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Abstracts of the 27th meeting of the Belgian Endocrine Society

ABSTRACTS

Who stole my cholesterol? A case report of night blindness and virtually absent serum betalipoproteins

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Clinical case

An 18-year-old woman presented with mild visual impairment and nyctalopia. Further analysis revealed impressive gastro-intestinal abnormalities, severe deficiencies of Vitamin A and all other fat-soluble vitamins and a complete absence of plasma beta-lipoproteins.

The patient's medical history was surprisingly unremarkable. As an infant, she was diagnosed with failure to thrive, easy vomiting and fatty stools, leading to a negative laparotomy at the age of 3 months. After "trial and error" elimination of dietary fats a normal further development into adulthood followed without any complaints other than her visual problems and a mild bleeding diathesis. At physical examination at 18 years, however, areflexia of upper and lower extremities became apparent, whereas laboratory analysis repeatedly and consistently showed severe vitamin deficiencies (A <12 µg/dL, E <0.3 mg/dL, and prothrombin time of 2.67 INR), extreme hypocholesterolemia (total cholesterol 30 mg/dl, LDL undetectable, HDL 30 mg/dl) and a complete absence of triglycerides (2 mg/dl). Free fatty acids and thyroid function were normal, as was Vitamin D (38.3 ng/mL) under oral substitution.

Blood smears showed pronounced acanthocytosis, compatible with both lipid and Vitamin E deficiencies, as well as with increased erythrocyte turnover rates (reticulocyte count 22‰, HbA1c 3.8%). In addition, a mild hepatic steatosis was found on ultrasound, whereas gastroduodenoscopy showed a marked yellowish-pale discoloration of the small bowel mucosa. Both findings reflect lipid retention in hepatocytes and enterocytes respectively. Electromyography revealed polyneuropathy; bone densitometry showed osteopenia without osteomalacia/rickets.

This so-called abetalipoproteinemia is a rare, autosomal recessive disorder, in which mutations of both alleles of the MTTP protein cause improper packaging and secretion of apoB-containing lipoprotein particles from enterocytes and hepatocytes. Subsequently, this results in intracellular lipid retention instead of chylomicron and VLDL secretion into plasma. Hence, malabsorption of lipids and lipid-soluble vitamins occurs; retinal degeneration and eventually blindness, often severe and debilitating neuropathy and coagulopathy follow and form the basis of the clinical diagnosis. Definitive confirmation involves sequencing the *MTTP* gene.

In our patient, only a heterozygous deletion of the entire *MTTP* gene was identified; we are therefore currently investigating whether a possible second mutation (c.393+3A>T in intron 4 of *MTTP*) could account for this extreme clinical presentation.

Treatment is supportive, consisting of a low-fat diet and intravenous supplementation of essential fatty acids and (if necessary, intravenous) highly dosed lipophilic vitamins. Early diagnosis and strict adherence to treatment largely determine prognosis and are vital for slowing down disease progression and preservation of neurological, ophthalmological and bone function.

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Severe secondary osteoporosis in a premenopausal woman: should a specific anti-osteoporotic treatment be started?

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Osteoporosis is one of the major complications in patients with endogenous Cushing's syndrome (CS). We present the case of a severe osteoporosis secondary to a cortisol-secreting adrenal adenoma in a premenopausal woman. We have monitored bone mineral density (BMD) and bone turnover markers (BTMs) over a 9-years period following the surgical cure of Cushing's syndrome.

A 33-year-old woman was diagnosed with severe osteoporosis and vertebral fractures. The physical examination raised the suspicion of a Cushing's syndrome witch was further confirmed by various studies and proved to be caused by an adrenal adenoma. Osteoporosis was considered to be secondary to endogenous hypercortisolism. A dual-energy x-ray absorptiometry (DXA) scan performed 2 months after successful surgery showed a significant spontaneous improvement in lumbar spine BMD. BTMs showed maximum values 5 months after surgery, followed by a gradual decrease to normal values. A 9-years follow-up with yearly DXA and BTMs evaluations showed complete spontaneous BMD recovery with normal and stable BTMs, in the absence of any specific antiresorptive therapy. Over this long period the patient did not present any new vertebral fracture.

Conclusion: Our case provides evidence that there is no need for any antiresorptive therapy in severe osteoporosis due to a cortisol-secreting adrenal adenoma after successful surgery, at least in premenopausal women.

Assessment of bone quality with trabecular bone score (TBS) in type 2 diabetes mellitus (T2DM)

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Patients with T2DM present an increased risk of fracture, despite the observation that bone mineral density (BMD) from DXA is often higher in T2DM compared with nondiabetic population. The paradoxical increase in fracture risk suggests that there are diabetes-associated alterations in material and structural properties. Because BMD is central to fracture prediction, a consequence of this paradox is a lack of suitable methods, including FRAX, to reliably predict fracture risk in patients with T2DM. TBS provides an indirect measure of bone quality by evaluating pixel gray-level variations in DXA images of the lumbar spine.

Objective: To compare DXA and TBS values between patients with T2DM and control subjects with similar FRAX scores.

Design and settings: We performed a cross-sectional analysis using BMD results from subjects participating in FRISBEE study, an ongoing prospective epidemiological study in a population-based cohort (Brussels, Belgium) of 3560 postmenopausal women aged 60-85 years. We investigated 260 subjects with baseline DXA examinations (Hologic) from the FRISBEE cohort among whom 65 had known T2DM at inclusion. Subjects were separated into 2 groups based on the presence of T2DM. We studied 3 controls for each diabetes case. Subjects were matched on age and baseline FRAX score for major osteoporotic fractures (with BMD). TBS (TBS iNsight software, MedImaps, France) was derived for each spine DXA examination.

Results: Age and FRAX scores were similar between the 2 groups: 69.9±5.8 years and 9.5±6.7 in T2DM vs 69.8±5.6 years and 9.9±6.7 in controls. BMD was higher in T2DM than in controls, significantly so at the total hip. On the contrary, mean TBS was significantly lower in T2DM (1.185±0.172; 1.14 to 1.22) compared with nonT2DM group (1.267±0.132; 1.24 to 1.28; p=0.005).

Mean TBS remained significantly lower in T2DM (1.22; 1.18-1.26) compared with nonT2DM group (1.27; 1.25-1.30; p<0.0001) after adjusting for BMI. TBS was positively correlated with the FRAX score in nonT2DM group (rs =-0.29), whereas no correlation was observed between these 2 parameters in the diabetic subjects (rs =-0.13).

Conclusion: Despite similar or higher BMD values, we found a lower TBS score in diabetic compared with nondiabetic subjects. These results are in line with the current view that 2DM induces microarchitectural deteriorations of bone tissue. Moreover, our data suggest that TBS might be a useful tool in the assessment of bone quality in T2DM.

A rare disease can hide another

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Pheochromocytoma is a rare catecholamine-secreting neoplasm occurring in less than 2% of patients with hypertension. The prevalence is estimated to 1/500 000. Typically paroxysmal symptoms (hypertension with tachycardia and palpitations, pulsatile headaches, diaphoresis, pallor, dyspnea) are present in half of patients but 10% are also completely asymptomatic. Pheochromocytomas represent 10% of adrenal incidentalomas. Pheochromocytomas must be considered as potentially malignant tumors because they can give local or distant metastases (± 10% of cases) as long as 20 years after resection. Therefore, a lifelong follow-up is recommended to detect recurrent or metastatic disease. However, a "malignant" pheochromocytoma is histologically and biochemically the same as a "benign one". This is the reason why it has recently been proposed to abandon these terms (malignant and benign) and to replace them by metastatic or not. The only curative treatment is surgery after cautious preparation in order to control blood pressure and prevent intraoperative hypertensive crises.

A 23-year-old man complained for recent discomfort characterized by paroxysmal headache and palpitations with unusual fatigue and epistaxis. Being a nurse, he measured his blood pressure that was repeatedly above 200 mmHg of systolic pressure. He didn't take any medication or drug. He had no medical history except the removal of an unsightly frontal skin lesion. Interestingly, his father and especially his twin sister had also hypertension. Clinical examination was common except for the presence of « café au lait » spots and a subcutaneous tumefaction on the right forearm. Biology did not support hyperaldosteronism or Cushing's syndrome. **Repeated 24-hours urine fractionated metanephrines and catecholamines measurements** showed elevation of catecholamines and (nor)métanephrines levels between 7- and 10-fold the upper limit of reference range (in 2 independent urine collections). Abdominal CT-scan revealed a voluminous mass of 50x30 mm with a high density (+40 HU without contrast) in the left adrenal gland. 18F-FDG PET-CT imaging showed a moderate FDG-avid adrenal lesion without other pathological uptake. After adequate preparation, patient underwent left adrenalectomy and excision of the forearm tumefaction. Histopathology confirmed the suspected diagnosis of pheochromocytoma and neurofibromatosis.

Although the majority of pheochromocytomas are sporadic, approximately 30% of them result from inherited mutations, those affecting germlines being associated to familial syndromes such as MEN2, VHL (von Hippel-Lindau), PGL (hereditary paragangliomas), NF1 (neurofibromatosis). The development of gene-panel will allow more wide-spread genetic testing, even in patients with unilateral, no syndromic or metastatic features and no positive family history of pheochromocytoma or paraganglioma. In our case, the syndromic phenotype orientated search to NF1 gene mutation. The genetic testing is still pending.

This case illustrates the importance, when a pheochromocytoma is diagnosed, to keep in mind the possibility of a genetic syndrome to address patients for genetic counseling. Indeed, the presence of a predisposing mutation will personalize the follow-up management (type and frequency of biochemical testing and imaging) to detect and intervene quickly in case of recurrence or metastatic disease.

Should we screen for pituitary metastases in patients with advanced HER-2 positive breast cancer? A clinical case report and a review from current literature

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Aim of the case report

Breast cancer is frequently diagnosed in middle-aged and elderly women and its metastases are frequently present. Metastasis to the pituitary gland region occurs in about 6-8%. Interestingly, in autopsy studies, pituitary metastases are discovered in up to 13%. This difference suggests underreporting with a subsequent doctor's unawareness of pituitary involvement. This pituitary dysfunction may negatively affect patient's quality of life. Moreover, after studying current therapeutic guidelines, no advise was given about whether to screen the pituitary function in patients with aggressive breast cancer. Treating our case patient, the question raised whether there is a clinical need for routine pituitary hormone's screening in specified patients suffering from advanced breast cancer.

