiation as well as signaling pathways involving fibroblast growth factor, retinoic acid, bone morphogenetic protein among others. Deletion of one copy of TBX1 impacts on the development of pharyngeal arch and, besides initiating one of the cardiovascular malformations, a deletion in chromosome 22q11.2 can result in an associated heart defect (Tetralogy of Fallot).6

Case report

DiGeorge syndrome (DS). Hypocalcemia has been reported to occur in up to 1 per 347 to 992 fetuses.1 Patients present with velocardiofacial syndrome (VCFS) or DiGeorge syndrome (DS). Hypocalcemia has been reported to occur in up to 80.4% of cases.2

References


Endocrine Abstracts (2022) Vol 88

022 Rapid growing thyroid nodule: the good one in the bad clothes

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Background

Primary thyroid lymphoma (PTL) is a rare thyroid tumor that accounts for only 5% of thyroid malignancies, but is associated with higher mortality than differentiated thyroid cancer. The major risk factor for thyroid lymphoma is the presence of Hashimoto’s thyroiditis (HT) with an estimated 60-fold increased risk. The lymphoctic infiltrate in HT appears to develop into lymphoma in a minority of patients. The differential diagnosis between Hashimoto’s thyroiditis and thyroid lymphoma can be difficult.

Case report

We report a 34-year-old man who was referred to the endocrinologist for a large, rapidly growing thyroid nodule. The patient had not noticed the nodule until 2 months earlier. He had no known thyroid disease. Blood analysis showed normal thyroid hormone levels with positive antithyroid autoantibodies (TSH 1.97 mUI/L; free T4 14 pmol/L; Tg 437 mUI/L; aTPO 283 mUI/L; and TRAB 1.84 mUI/L). Ultrasound examination (US) showed a large solitary hypoechogetic thyroid nodule of 53 mm in the right lobe, EU/TIRADS V. Scintigraphy confirmed the large nodule in the right lobe with low iodine uptake. Fine needle aspiration cytology was performed and showed the prevalence of lymphoid population with abundant presence of CD20+ lymphocytes by immuno-histochemistry (IHC). The diagnosis of lymphoproliferative disease could not be made. To obtain a definite diagnosis, an anatomical pathological examination with flow cytometry was necessary. The patient underwent a right hemithyroidectomy. The postoperative anatomopathological examination showed a lymphocytic infiltrate with the formation of germinal centers, with CD20+ and CD10+ lymphocytes, and expression for both chain kappa and lambda by plasma cells. There was no (14; 18) chromosome translocation on BCL2 FISH, making the diagnosis of lymphoma less likely. Following the results of the pathological examination and IHC, the diagnosis of a thyroid nodule in the context of Hashimoto’s thyroiditis was made. Given the diagnostic complexity, a ¹⁸F-FDG PET-CT scan was also performed which showed no signs of malignancy or extrathyroidal disease.

Discussion

The reported case describes a difficult diagnosis between Hashimoto’s thyroiditis and thyroid lymphoma in a patient presenting with a single large thyroid nodule. There is a correlation between the presence of Hashimoto’s thyroiditis and the occurrence of thyroid lymphoma (25-75% of patients with PTL also have a diagnosis of Hashimoto’s). The association between HT and PTL seems to originate from the development and alteration of intrathyroidal lymphoid tissue in HT. Cytological examination (FNAC) with IHC is often sufficient for definitive diagnosis, but in rare cases, histology is necessary for a definite diagnosis (as in our patient). The two pathologies share similarities on FNAC with IHC. The cellular infiltrate of PTL is characterized by CD20+ and CD19+ lymph nodes and the presence of K/L monoclonality (usually between 3-4), whereas the cellular infiltrate of the nodular form of Hashimoto’s disease “lymph node-like pattern” is characterized by a CD19+ lymph node body variable K/L Lambda monoclonality (usually between 0.5 to 3.0). The diagnostic difficulty in our patient was due to the presentation with a large and rapidly growing nodule, with FNAC showing a large CD20+ lymphocyte population, for which a definite diagnosis could only be made with histology and other diagnostic tests such as PET-CT to exclude extra-thyroidal involvement.

Conclusions

We present the case of a 34-year-old man with a large, rapidly growing thyroid nodule. Faced with a large and fast-growing nodule, one immediately thinks of a possible malignancy such as PTL or anaplastic thyroid cancer, but a similar clinical presentation can also be observed in the presence of Hashimoto’s thyroiditis. In these cases, only a biopsy can confirm or deny the diagnosis of malignancy. References

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Is this just vitiligo? Nelson is hiding
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Introduction
Autoimmune disease is a rare event occurring after remission of Cushing’s syndrome. We report on the appearance of new onset vitiligo in a patient treated for Cushing disease due to an invasive pituitary adenoma, after bilateral adrenalectomy.

Case report
A 64-year-old man presented to our endocrinology clinic with progressive lumbar pain that had developed two months earlier. He had undergone bilateral adrenalectomy for Cushing’s syndrome (CS) four years ago and transsphenoidal resection for Nelson tumor two years later. On physical examination, the patient had remarkable hyperpigmentation due to ACTH hypersecretion periorbital, periauricular and in the lower-neck region (figure 1). These findings were evident in his case due to the extensive facial vitiligo. Findings on bone scintigraphy were suggestive for metastatic lesions (figure 2) and CT-guided bone biopsy confirmed our suspicion of bone-invasive pituitary carcinoma. The patient was referred to the oncology department as a candidate for immunotherapy but opted for palliative care because of his weakened general condition.

Discussion
This case highlights the fact that hypercortisolism induces a state of immunosuppression. After treatment and normalization of cortisol hypersecretion in Cushing’s syndrome, rebound immunity may result in overt autoimmune diseases, in case vitiligo. In a study by de Mota et al. it was reported that 8 out of 78 (10.3 %) adult patients with endogenous CS presented with a new autoimmune or allergic disease after treatment [1]. Other studies have reported an increased incidence of autoimmune thyroid disease in patients after treatment of CS [2, 3]. There have been descriptions of other forms of autoimmunity after cure of CS, mainly in case reports, such as rheumatoid arthritis, celiac disease, and systemic lupus erythematosus [2, 4-5]. This immunological phenomenon has been described in both ACTH-dependent and -independent cases but a lot of questions remain open to discussion. What is the underlying pathophysiological mechanism? Would autoimmunity be there if CS had not occurred? Is autoimmunity a transient phenomenon in these patients?

Conclusion
We present the case of a 64-year-old man with rapidly developing vitiligo, after bilateral adrenalectomy for an invasive pituitary ACTH secreting adenoma. The diagnosis of a metastasized pituitary carcinoma was confirmed. Patients with CS are considered immune-depressed. After treatment of CS, patients are at risk for developing autoimmune diseases. Early recognition of these autoimmune conditions and appropriate treatment are warranted.

References

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Figure 1 and 2