Case presentation

An 82-year-old female presented for a second opinion at our endocrinology ward with symptoms of tiredness, polydipsia, polyuria and a progressive loss of vision in her left eye. Evaluation of the hormone profile revealed a hypopituitarism. MRI scanning showed a pituitary mass, invading and oppressing the optic chiasm that increased in size (compared with prior MRI some months earlier). Accordingly, our working hypothesis was metastatic disease. Indeed, we found the primary tumor in her left breast and enlarged axillary lymph nodes. Histology on extirpated lymph node confirmed breast cancer with positive staining of Human Epidermal growth factor Receptor 2. Our patient refused pituitary biopsies to confirm breast cancer metastasis.

Due to its aggressive nature, tumor treatment was immediately started. It consisted of high dose steroids, Trastuzumab (Herceptin) and stereotactic radiotherapy in order to obtain regain of vision by debulking the local tumor mass. Hypopituitarism was treated with hormone substitution on all deficient hormones. Unfortunately, she experienced a worsening of her physical condition, forcing us to discontinue therapy. Our patient died seven weeks after her breast cancer diagnosis was given. No autopsy was performed.

Conclusions

- Breast cancer metastasis often negatively affects pituitary function and consequently patient's quality of life. In parallel with aggressive tumor treatment, complete hormone substitution may significantly improve patient's performance scale.
- Standard pituitary screening is actually not enclosed in clinical guidelines concerning advanced breast cancer; subsequently, clinical inertia is present on this topic.
- Against this background, we urge for future studies, with special emphasis on those patients with a young age (≤40 years), concomitant thoracic localization and HER-2 positive histology.

Long –term testosterone replacement therapy maintains bone density but has only limited osteoanabolic effects : a study in CHH patients

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Keywords: Congenital hypogonadotropic hypogonadism, DEXA, BMD, Testosterone replacement therapy

Background: Congenital hypogonadotropic hypogonadism (CHH) is a rare condition (incidence 1:5000) characterized by low testosterone levels and low to

normal gonadotropin levels. Men with CHH lack testosterone secretion making them an unique human model in which to study the impact of long term testosterone replacement therapy (TRT).

Aims: Impact of long-term TRT on femoral and lumbar bone density in CHH men. Furthermore, we assessed if an increase in BMD can be maintained after years of therapy.

Methods: In this single-centre retrospective study data of 23 males (age range 12-57 years) with CHH were included. BMD was assessed by dual-energy X-ray absorptiometry at the lumbar spine and femur and expressed as a T-score. Men were followed up for a mean duration of 16 years (range 2-41 yr). Data from a prospective study on femoral and lumbar bone density in healthy middle aged men (n = 76, age range 40-55 yr) served as a reference on normal BMD change.

Results: In 6 patients (treatment naive group) BMD was measured before start of TRT. The other 17 (pretreated group) had received TRT on average for 8.29 years (range 1- 25 yr) before first BMD measurement. Mean BMD at first measurement was respectively -3.76 ± 0.55 and -1.69 ± 0.32. In the treatment naive group average lumbar and femur increase was respectively 2.26 ± 0.33 and 1.36 ± 0.30. In the pretreated group average lumbar increase was 0.52 ± 0.12 vs 0.01 ± 0.10 in the femur. During prolonged TRT BMD was stable except in those patients (n =3) who interrupted treatment. The reference population showed a small, but significant decrease in the mean total femur T-score.

Discussion: T-score improved or stabilized under TRT therapy. Nevertheless continuous TRT is needed to maintain this effect. BMD at first measurement was significantly lower and remained significantly lower than controls during the entire observational period. Despite some initial improvement on lumbar BMD, the majority (60.87%) remains in the osteopenic/osteoporotic range.

Clinical case report: PD1 inhibitor induced type 1 diabetes mellitus

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Background

Cancer immunotherapy is a successful and fast growing field. Pembrolizumab (Keytruda) and nivolumab (Opdivo) are approved for malignant melanoma and several other cancer types, including non-small cell lung cancer (NSCLC). They are two IgG4 monoclonal antibodies targeting the programmed cell death-1 (PD-1) receptor. This receptor is important in maintaining selftolerance and is therapeutically targeted by immune checkpoint inhibiting monoclonal antibodies (mAb) to enhance antitumor immune responses. However, immune checkpoint blockade is associated with a risk for immune-related adverse events (irAE) potentially affecting the endocrine organs.

Auto-immune diabetes mellitus and the associated diabetic ketoacidosis (DKA) are examples of rare irAEs (pembrolizumab: 0.2% (1), nivolumab monotherapy: 0.9%, nivolumab and ipilimumab combination therapy: 1.5% (2)).

Here, we report a case of autoimmune diabetes mellitus (DM) presenting with diabetic ketoacidosis (DKA) in a woman with a metastatic uveal melanoma receiving Pembrolizumab.

Case report

We present a 73-year-old woman with a history of an uveal melanoma of the right eye. She underwent an enucleation of the eye in September 2015 and maintained stable disease after this procedure.

In March 2017 she presented with right-sided abdominal pain due to new metastatic liver disease and treatment with Keytruda (pembrolizumab) was started. She received 2 infusions (2mg/kg q3w). Two weeks after the second infusion, she presented with complaints of anorexia, vomiting, polydipsia and headache at the emergency department. Further workup showed signs of a severe diabetic ketoacidosis with a glycaemia of 540 mg/dl (Table 1. Laboratory values at admission). Arterial blood gas values confirmed an acidosis with a pH of 7.10 and very low bicarbonate of 6.8 mmol/l. Capillary β-hydroxybutyrate levels were 6.9 mmol/l. Autoimmune adrenalitis (occurring in up to 4.3% of cases) and hypophysitis (in 1.2% of cases) were ruled out. She was immediately treated with intravenous insulin and fluid, according to our hospital diabetic ketoacidosis protocol.

After a 24 hours stay in the intensive care unit, she was transferred to the department of endocrinology for further management. Further testing revealed a HbA1c level of 7.1% or 54 mmol/mol and c-peptide of 0.11 nmol/L. This suggests sudden deterioration in glycemic control, corresponding to the pathophysiologic mechanism of type 1 diabetes mellitus. Detailled analysis of β-cell auto-antibodies showed an elevated glutamic acid decarboxylase antibody (GADA) of 27,881 WHO U/ml (normal <23) and elevated islet cell antibodies (ICA)

(400 JDF units, normal <12). Insulinoma antigen-2 antibodies (IA2A), Zinc transporter 8 antibodies (ZnT8A) and insulin antibodies were negative. At discharge she was treated by means of a basal-bolusinjection schedule with acceptable glycemic control.

Conclusion

We report a new case of autoimmune diabetes induced by anti-PD-1 therapy with positive ICA and GADA. Autoimmune or type 1 diabetes mellitus (T1DM) is a rare irAE of PD-1 inhibitors, occurring in 0.2% of cases. We hypothesize that the onset of diabetes in our patient was due to an auto-reactive CD8+T cell clone that was activated when pembrolizumab therapy was started and the PD-1 pathway was blocked..

Since the use of immunotherapy is expected to increase, the incidence of immune-related adverse events is also expected to rise. Therefore, it is essential that all clinicians are aware of diabetic ketoacidosis as a rare and life-threatening side effect of immunotherapy. Blood glucose monitoring during anti-PD-1 therapy is necessary.

Further research should focus on the identification of biomarkers that can predict which patients will develop this irAE and screening protocols should be considered.

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Complications of Chronic Primary Hypoparathyroidism: a Retrospective Study in a Tertiary Care Center

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Context: Chronic primary hypoparathyroidism and its medical treatment can lead to symptoms and complications affecting quality of life. Current standard therapy consists of calcium supplements and active vitamin D. The European and US endocrine societies have recently published management guidelines.

Objectives: Characterize a cohort of chronic primary hypoparathyroid patients and determine renal and cerebral complications in the total cohort and according to the disease etiology.

Design and setting: Cross-sectional retrospective study of patients with chronic (>1 year) primary hypoparathyroidism including pseudohypoparathyroidism, at least treated with active vitamin D in follow-up (>1 year) in the year 2015 in the outpatient endocrine clinic in the University Hospitals Leuven, Belgium, a tertiary care center.

Patients: 170 patients were included: 143 (84%) with postsurgical hypoparathyroidism, 16 (9%) with nonsurgical hypoparathyroidism and 11 (7%) with pseudohypoparathyroidism. The majority of patients was female (62%), mean age was 58 ±16 years and mean duration of disease was 14 ±12 years.

Main Outcome Measures: History of kidney stones, history of seizures, renal and cerebral calcifications.

Results: History of kidney stones was present in 15% of patients. Imaging of the kidneys was performed in 52% of patients and 22% of them showed renal calcifications. When analyzing the different subgroups according to disease etiology no difference was seen in renal calcifications. History of seizures was present in 9% of patients. Brain imaging was performed in 26% of patients and 25% of them showed cerebral calcifications. A history of seizures and the presence of cerebral calcifications were significantly higher in the pseudohypoparathyroid ($p < 0.001$ and $p < 0.001$, respectively) and nonsurgical hypoparathyroid ($p < 0.01$ and $p < 0.05$, respectively) group compared to the postsurgical hypoparathyroid group. No correlation was found between a history of seizures and the presence of cerebral calcifications.

Conclusions: Patients with chronic hypoparathyroidism frequently develop renal and cerebral calcifications. Pseudohypoparathyroid and nonsurgical hypoparathyroid patients suffer more from seizures and cerebral calcifications than postsurgical patients. Whether therapy with rhPTH 1-84 will be able to lower the rate of complications in the future remains a question.

Characteristics and cardiovascular complications of a large cohort of adults diagnosed with type 2 diabetes < 45 years

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Aims: Evaluate the characteristics and cardiovascular complications of a large Belgian cohort of adults diagnosed with type 2 diabetes (T2DM) < 45 years.

Methods: Retrospective analysis of 886 patients diagnosed with T2DM < 45 years and 933 T2DM patients diagnosed at age 60-70 years.

Results: Of the young-onset T2DM cohort, age at diagnosis was 37.3±6.4 years, 44.1% were women and 12.1% were from an ethnic minority (EM) background. Age of patients at the last visit was 57.3 ±12.5 years with a diabetes duration of 20.5±11.8 years, 32.4% were overweight and 56.8% were obese. Mean HbA1c was 7.3% ± 1.3 with 81.9% receiving insulin. 49.9% was hypertensive and 34.1% did not reach the LDL cholesterol target in primary or secondary prevention. At last visit, compared to women, men had a higher HbA1c [7.3%±1.4 (56mmol/mol±15) vs. 7.1%±1.2 (54mmol/mol±13), p=0.021] and higher rates of cardiac events, remaining significant after adjustment for confounders (24.3% vs. 14.8%, p=0.010). Compared to Caucasians, EM patients were younger at diagnosis (35.4±6.8 years vs. 37.6±6.2 years, p=0.001) and were less often obese at last visit (43.3% vs. 55.6%, p=0.007). Compared to the first visit, glycemic control improved [7.3%±1.3 (56mmol/mol±14) vs. 7.9%±1.7 (62mmol/mol±19), p<0.0001] and there was a lower body mass index (BMI) (31.2±5.8 vs. 31.7±5.8, p=0.009) at last visit. Compared to the older-onset T2DM cohort, young-onset T2DM patients showed a higher HbA1c [7.3±1.3% (56mmol/mol±14) vs. 6.9±1.0% (51mmol/mol±11), p=<0.0001] and a higher BMI (31.2±5.8kg/m² vs. 29.6±5.5 kg/m², p=<0.0001).

Conclusions: These data highlight the heavy toll a diagnosis of T2DM <45 years brings with it. These individuals have high rates of cardiovascular events at a relatively young age. In our population, men are at particularly high risk for myocardial infarctions.

Three-year follow-up of hematocrit levels in trans persons on gender affirming hormonal treatment: results from the European Network for the Investigation of Gender Incongruence (ENIGI)

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INTRODUCTION: In trans persons on gender affirming hormonal treatment, a decrease (trans women) or increase (trans men) in serum hematocrit levels is often observed. To date, no specific reference ranges for results of hematocrit levels in trans persons on gender affirming hormonal treatment, have been established, nor is it clear at which time point during the transition period these specific reference ranges would start to apply. The lack of suitable reference intervals in these populations places them at a higher risk for diagnostic errors. As in testosterone treatment in hypogonadal men, the induction of erythrocytosis in trans men on testosterone treatment is a concern.

AIMS: To determine when changes in serum hematocrit levels occur and what the expected values of serum hematocrit levels are in trans persons on gender affirming hormonal therapy.

METHODS: This study is part of the ENIGI study, a prospective cohort study in four major European gender clinics. In Ghent and Amsterdam, we were able to include 625 hormone naïve trans persons before the initiation of gender affirming hormonal therapy. Gender affirming hormonal therapy was initiated during the first visit and consisted of estrogens and anti-androgens in trans women, and testosterone in trans men. Serum hematocrit levels were prospectively analyzed (baseline, 3, 6, 9, 12, 18, 24 and 36 months of gender affirming hormonal therapy).

RESULTS: In trans men, serum hematocrit levels gradually increased during the first 12 months, with the most pronounced increase occurring during the first three months (from 41.1% [38.2 – 44] at baseline to 43.8% [43.8 – 46.0] at three months) and reaching peak levels at 12 months (46.0% [44.0 – 47.0]). Trans men

Both first authors contributed equally.

receiving testosterone esters had a larger prospective increase in serum hematocrit levels compared to trans men receiving testosterone undecanoate (mean difference 1.9 hematocrit percentage, [-3.962 – -0.420]). After three months of gender affirming hormonal therapy, eight trans men had a serum hematocrit level of ≥ 50.0% (range 50.0 – 51.0%). The maximum measured level of serum hematocrit was 54.0%. Trans men on testosterone undecanoate were less likely to develop erythrocytosis, compared to trans men taking testosterone esters or gel. In trans women, serum hematocrit had dropped from 45.1% [42.7 – 47.5] at baseline to 41.0% [39.9 – 43] after three months, after which only relatively small further decreases were observed. After the first year of gender affirming hormonal therapy, serum hematocrit levels remained stable. In addition, estrogen mode of administration did not influence serum hematocrit levels.

CONCLUSIONS: Gender affirming hormonal therapy leads to a decrease in serum hematocrit levels in trans women and an increase in trans men. After three months of gender affirming hormonal therapy, 95% CI of serum hematocrit levels have shifted towards those of the perceived gender. We suggest consulting the reference range for men in trans men after the initiation of testosterone therapy and consulting the reference range for women in trans women in whom effective androgen deprivation has been established. In addition, we describe low erythrocytosis rates in trans men on testosterone therapy. Therefore, we have no reasons to assume that the often observed mild increase in serum hematocrit levels is associated with an increased thrombotic risk. As trans men on testosterone undecanoate exhibited lower erythrocytosis rates compared to trans men on testosterone esters or gel, switching therapy to testosterone undecanoate seems a valid option if the hormone prescribing physician and/or the patient are concerned about elevated serum hematocrit levels.

A dramatic immunological phenotype of mice deficient in Growth Hormone-Releasing Hormone (GHRH)

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Background and aim of the work: A debate is still open about the precise role of the somatotrope GHRH/GH/IGF-1 axis upon the immune system. The objective of these studies was to directly address this question through the use of *Ghrh*$^{-/-}$ mice. These mice present a dwarf phenotype due to a severe deficiency of their somatotrope axis (1), and are resistant to experimental allergic encephalomyelitis (2). In basal conditions, thymic parameters and T-cell responses of *Ghrh*$^{-/-}$ mice are not severely affected. However, a severe splenic atrophy and relative B-cell lymphopenia are constantly observed (3).

Methods: On this basis, we investigated vaccine and anti-infectious responses of *Ghrh*$^{-/-}$ mice toward *Streptococcus pneumoniae,* a T-independent pathogen. We established a murine experimental model of *S.pneumoniae* protected infection and then evaluated the transcriptional, humoral and cellular responses in *Ghrh*$^{-/-}$ compared to their wild type (WT) counterpart.

Main results: *Ghrh*$^{-/-}$ mice were unable to trigger production of specific IgM and IgG against serotype 1 pneumococcal polysaccharide (PPS) after vaccination with either native PPS (Pnx23) or protein-PPS conjugate (Prev-13) vaccines. These vaccines both include the serotype 1 (our *S.pneumoniae* strain) and provide an effective protection in mice. A short GH supplementation to *Ghrh*$^{-/-}$ mice restored IgM and IgG response to Pnx23 vaccine but not to Prev-13. This suggests that GH could exert distinct impacts upon specific splenic areas.

After intranasal instillation of a non-lethal dose (defined by the full clearance by WT C57BL/6 mice after 24h) of serotype 1 *S.pneumoniae*, *Ghrh*$^{-/-}$ mice exhibited a dramatic susceptibility. This was proved by a marked time-dependent increase in pulmonary bacterial load, a septicemia already 24h after infection, and a survival limit of 72h. We also observed a dramatic decrease in B- and T-cell populations and an increase in proportion of inflammatory macrophages in the lungs. In marked contrast, WT and heterozygote mice completely cleared *S.pneumoniae* infection after 24h.

Transcriptional analyses showed higher expression levels of *Ifng*, *Il10*, *Cd40* and *Cxcl9* in the whole lungs of

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infected *Ghrh*$^{-/-}$ mice, whereas *Tgfb* and *IgGj* expression was unchanged.

Conclusion: This animal model shows that the somatotrope GHRH/GH/IGF-1 axis plays an important and unsuspected role in the vaccine response and immunological defense against *S.pneumoniae*.

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The use of CGM as a new screening tool in the diagnostic work-up of insulinoma

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Aim: To describe a young woman presenting with profound fatigue, recurrent episodes of syncope and generalized tonic-clonic (TC) seizures as neuroglycopenic symptoms. Hypoglycemia was objectified on blood examination and continuous glucose monitoring (CGM). An insulinoma was diagnosed with a fasting test. This is, to our knowledge, the first time in Europe where CGM was used in a non- diabetes setting, as a screening tool to select those patients for a fasting test in the diagnostic work-up for insulinoma.

Methods: We describe a patient starting from presentation at the emergency department with tonic-clonic seizures to the diagnosis of insulinoma. We discuss clinical, biochemical and imaging findings together with the procedure of the CGM and the fasting test.

Results: A 24 year old woman presented with profound fatigue and recurrent episodes of syncope, absences and generalized TC seizures. At the beginning, blood examination, elektro-encefalogram (EEG), computed tomography (CT) scan, magnetic resonance imaging (MRI), holter electrocardiogram (ECG) and transthoracic echocardiogram (TTE) showed no abnormalities. The TC seizures decreased under anti-epileptic therapy, but the fatigue and episodes of syncope persisted, which was suggestive for an endocrine etiology. After six months, blood results were positive for non- diabetes hypoglycemia. To determine the nature of this hypoglycemia, two weeks CGM was performed, combined with a diary in which glycopenic complaints were collected. CGM confirmed hypoglycemia by demonstrating an average blood glucose of 80 mg/dL, 78% of measurements under this level and a total of 25 hypoglycemias. The hypoglycemic spells showed a diurnal distribution by clustering around 2-6 at a.m. and 12-2 p.m., and were associated with a profound fatigue. The next step was a fasting test, which was positive after 36 hours because of loss of consciousness due to a decreased venous glucose level of 47 mg/dL. Associated insulin was within normal ranges, c-peptide and pro-insulin were decreased. There was a fast and full recovery after administration of 5 grams glucose intravenously. These findings were suggestive for the presence of an insulinoma. The 5 hours oral glucose tolerance test (OGTT), pituitary work-up and Synachtentest were normal. For localizing the insulinoma, MRI of the abdomen and Ga-68-DOTANOC combined positron emission tomography-CT (PET-CT) scan were performed, which showed no mass. This necessitated an angiography combined with intra-arterial calcium-stimulated venous sampling (ASVS) of the pancreas. Angiography showed an anatomical aberration, which made it difficult to interpret the ASVS test results. There was an increasing insulin concentration in different pancreatic areas. Endoscopic ultrasound showed no pancreatic masses. Genetic analysis excluded multiple endocrine neoplasia type 1 (MEN-1) syndrome, which could be associated with insulinoma. At the moment of writing this case report, the woman had not yet been into surgery for resecting the insulinoma. We await the results of the peri-operative findings, such as palpation by the surgeon, and the anatomopathology for confirmation of the insulinoma.

Conclusion: Patients often initially present with glycopenic symptoms that do not suit hypoglycemia. The first step to detect hypoglycemia in an ambulant setting may be in CGM, which is an easy and precise test to objectify daily glycemic fluctuations. After CGM screening, a fasting test exclusively diagnoses an insulinoma. Future studies will learn us whether CGM may be a diagnostic tool in the analysis of a pancreatic neuro-endocrine tumor.

Prognostic value of the nonthyroidal illness syndrome in the pediatric intensive care unit and impact hereon of nutritional management in relation to clinical outcomes

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Aim: The non-thyroidal illness syndrome (NTI) is characterized by an increased peripheral inactivation of thyroid hormone, with lowering of circulating T3 and a rise in rT3, in the absence of a rise in TSH. It typically occurs with fasting, where it acts as an adaptive response to limit catabolism. It is also a hallmark of critical illnesses both in adults and in children. In critically ill children, the prognostic value of the NTI has not been well documented. Also, the impact on the NTI of nutritional management has not been investigated. Accepting a large macronutrient deficit up to day 8 of pediatric critical illness, with use of enteral feeding only which is often not tolerated (late PN), has shown to accelerate recovery as compared with early provision of parenteral nutrition (early PN) in the PEPaNIC RCT (1). In this study, we assessed the prognostic value of the NTI in the PICU, documented the impact of late PN versus early PN on the NTI, and investigated whether any impact of this intervention on NTI explained some of the late PN outcome benefits.

Methods: This is a preplanned secondary analysis of the PEPaNIC RCT. Serum TSH, total T4, T3 and rT3 concentrations were quantified in 64 healthy children, in 982 patients upon PICU admission, and in 386 early PN and 386 late PN patients matched for baseline risk factors upon PICU admission and at day 3 or PICU discharge for shorter PICU stay. The corresponding T3/rT3 ratio was calculated. Associations between baseline thyroid hormone concentrations, and between changes from baseline in thyroid hormone concentrations, and the time to live PICU discharge and risk of acquiring a new infection in PICU were assessed with use of multivariable Cox proportional hazard and logistic regression analyses, all adjusted for baseline risk factors.

Main results: Upon PICU admission, critically ill children revealed lower serum concentrations of TSH, T4 and T3, and elevated rT3, resulting in a lower T3/rT3 ratio, than matched healthy children ($P<0.0001$). Adjusted for baseline risk factors, a higher baseline serum T4 and higher T3/rT3 ratio were independently associated with an earlier live PICU discharge and a lower risk of acquiring a new infection in PICU. Late PN, as compared with early PN, reduced T4, T3 and the T3/rT3 ratio further and increased rT3 ($P\leq0.001$, adjusted for risk factors). The further lowering of T4 statistically reduced the benefit of late PN for the studied outcomes ($P<0.0001$), whereas further reduction of the T3/rT3 statistically explained part of the benefit ($P\leq0.004$). This effect was more pronounced in infants (younger than one year) than in older children.

Conclusions: Accepting a large macronutrient deficit early during pediatric critical illness further aggravated the NTI. Statistical analysis suggested that the effect on the central component with lowering of T4 could possibly be harmful, whereas the further accentuated peripheral inactivation of thyroid hormone could be a beneficial adaptation to critical illness in children.

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Clinical case report : Oncocytic adrenocortical neoplasm: a rare cause of potentially malignant adrenal mass

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A 32-year-old woman was admitted for an important weight loss (30 kg in the last 6 months). Physical examination was normal except a very low BMI (13 kg/m^2). Patient was addicted to alcohol and complained of abdominal pain and diarrhea. Biology showed macrocytic anemia, liver test alterations and hypoalbuminemia. An

abdominal CT-scan revealed a hepatomegaly with severe liver steatosis, an atrophic pancreas without calcifications and a mass of 39 x 33 x 40 mm in the left adrenal gland. This adrenal incidentaloma had a +20 HU density without contrast and contained calcifications. Despite normal blood pressure and absence of any clinical sign of Cushing's syndrome, hormonal assays were performed to exclude a secreting tumor: aldosterone, cortisol and androgens were in normal range. Repeated 24-hour urine fractionated metanephrines and catecholamines measurements showed elevation of adrenaline, noradrenaline, dopamine and normetanephrine levels between 1.7- and 3.5-fold the upper limit of reference range (in 2 independent urine collections). 18F-FDG PET/CT imaging showed an FDG-avid adrenal lesion without other pathological uptake. A left laparoscopic adrenalectomy was performed.

On macroscopic examination, removed specimen measured 45 x 35 x 50 mm and weighted 50g. The lesion was solid, nodular, encapsulated with a hemorrhagic center. Immunohistochemistry showed positivity for Synaptophysine, Vimentine, Melan-A, α-Inhibin-A and NSE confirming the adrenal origin. However, negativity for Chromogranin A and S-100 was not in favor of a neuro-endocrine tumor (pheochromocytoma). The microscopic aspect (large polygonal cells with abundant mitochondria within a granular eosinophilic cytoplasm) orientated the diagnosis towards an oncocytic variant adrenal tumor. Ki67 was below 2% but several signs were in favor of malignancy: anisonucleosis, atypical mitoses and capsular invasion.

Oncocytomas can occur in various organs, especially in kidneys where they represent 3–7% of all renal neoplasms. Oncocytomas have also been reported in endocrine tissues: thyroid, pituitary, parathyroid. They are usually considered as benign. Oncocytomas of the adrenal gland are particularly rare, although exact overall incidence is unknown. They have been reported in a wide age range (between 15 and 77 years). They are twice as frequent in women and three times more in left side. There are no identified environmental or genetic risk factors. They are usually incidentally identified and the majority of them are non-functioning. The histological Weiss score for adrenocortical tumor cannot be used to predict malignancy in oncocytoma tumors. The Lin-Weiss-Bisceglia score is more specific for oncocytomas. This score proposes major and minor criteria as part of a malignancy scoring system. The three major criteria are: high mitotic rate (> 5 mitoses per 50 high power fields), atypical mitoses and venous invasion. The four minor criteria are: tumor size > 10 cm or > 200 g, tumor necrosis, capsular or sinusoidal invasion. The presence of any one or more major criteria categorizes the lesion as a malignant oncocytoma.

In our case, the patient exhibited one major criterion indicating a malignant potential for this oncocytic carcinoma. Nevertheless, it remains doubts over the validity of such scoring system and its clinical and prognostic value due to small numbers of data and limited long term follow-up. This case illustrates the importance of a complete anatomo-clinical characterization to identify new markers of aggressiveness and to rationalize the post-operative management in terms of complementary treatments and/or follow-up.

High circulating Activin A is associated with cachexia and poor survival in cancer patients

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Background: Cachexia is a complex multifactorial syndrome, characterized by loss of skeletal muscle and fat mass, which affects the majority of advanced cancer patients and which is associated with poor prognosis. Several recent experimental evidences pinpoint the possible role of Activin A (ActA) as a driver of cancer cachexia.

Aim: Our goal was to investigate the role of ActA in the development of cachexia and its prognostic value of survival in cancer patients.

Methods: One hundred fifty two patients with colorectal or lung cancer were prospectively enrolled at the time of diagnosis or relapse between January 2012 and March 2014. At baseline, patients had clinical, nutritional and functional assessment. Body composition and muscle density were measured by CT-scan. Plasma ActA concentrations were determined. Overall survival (OS) was analyzed since inclusion to 24 months later.

Results: Cachexia, characterized by a decreased of muscle mass and function, was associated with anorexia (SNAQ score), reduced physical function (ECOG, QLQC30), lower quality of life (QLQC30) and more symptoms (QLQC30). Interestingly, ActA levels were increased in cachectic patients compared to those without cachexia (+40%, $p<0.001$) and were correlated positively with weight loss ($R=0.323$, $p<0.001$) and negatively with muscle density ($R=-0.225$, $p<0.01$) and muscle strength ($R=-0.207$, $p<0.05$). In addition, a high level of ActA (≥408 pg/ml) was a prognostic factor of survival

independently of tumor stage or inflammation markers. Low muscularity was also associated with low survival.

Conclusion: High circulating ActA is associated with cachexia syndrome and poor survival in cancer patients. Given, the known muscle atrophic effect of ActA, our study suggests that ActA seems to influence survival in cancer patients by contributing to the development of cachexia and loss of skeletal muscle mass.

Combined transcriptome and proteome profiling of the β-cell response to the saturated free fatty acid palmitate unveils novel genes affecting β-cell function

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Background and aims: Chronic exposure to excess saturated free fatty acids impairs insulin secretion and induces pancreatic β-cell apoptosis, and hence contributes to the development of type 2 diabetes. To identify molecular mediators of the lipotoxic β-cell demise, we performed RNA-sequencing of human islets and time course proteomic profiling of β-cells following exposure to palmitate, the most common saturated fatty acid in man.

Material and methods: Six human islet preparations from non-diabetic organ donors were RNA-sequenced after exposure to palmitate for 48h. Clonal rat INS-1E β-cells exposed to palmitate for 4, 16 or 24h were proteome profiled using an iTRAQ method (n=2). Genes modified by palmitate at both mRNA and protein level were analyzed by IPA software to assess enriched pathways. Regulatory networks were inferred from palmitate-modified genes and known regulations present in biological databases, using random forest algorithms. Selected genes were silenced by RNA interference in INS-1E cells and human islets (n=3-6 independent experiments).

Results: Comparison of the transcriptome and proteome of palmitate-treated β-cells revealed 85 up- and 122 downregulated genes/proteins common to both datasets. Pathway analysis by IPA indicated that upregulated genes were involved in fatty acid oxidation, oxidative stress, mitochondrial dysfunction and ERK/MAPK signaling, whereas downregulated genes were involved in cell cycle, cAMP signaling and LXR/RXR signaling. Manual curation into functional categories showed that palmitate-modified genes principally regulated fatty acid metabolism, endoplasmic reticulum (ER) stress, apoptosis and amino acid transporters. Given the important role of the ER stress response in β-cell lipotoxicity, we examined the function of CREB3L2, a transcription factor reported to act as an ER stress transducer. We confirmed that palmitate induces CREB3L2 and found that CREB3L2 silencing decreases glucose-stimulated insulin secretion, suggesting a protective role for this gene in β-cell function. Network inference analysis suggested that FOXO1, USF1, STAT3, HNF1 and BACH1 are key mediators of lipotoxicity. We investigated the role of BACH1, an oxidative stress-related transcription factor. BACH1 silencing increased insulin release, indicating that this gene mediates β-cell dysfunction.

Conclusions: The present study is the first to combine transcriptomic and proteomic profiling of palmitate-treated β-cells and infer regulatory networks. Our data point to important pathways and mediators of lipotoxicity and unveil novel transcription factors involved in pancreatic β-cell dysfunction and death in type 2 diabetes.

Clinical case report category: Transient hypophysitis in a patient treated by duvelisib for chronic lymphocytic leukemia

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We report the case of a 67-year-old male patient, suffering from progressing chronic lymphocytic leukemia (CLL) and treated with the tyrosine kinase inhibitor (TKI) duvelisib for 6 months, who was admitted for severe health alteration and recent headaches. Laboratory studies on admission showed hyponatremia,

hypoglycemia, and elevated white blood cells and lymphocyte counts (Table1). The evaluation of the hormonal status confirmed complete anterior hypopituitarism (Table1), and the pituitary MRI showed a symmetrical and homogeneous enlargement of the gland with marked gadolinium enhancement indicating hypophysitis. The administration of duvelisib was stopped, and the patient's condition rapidly improved on hydrocortisone (100 mg/12 h intravenously for 2 days followed by 20 mg/d orally) and L-thyroxine (100µg/d). Ibrutinib was started 3 weeks later as a new treatment line for CLL. Hormonal control was markedly improved 1 month after duvelisib withdrawal (Table 1), and a complete recovery of normal pituitary function and morphology was observed at 6 months (Table 1). A PET-CT showed multiple lymphadenopathies and a hypermetabolic pituitary gland, but no argument for a Richter's transformation.

We report for the first time a reversible inflammatory process involving the pituitary gland in a patient treated with duvelisib. Although no histological confirmation was obtained, the diagnosis of duvelisib-induced hypophysitis is strongly suggested by the event chronology, the selective involvement of anterior pituitary, the typical features on MRI, and the rapid and complete reversibility of endocrine abnormalities after drug withdrawal. A pituitary infiltration by leukemic cells cannot be fully excluded as it has been exceptionally described [1]. However, it is usually much more heterogeneous, systematically involves the hypo-thalamus and/or meninges, and is not so quickly reversible, even after hydrocortisone administration.

Duvelisib is a phosphatidyl-inositol 3 (PI3)-kinase inhibitor, more specifically of the γ and δ subunits expressed by lymphocytes and monocytes, which has been recently proposed in the treatment of progressing CLL [2]. It results in a marked inhibition of the mitogenic PI3K/AKT/mTOR pathway. Endocrine side effects of duvelisib have been already reported, involving the thyroid, the gonads, and the adrenal glands [3], but to the best of our knowledge, no case of hypophysitis had yet been reported. Of note, lymphocytic hypophysitis has been described as a side effect of other oncologic drugs such as immune checkpoint inhibitors [4]. The presumed underlying mechanism is a dysruption of the T regulatory cells which may favor the development of autoimmune diseases.

Table 1 Evolution of natremia, white blood cell (WBC) count, lymphocyte count and hormonal parameters over time.

Date	Normal values	3/25/2016	4/27/2016	9/21/2016
Sodium (mmol/L)	135-145	127	140	144
WBC ($\times 10^3$/µl)	4.0-10.0	94.5	201.2	6.1
Lymphocytes ($\times 10^3$/µl)	0.8-5.0	78.5	197.5	3.5
Cortisol (nmol/L)	150-500	55	341[a]	218[a]
Free T4 (pmol/L)	12.0-22.0	5.2	18.5	18.0[b]
TSH (mU/L)	0.27-4.00	0.88	1.51	2.75[b]
IGF-1 (µg/L)	81-225	51	191	122
Testosterone (nmol/L)	9.5-28.0	0.025	8.00	12.10

Duvelisib was stopped on 25/03/2016, and Ibrutinib was started on 14/04/2016
[a]Values obtained off hydrocortisone for 24 h
[b]Values obtained off L-thyroxine 50 µg for 24 h

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A case report of an invasive giant prolactinoma extremely sensitive to low-dose cabergoline treatment with rapid tumor shrinkage complicated by CSF rhinorrhea

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Introduction: Prolactinomas are the most common pituitary tumors, and dopamine agonists are an effective first-line treatment in most cases. Giant prolactinomas (≥4 cm) are rare (2–3%), usually present in men, and are often accompanied with very high prolactin levels, that may be resistant to medical treatment.

Case report: A 42-year-old man presented with headaches, decreased libido, gynecomastia, and several episodes of absence seizures. MRI brain revealed a large mass (44x80x51mm) involving the pituitary sella that invaded the whole sphenoidal sinus and both cavernous sinuses, with extension towards the posterior fossa. There was massive suprasellar expansion up to foramen of Monro, compressing the optic nerves and chiasma. Serum prolactin was markedly elevated at 32 000 mcg/l (normal: 4–15.3 mcg/l) and associated with hypogonadotropic hypogonadism (serum testosterone: 1.4 nmol/l, LH <0.1 IU/l, FSH 1.0 IU/l). Thyroid, adrenal, somatotrope and posterior pituitary function was normal. Cabergoline was commenced with initial dose of 0.125 mg/week with a rapid fall in serum prolactin (6937 mcg/l within 4 weeks). With further dose titration to 0.25 mg/week, and thereafter finally to 0.5 mg/week, prolactin levels continued to decline (up to 930 mcg/l at 26 weeks). Repeat pituitary MRI scanning demonstrated a progressive reduction in tumor volume. This was, however, complicated by CSF rhinorrhea due to an osteo-meningo sphenoidal defect caused by the expansive tumor mass. The patient was referred to a neurosurgeon and promptly operated. A transnasal partial resection of prolactinoma with repair of CSF rhinorrhea was performed. Pathology studies revealed a prolactin secreting pituitary adenoma, Ki67 1%. An increase in post-operative prolactin levels was observed (3253 mcg/l). Cabergoline treatment was not restarted because of post-surgical complications (cerebral hemorrhage, ischemic stroke and chronic subdural hematoma).

Conclusion: Medical therapy with dopamine agonists can be an effective strategy and is the first line of treatment for giant prolactinomas. Careful supervision in cases with locally invasive tumors might decrease the risks of complications caused by rapid changes in adenoma volume with even low dose dopamine agonists.

Clinical Study: Normocalcemic Primary Hyperparathyroidism: a Comparison with the Hypercalcemic Form in a Hospital-based Population

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CONTEXT: Normocalcemic primary hyperparathyroidism (NPHPT) is a formally recognized variant of primary hyperparathyroidism (PHPT), characterized by normal total and ionized serum calcium concentrations and elevated parathyroid hormone (PTH) levels, in the absence of secondary causes for hyperparathyroidism. NPHPT has been studied previously, but data are limited and confounded.

OBJECTIVE: We aimed to compare the clinical and biochemical data of normocalcemic and hypercalcemic subjects in a hospital-based population.

METHODS: We retrospectively analysed the medical records of 131 subjects diagnosed with PHPT in UZ Brussel between 2007 and 2016, including 25 normocalcemic and 106 hypercalcemic subjects. The mean values of age, BMI, sex, serum 25-OH vitamin D levels and urinary phosphate excretion were comparable between both groups.

RESULTS: Subjects diagnosed with NPHPT had significantly lower plasma PTH levels, lower urinary calcium excretion and lower serum creatinine levels compared to the hypercalcemic subjects with PHPT. Corresponding eGFR values were higher in the normocalcemic group. Normocalcemic subjects with PHPT presented with a high prevalence of nephrolithiasis (36%), fragility fractures (12%) and osteoporosis (25%). Clinical manifestations and BMD measurements revealed no statistical significant differences between both groups.

CONCLUSION: Our data show a relative prevalence of 19% NPHPT in PHPT. NPHPT may present the earliest form of PHPT with an extension in time, but is not an indolent disease state. Normocalcemic subjects should be managed as hypercalcemic subjects with PHPT. Hypercalcemia is related to the development of renal insufficiency in PHPT. Further research regarding the pathophysiology and natural course of NPHPT is required.

A compound heterozygous mutation in the luteinizing hormone/chorionic gonadotrophin receptor gene leading to Leydig cell hypoplasia type 1

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Introduction: Male sexual differentiation depends on proper signaling via the luteinizing hormone/chorionic gonadotrophin receptor (LHCGR). When stimulated by the human chorionic gonadotrophin (hCG) in early fetal life and afterwards by LH, the LHCGR will induce testosterone synthesis, which is necessary for the differentiation of male internal and external genitalia. An impaired LHCGR will disturb the normal male sexual differentiation. This will lead to Leydig cell hypoplasia type 1 with a female phenotype at birth (46,XY Disorder of Sex Development - DSD) in case of complete inactivation of the receptor or to Leydig cell hypoplasia type 2 presenting with male external genital anomalies ranging from micropenis to hypospadias for incomplete inactivations. Inactivating mutations of the *LHCGR* are very rare and so far, only around 20 cases of Leydig cell hypoplasia type 1 have been reported.

Aim of the work: To study a case of Leydig cell hypoplasia type 1 caused by a compound heterozygous *LHCGR* mutation and to reveal the mechanisms by which these mutations lead to a female phenotype in a 46,XY patient.

Methods: Sequencing of the *LHCGR* gene was done. Functional studies were performed after transfection of HEK293 and HeLa cells with the mutant and wild-type (WT) *LHCGR* genes. Generation of cAMP was measured. Membrane and intracellular localizations of the mutant receptors were analyzed by flow cytometry and immunocytochemistry. Endoplasmic reticulum (ER) stress was also assessed.

Main results: A novel compound heterozygous mutation of the *LHCGR* gene was identified: a 4 amino acid deletion (delLHCGR) on the paternal allele and a 9 amino acid duplication (dup LHCGR) on the maternal one. Both mutations were located in the region coding for the signal peptide of the LHCGR.

cAMP generation was significantly reduced for the mutant receptors compared to WT. Flow cytometry and immunocytochemistry studies showed that the dupLHCGR had reduced membrane expression, though found intracellularly, whereas the delLHCGR had a very low both membrane and intracellular expression. ER stress assays revealed a slightly higher ER stress induced by the abnormal dupLHCGR, whereas ER stress was significantly lower than that of the WT LHCGR in the case of the delLHCGR.

Conclusions: We report a novel case of Leydig cell hypoplasia type 1 in a patient with a compound heterozygous mutation of the *LHCGR* gene. Our studies reveal different mechanisms of LHCGR dysfunction for the two mutants – the delLHCGR is probably barely translated, whereas the dupLHCGR is most likely synthesized, but its intracellular trafficking is impaired. This is of particular interest as both mutations are located in the region coding for the signal peptide, whose main function is to target nascent proteins to the ER. Our study therefore illustrates that different mutations in the signal peptide of the same protein can impair protein function by inducing different intracellular anomalies.

Long-term management of resistant acromegaly with pasireotide LAR in 2 cases with a familial AIP mutation

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Introduction: *AIP*-related somatotropinoma patients tend to be resistant to medical therapy with somatostatin receptor (SSTR) subtype 2 specific somatostatin analogues (SSA). Pasireotide is a newer multiple SSTR

binding SSA with activity primarily at SSTR5 and SSTR2, which has not been widely studied in *AIP*-mutated patients.

Results: Case 1: A 29-year old male was diagnosed with a GH-producing pituitary macroadenoma (25x18x23 mm). He was from a FIPA kindred and his sister had acromegaly due to a pituitary macroadenoma (25mm) at age of 24 that was cured by neurosurgery. A familial *AIP* mutation p.Gln217X was revealed in the index patient, his sister and an unaffected nephew. The patient underwent partial resection of a GH and prolactin positive adenoma. He was treated for post-operative corticotroph, thyrotroph and gonadotroph deficiencies but GH hypersecretion by the residual tumor required adjuvant medical treatment. He was treated with SSTR2 specific agents (lanreotide autogel and octreotide LAR), but without hormonal control. Addition of cabergoline did not improve hormonal suppression. An increase of tumor residue size was observed on SSA treatment and the residual tumor approximated the chiasma, which precluded safe surgery and pegvisomant therapy, while the patient declined radiotherapy.

Case 2: A female patient aged 19 years presented with acromegaly due to an invasive pituitary macroadenoma (37mm). A c.343delC *AIP* mutation in AIP was detected in the patient, and in her father and sister neither of whom had a pituitary tumor. She underwent neurosurgical resection but GH/IGF-1 levels remained elevated due to remnant tumor. An octreotide test (100 µg sc) showed a paradoxal increase in GH levels. Immunohistochemistry revealed a small amount of SSTR2 and high expression of SSTR5 in the pituitary tumor.

Both patients began pasireotide LAR and were uptitrated to 60 mg/month. The clinical signs of acromegaly improved, GH/IGF-1 was controlled and tumor size was stable in the case 1 and significantly decreased within 12 months in the case 2. Pasireotide was associated with worsening of existing impaired glucose control and treatment with antidiabetic medication was required. A switch to octreotide LAR in case 2 led to renewed elevation in GH/IGF-1 and pasireotide was reinstated. After 2 years of treatment the dose of pasiriotide was decreased to 40 mg/4 weeks and further follow-up showed tumor shrinkage and an empty sella. Glucose metabolism worsened over time despite existing therapy and exogenous insulin treatment was required in the case 1.

Conclusion: In these two aggressive *AIP* mutation positive acromegaly cases, resistance to surgery and SSTR2-specific SSA was seen. Pasireotide permitted clinical, hormonal and tumoral improvement, albeit at the cost of long-term worsening of hyperglycemia requiring antidiabetic therapy.

Adrenocortical mass in a hyperandrogenic obese adolescent

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Background Pure androgen producing adrenocortical tumors are extremely rare in children as well adults. Their low incidence, variable androgen secretion profile as well as clinical presentation can lead to problems in precise diagnosis, especially when occurring in male adolescents, where mild virilisation can resemble a normal male puberty development. We describe the diagnostic workup of adrenal hyperandrogenism in a 17 year old obese adolescent with a nodular lesion at initial ultrasound.

Case presentation A 17-year-old obese male adolescent was referred for very elevated DHEAS concentrations and mildly elevated 17-OH progesterone and androsteendione concentrations. His only symptom was a more pronounced acne in the recent years.

Increased concentrations of DHEAS (8.97 (upper limit < 4.9) mg/L, 17-OH progesterone (1.7 (< 1.4) µg/L), and androstenedione (4929 (< 4800) ng/L) were confirmed. Serum electrolytes, cortisol, ACTH, renin, aldosterone, gonadotropins, testosterone and estradiol concentrations were normal. Urinary cortisone and cortisol metabolites were normal. An ACTH stimulation test excluded 21 hydroxylase, 17 hydroxylase and 3 -beta hydroxysteroiddehydrogenase deficiency.

Abdominal ultrasound and subsequent MRI showed a 9 mm non-cystic mass lesion in the left adrenal. Adrenal venography showed a high ratio of DHEAS and androstenedione in the left adrenal vein, as compared to peripheral vein levels. The diagnosis of a left androgen secreting adenoma was made. A left adrenalectomy was performed laparoscopically and was followed by a reduction in androgen levels in the first postoperative week. Histologically a nodular hyperplasia was diagnosed.

Conclusion Although late onset congenital adrenal hyperplasia is much more prevalent, adrenocortical tumors should always be considered in the differential diagnosis of adolescents with hyperandrogenism. High levels of DHEAS concentrations, lack of stimulation after ACTH and/or of suppression after corticosteroid treatment and demonstration of a lesion in the adrenal gland should raise the possibility of an underlying adrenocortical tumor.

Pituitary hyperplasia in a female adolescent: a challenging diagnosis

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Introduction

Pituitary hyperplasia, defined as an increase in adenohypophyseal cell numbers and manifesting radiologically as pituitary enlargement, occurs in heterogeneous settings and remains under-recognized (1). Increased awareness of physiological hyperplasia and its natural history in female adolescents, should circumvent unnecessary trans-sphenoidal surgery (1,3).

Case report

A 12-year-old girl was referred to the pediatric endocrinology clinic for pituitary enlargement discovered after neuroimaging in the work-up of frequent headaches, photophobia and the recent onset of concentration and memory problems. The headaches seemed to be triggered by stress and were treated by intermittent use of paracetamol or an NSAID. Additionally, the girl suffered from increasing fatigue and periodic, unexplained fevers following an atypical pneumonia (*M. pneumoniae*). A cranial CT scan hinted a pituitary microadenoma, but MRI provided diagnosis of a non-cystic macroadenoma. Hormonal work-up showed an elevated IGF-1 for age, slightly elevated TSH (7.1 mU/L) and FT3 (6.1 pg/ml) levels, normal serum cortisol and urinary free cortisol excretion, as well as normal PRL, LH, FSH and estradiol levels for the pubertal stage. A GH-secreting pituitary adenoma was suspected. Indeed, in the past 2 years her weight had increased excessively, her growth had accelerated and since the last year her breast development had also started. A lifestyle weight management program had only transient success. Family history included paternal obesity, but no history of endocrine diseases. At physical examination weight was 82 kg (+2.2 SD), height 156 cm (0 SD), Tanner stage A2P3M4 and blood pressure 125/65 mmHg. Eye movements and visual fields were normal. Truncal white striae were present, but no hirsutism. Repeated MRI of the brain showed an enlarged anterior pituitary (maximal cranio-caudal diameter of 10.8 mm) with a slightly thickened stalk. The pituitary was isointense on T1 and T2, with homogenous enhancement after the administration of gadolinium. A suprasellar extension of the pituitary approached the optic chiasm, but there was no evidence of compression on the chiasm nor the optic nerves. No pituitary hormone excess was concluded as elevated TSH and FT3 could be explained by obesity and elevated IGF1 by both advanced puberty and obesity. Bone age was slightly advanced (13 years and 3 months). Repeated basal GH values were normal. Screening for thyroid antibodies was negative, leaving two possible diagnoses for the pituitary enlargement: pituitary hyperplasia or non-secreting pituitary macroadenoma.

Her headaches remained unchanged despite maximal analgesia and her fatigue became especially debilitating with 3/5 days of homeschooling in the following months. The uncertain etiology of the pituitary enlargement, the possible future risk for compression of the optic chiasm, and the increasing severity of the headaches prompted the proposal of neurosurgical intervention. However, after multidisciplinary consultation a residential revalidation program, including a psychological and weight loss intervention was opted, as well as serial cranial MRI and hormonal status every 3 months. The program resulted rapidly in weight loss and menarche came after 6 months. Hormonal status remained stable, as did the aspect and size of the pituitary on MRI, which after two years of follow-up resulted in the diagnosis of pubertal, physiological pituitary hyperplasia.

Discussion

'Normal' pituitary dimensions have been empirically defined from limited radiological studies, showing greater dimensions in females than males and increasing up to the age of 20 – 29 years, but in generally remaining below 9 mm (1). Physiological pituitary hyperplasia by increasing gonadotrope cell numbers occurs physiologically in adolescence and is important to consider in the evaluation, as it does not require medical intervention. Primary ovarian failure, producing gonadotrope hyperplasia with pituitary enlargement, can easily be detected at initial investigation. In some cases, an association with polycystic ovary syndrome has been found (1,3). Mutations in the *PROP1* gene have also been associated with pituitary enlargement in adolescents, but this condition is usually identified by combined pituitary deficiencies (4).

Conclusion

The greatest pituitary heights are seen in young pubertal females. The differential diagnosis of any pituitary enlargement should include physiological pituitary hyperplasia, even when mass-effect signs are present on neuroimaging. Clinical surveillance and treatment of any associated condition should be initiated. Surgery is to be avoided in the absence of urgent deficits since the pituitary enlargement rarely progresses.

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Brain calcifications as late presenting sign of pseudohypoparathyroidism: missed window of treatment opportunity

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Background

Bilateral brain calcifications also known as Fahr's syndrome can be idiopathic or associated with underlying developmental, metabolic, infectious, and endocrine conditions, in particular hypoparathyroidism and pseudohypoparathyroidism (PHP) (1, 2).

Case

In February 2017 a 69-year old female patient was referred by the neurologist because of bilateral cerebral calcifications and hypocalcaemia. In retrospect, the cerebral calcifications were first observed in 2006 on a brain CT scan performed because of a head trauma. Serum calcium at that time was 1.66 mmol/L (ref. 2.15-2.55) but surprisingly no further action was undertaken. Ten years later she presented to the neurology department because of recurrent falls and difficulties with short-term memory since 1 year. Clinical examination revealed a bradykinetic-rigid picture without lateralisation. MMSE score was 22/30. CT and MRI confirmed the presence of the bilateral cerebral calcifications, in particular of the basal ganglia. Genetic screening for the familial form of Fahr's syndrome was negative (platelet-derived growth factor receptor beta, sodium-dependent phosphate transporter 2). Hypocalcaemia was confirmed and the patient was referred to the endocrinology department.

Further work-up confirmed hypocalcaemia (2.02 mmol/L) together with a high normal phosphataemia (1.44 mmol/L, ref. 0.81-1.45), and an elevated PTH (83.1 ng/L, ref. 14.9-56.9). Along with the normal serum 25-hydroxyvitamin D (36.3 µg/L) and low normal 1,25-dihydroxyvitamin D (30.2 ng/L, ref. 20-80), the diagnosis of pseudohypoparathyroidism or PTH resistance was confirmed. Clinical examination showed a round facies, short stature (1.55 m), obesity (BMI 30 kg/m^2), normal metacarpals. Genetic testing revealed the presence of a methylation defect in the GNAS gene, more precisely a hypomethylation of exon 1A/B which is compatible with a type Ib PHP.

As PHP is an inherited disorder screening of the first degree relatives was performed, resulting in the diagnosis of PHP in the 43-year old son (calcium 1.84 mmol/L, phosphate 1.11 mmol/L, PTH 131 ng/L, 25-hydroxyvitamin D 9 µg/L, 1,25-dihydroxyvitamin D <10 ng/L). Remarkably, retrospective study of his medical file showed that he also had been diagnosed with bilateral cerebral calcifications on a previous brain CT scan in 2006, which was performed following a severe polytrauma. In addition he suffered from epileptic insults and a low calcium was measured in the past, but like his mother he had not been further medically explored.

In both patients medical treatment with active vitamin D and calcium supplements has recently been initiated. The presence of other hormonal resistances (TSH, LH) was ruled out. In July 2017, the frequency of falls in the index patient was decreased, MMSE was 24/30.

Discussion

PHP is a rare endocrine disorder. When left untreated complications can occur such as seizures, parkinsonism, cataract. In PHP Ib there is a genetic imprinting defect that involves a methylation defect of the maternal allele on the Gs-α coding GNAS locus. It therefore can only be transmitted by the mother in an autosomal dominant way. Resistance for other hormones, like TSH and LH also acting via GNAS signaling can also be present.

In order to prevent delay in diagnosis and treatment (pseudo)hypoparathyroidism should always be ruled out when bilateral brain calcifications are observed as

well as in patients presenting with parkinsonism or seizures. In both the presented clinical cases the diagnosis of PHP could have been made a decade earlier, with the potential of affecting the clinical evolution and quality of life.

Despite being a rare disease, non-endocrine specialists - in particular radiologists and neurologists - should be aware of PHP and its endocrine treatment. Apart from the fine tuning of the medical treatment, the endocrinologist has a pivotal role in the lifelong multidisciplinary coordination of this complex and vulnerable patient group.

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Thyroid hormone resistance based on a causative mutation in the thyroid hormone receptor β (THRB) gene

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1. INTRODUCTION

Interpretation of thyroid function tests (TFT) is usually straightforward.However, in a minority of cases the results of thyroid hormone and TSH measurements either conflict with the clinical picture or form an unusual pattern. Establishing the correct diagnosis is critical for the outcome of every patient with aberrant TFT. This is illustrated in the following case report.

2. CASE REPORT & RESULTS

A 52-year-old woman was referred because of aberrant thyroid function tests. She reported various complaints including constipation, low energy level, cold feeling, fatigue, difficulty losing weight and anxiety. Laboratory results show an elevated TSH (6,6 mU/L, reference 0,27-4,2) as well as elevated peripheral thyroid hormone levels (fT4: 2,5 ng/dL, reference 0,9-1,7 and fT3: 6,6 pg/mL, reference 2,5-4,4).

In 2009 she received 5 mCi I-131 because of an "enlarged thyroid with tendency to hyperthyroidism". Post-radioiodine thyroxine replacement was initiated, though this was later discontinued for unknown reasons. She has several relatives with thyroid dysfunction (father, uncle, aunts and grandmother) but we have no further information about the underlying origin.

She takes analgesics for back pain, and is treated with amlodipin and omeprazole. She is a smoker (5 cigarettes a day) and drinks alcohol occasionally.

On clinical examination we notice a high diastolic pressure (136/101 mmHg), normal pulse rate (77/min). BMI is 24,5 kg/m². Further examination reveals normal cardiac and lung auscultation and a palpable thyroid. On ultrasonography the thyroid appears enlarged and contains multiple nodules. Technetium scintigraphy showed an eager uptake (1,8%, reference value in our center 0.5-2%) of tracer in both thyroid lobes.

3. DISCUSSION

The finding of elevated serum thyroid hormone (TH) levels with non-suppressed TSH levels is not compliant with a normal hypothalamic-pituitary-thyroid feedback system. In this situation, a distinction between "falsely" and "really elevated" TFT should always be made. "Falsely elevated" tests refer to lab interference, e.g. leading to falsely elevated TSH but underlying thyrotoxicosis, or vice versa: falsely elevated serum TH levels but underlying hypothyroidism. Differential diagnosis for "really elevated" tests is central hyperthyroidism due to a thyrotropin-producing pituitary adenoma and resistance to thyroid hormone (RTH). Familial dysalbuminemic hyperthyroxinemia would be another possible explanation for the elevated TH test but would not explain the elevated TSH level.

Lab interference was considered less likely given that TFT were also aberrant on another analytical platform. After administration of thyrotropin releasing hormone we notice an increased response of TSH congruent with the elevated basal TSH, this made central hyperthyroidism unlikely. Finally, genetic analysis confirmed a causative mutation in the thyroid hormone receptor β (THRB) gene (c.959G>A; p.R320H). RTH-β is the most prevalent form of RTH and is caused by a mutation in THRB, this leads to deficient TH binding and action in THRβ-expressing tissues. The resulting imbalance in TH action in THRα- and THRβ–expressing tissues explains the symptoms of RTH-β: tachycardia, hyperactivity, raised energy expenditure, delayed bone age, constipation, learning problems and hearing deficit.

This patient was treated with L-thyroxine, at a dose of 150 µg a normalisation of TSH (0.97 mU/L) was seen whereas TH levels remained elevated. The clinical improvement was modest (less anxiety, less constipation).

4. CONCLUSION

This case illustrates the necessity of thoroughgoing evaluation of underlying disease in patients with abnormal TFT before intervening. If done so in this patient, administration of I-131 could have been avoided.

Non-alcoholic fatty liver disease and its relation with sex steroids in men with obesity

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BACKGROUND: Obesity associates with co-morbidities as non-alcoholic fatty liver disease (NAFLD). Obese men often present with low testosterone (T) levels. As sex steroids undergo hepatic metabolisation and their serum levels depend on hepatic sex hormone binding globulin (SHBG) secretion, NAFLD could contribute to this phenomenon. Previous studies however were contradictory and not based on state-of-the-art technology as mass spectrometry or biopsy-proven NAFLD.

OBJECTIVE: To assess the relation between biopsy-proven NAFLD and sex steroid levels in obese men undergoing gastric bypass surgery (GBS).

MATERIALS AND METHODS: This cross-sectional study included 70 obese men (mean age 45±11 years; BMI 42.0±5.5 kg/m^2) undergoing GBS and 70 healthy, age-matched control men (mean age 45±11 years; BMI 23.6±1.8 kg/m^2). In the GBS group blood samples and liver biopsies were collected during surgery, whereas only blood samples were collected in the control group. T and estradiol (E2) measured using LC/MS-MS, SHBG by immunoassay and free hormone fractions were calculated. Surgical liver biopsies scored using NAFLD activity (NAS) and Steatosis, Activity and Fibrosis (SAF) scores.

MAIN RESULTS: Obese men showed lower T, free T (FT) and SHBG levels, lower (F)T/(F)E2 ratio (all p<0.001) and higher FE2 levels (p=0.019) compared to controls. Within the GBS patients, inverse correlations between NAS and FT levels were found (r_s=-0.258, p=0.031). Besides, with increasing grade of steatosis, trends towards lower T and FT levels (p<0.05), and lower (F)T/(F)E2 ratios were observed (p<0.083). The correlation between steatosis and T remained significant after adjusting for age and BMI (F(2,61)=3.580, p=0.034). No associations between sex steroid levels and other NAFLD features were detected. Using SAF, lower FT levels correlated with steatohepatitis (p=0.014). Remarkably, no differences in SHBG or (F)E2 levels according to NAFLD severity were found.

CONCLUSION: This study confirmed lower T levels in men with obesity as compared to normal-weight men. Moreover, a higher NAS or the presence of NASH is associated with lower T and FT levels. The grade of hepatic lobular inflammation, ballooning and fibrosis does not seem to be associated with sex steroid levels, whereas an association with steatosis was found possibly related to an altered aromatase activity.

Heparin-induced hyperkalemia - An underestimated cause of hyperkalemia

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Case presentation A 22-year old woman with a recent lung transplantation (due to cystic fibrosis) developed hyperkalemia (5.6 mmol/L) five days after initiation of unfractioned heparin for an extensive thrombosis of the pulmonary veins, left atrium, vena cava superior and right atrium. The hyperkalemia progressed to 6.1 mmol/L, while the plasma sodium declined to 134 mmol/L. The patient took methylprednisolone as immunosuppressant, and adrenal insufficiency was excluded by normal ACTH-stimulation test. Plasma aldosterone was 110 ng/mL (normal range 12 – 150 ng/mL) while plasma renin activity was in the lower normal range 0.8 ng/mL/h (normal range 0.5 – 2.6 ng/mL/h).

Case evolution Unfractioned heparin was switched to low-molecular-weight heparin and treatment was

started with fludrocortisone 0.05 mg per day, resulting in the correction of the hyperkalemia.

Background Both unfractioned heparin and low-molecular-weight heparin can cause hyperkalemia (4-8%) at low doses and irrespective of anticoagulation effect or administration route. Direct inhibition of adrenal aldosterone production is the likely mode of action. Development of clinically relevant hyperkalemia is limited to patients with predisposing renal insufficiency, such as diabetic nephropathy, renal tubular acidosis type 4 or metabolic acidosis. In such high risk patients, it is advised to check plasma sodium and potassium level 3 to 5 days after initiation of therapy.

Conclusion If hyperkalemia develops a few days after initiation of heparin treatment in a patient with compromised renal function, heparin-induced hyperkalemia should be considered.

Prevalence of thyroid dysfunction and autoimmunity in the older population and implications of age-specific reference ranges

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OBJECTIVE: To investigate the prevalence of thyroid dysfunction and autoimmunity (TAI) and to determine age-specific reference ranges in individuals <60 and ≥60-year-old. Furthermore we investigated the impact of the age-specific reference ranges on the prevalence of thyroid dysfunction.

DESIGN: Retrospective analysis of laboratory data collected over six months in 2015, mainly from individuals consulting the outpatient clinic.

METHOD: Data from 676 individuals were withheld, after having applied strict exclusion criteria to avoid confounders. After exclusion of individuals with TAI (TPO-abs >60kIU/L) and/or outliers, data of 547 individuals were used to determine age-specific reference ranges. The prevalence of subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (sch) was determined according to the reference ranges from the commercial assay and also according to the calculated age-specific reference ranges from our study population.

RESULTS: From the 676 individuals included, 559 (83%) were <60year-old and 117 (17%) ≥60year-old. The prevalence of sch and TAI was comparable between both groups (8.6% vs. 13.7% and 15.4% vs. 20.5% respectively). The prevalence of SCH was significantly higher in individuals ≥60years, compared to that in individuals <60years (14.5% vs. 5.4%; p<0.001). The calculated 2.5 and 97.5 percentile for the age-specific TSH range was 0.24 and 4.4 mIU/L in individuals <60years and 0.15 and 8.2mIU/L in individuals ≥60years. When these the prevalence of sch and SCH was then determined on the basis of the age-specific reference ranges, the prevalence of SCH significantly decreased in individuals ≥60years (14.5% to 5%; p=0.027) and it then became comparable with that in individuals <60years (5% vs. 3%).

CONCLUSIONS: The prevalence of SCH was higher in individuals ≥60years, compared to that in individuals <60years, but when age-specific TSH reference ranges were used, it was comparable between both study groups. In order to avoid misclassification in older individuals, it is important to use age-specific reference ranges in daily clinical practice.

In young adult men, smoking is associated with a faster decline in trabecular bone mass but does not affect changes in cortical bone mass or bone geometry

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OBJECTIVE: The risk of developing osteoporosis is importantly determined by the acquisition of peak bone mass during growth as well as by subsequent bone loss. Although smoking has been associated with a disturbed

acquisition of peak bone mass, its effects on subsequent changes in bone mass and size are poorly known. We investigated whether smoking was a determinant of changes in DXA- and pQCT-derived bone parameters in a cohort of healthy men after completion of growth.

METHODS: 428 healthy men aged 25-45 years (mean 34.9 ± 5.3) participated in a longitudinal population-based sibling-pair study, with a mean follow-up of 12.4 ± 0.4 (range 11.2 – 13.6) years. Areal BMD (aBMD) was measured at the total body, proximal femur and lumbar spine using DXA. Trabecular volumetric BMD (vBMD) was assessed at the distal radius; cortical vBMD and bone geometry were assessed at the radial and tibial shafts using pQCT. Smoking habits were assessed using a validated health questionnaire. Associations between baseline smoking behavior (smoker / non-smoker) and bone changes were assessed using mixed-effects modeling.

RESULTS: In the overall cohort, aBMD decreased by 2.3 ± 3.0% at the total body, 1.7 ± 5.3% at the lumbar spine, 3.1 ± 4.6% at the total hip, and 6.0 ± 5.8% at the femoral neck (all p<0.001). Trabecular vBMD decreased by 1.6 ± 6.5%, whereas trabecular area increased by 1.57 ± 3.7% (both p<0.001). Cortical vBMD decreased by 0.5 ± 2.7% (p<0.001) at the radius and 0.2 ± 1.6% (p=0.047) at the tibia. Cortical area and periosteal and endosteal circumference increased by 1.3 ± 6.9%, 5.7 ± 5.9% and 11.9 ± 12.1% at the radius and 1.5 ± 4.2%, 3.3 ± 3.1% and 6.2 ± 7.3% at the tibia, respectively, whereas cortical thickness decreased by 5.8 ± 5.6% and 2.5 ± 7.1% (all p<0.001). Smoking at baseline was associated with a smaller increase in trabecular area and larger decreases in trabecular bone mineral content and vBMD in both unadjusted (p=0.031, p=0.012 and p=0.047, respectively) and baseline age-, height- and weight-adjusted analyses (p=0.038, p=0.009 and p=0.029). In contrast, smoking at baseline was not associated with changes in aBMD or cortical bone geometry.

CONCLUSION: In healthy adult men, aBMD as well as trabecular and cortical vBMD start to decrease early after peak bone mass attainment, but these changes are at least in part offset by increases in bone size. Smoking is associated with a faster decline in trabecular bone mineral content and vBMD, but does not affect changes in aBMD or cortical bone geometry.

MCL-1 is a key anti-apoptotic protein in human and rodent pancreatic β-cells

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Aim of the work: MCL -1 is an anti-apoptotic member of the BCL-2 protein family, whose depletion causes apoptosis in rodent β-cells *in vitro.* Importantly, decreased MCL- 1 expression was observed by histology in islets from T1D patients. Given the important role of MCL-1 in the survival of β-cells, the aim of this study was to clarify the role of MCL-1 both in human β-cells and in an *in vivo* murine model of T1D and to determine the mechanisms involved in the post-transcriptional regulation of the MCL-1 protein in β-cells.

Methods: The *in vitro* studies were performed in the human β-cell line EndoCβH1, the rat insulinoma cell line INS-1E and human islet cells exposed or not to IL-1β or TNF +, IFN$_\gamma$. Knockdown of the proteins of interest were performed by the use of specific small interfering RNAs while overexpression was achieved using adenoviral vectors. To evaluate the role of Mcl-1 *in vivo*, a β-cell specific *Mcl-1* knockout (βMcl-1 KO) mouse was generated. Both βMcl-1 KO and wild type mice were subjected to multiple low-dose streptozotocin (MLDS) treatment. Non-fasting blood glucose levels were measured every 7 days for 10 weeks. Pancreases were then collected for histological analysis and measurement of insulin content.

Results: Exposure of EndoC-βH1 cells to IL-1β+IFN-γ or TNF+IFN-γ for 24 hours decreased MCL-1 protein expression by 42 and 50%, respectively (p<0.05). Silencing MCl-1 sensitised EndoC-βH1 cells to apoptosis induced by the different cytokine combinations, (36-48% increase in cell death; p<0.01). In mirror experiments, overexpression of MCl-1 protected EndoC-βH1 cells and dispersed human islet cells against cytokine-induced apoptosis (36 and 52% protection, respectively; p<0.05). β*Mcl- 1* KO mice showed normal development and preserved islet function/ morphology under basal condition. Islets from β*Mcl-1* KO mice, however, were more susceptible to IL-1β + IFN-$_\gamma$- and TNF+IFN-$_\gamma$-induced β-cell apoptosis (50%-81% increase respectively, p<0.05 vs WT). Moreover, β*Mcl-1* KO mice displayed higher hyperglycaemia (50% increase AUC, p<0.05 vs WT) and lower pancreatic insulin content (54% decrease, p<0.05 vs WT) after MLDS treatment. Mechanistic studies in INS-1E cells

identified the kinase GSK3β, the E3 ligases MULE and βTrCP and the deubiquitinase USP9x as the key regulators of cytokine-mediated MCL-1 protein turnover in β-cells.

Conclusion: The present findings identify MCL-1 as a critical protein for preventing β- cell death in T1D and unveil the role for E3 ligases and ubiquitination in its down- regulation by pro-inflammatory cytokines. Development of strategies to prevent MCL-1 loss in the early stages of T1D may enhance β-cell survival and thereby serve as a relevant adjuvant therapy to delay or prevent disease progression.