



Abstracts for Acta Clinica Belgica "25th meeting of the Belgian Endocrine Society"

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Pseudohypoparathyroidism 1B caused by methylation changes at the GNAS locus

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Introduction: Pseudohypoparathyroidism is a rare disease caused by resistance to parathyroid hormone (PTH) down-stream of the PTH-receptor level. There are various subtypes. The main laboratory findings are hypocalcemia, hyperphosphatemia, and elevated PTH levels, but resistance to other hormones can occur. Patient and methods: at our outpatient clinic we treated a 34-year-old woman, who was diagnosed with primary hypothyroidism at the age of 20 (anti-TPO negative). Physical examination showed short stature but otherwise no other signs of Albright's hereditary osteodystrophy (AHO), which are typically observed in pseudohypoparathyroidism type 1A. Three years later she was diagnosed with hypocalcemia despite elevated PTH levels for which she was treated with calcitriol and calcium. Because of the lack of AHO features, it was decided to search for GNAS methylation changes and evidence for allelic loss at this locus. MS-MLPA revealed loss-of-methylation at GNAS exons AS and A/B, a gain-of-methylation at GNAS exon NESP55, but no change at GNAS exon XL; there was no evidence by MLPA for an allelic loss within GNAS and STX16. Her family history was negative for calcium disorders and thyroid disease, and we therefore concluded that she is a sporadic case of pseudohypoparathyroidism 1B. Implications of the disease with a short review of the literature will be presented.

A case of severe ectopic adrenocorticotrophic hormone syndrome with olfactory neuroblastoma. Endocrine looks can be deceiving

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Background: Esthesioneuroblastomas (olfactory neuroblastoma) were first described in 1924 by Berger et al. and account for 3–10% of intranasal tumors^{1,2,3}. In extremely rare cases, Cushing's syndrome due to ectopic ACTH production, a rare condition on its own⁴, can accompany an esthesioneuroblastoma. To our knowledge, only a few cases (12) of ectopic ACTH secreting neuroblastoma are now described in the literature.

Case report: A 61-year-old Caucasian woman was admitted at the department of oncology in April 2015 with a history of an olfactory neuroblastoma, diagnosed in 2003. She was treated with craniofacial surgical resection and resection of the right lymph nodes in the neck. During follow-up there were metastasis in the right parotid gland and lymph nodes at the right side of the neck, which were resected. After a disease free period, she presented in March 2015 with progressive paraparesis, due to a bulging mass in the sixth thoracic vertebra. An urgent laminectomy was performed. Bone DEX-scintigraphy showed new disseminated bone metastases and adjuvant chemotherapy (Cisplatin/Etoposide) was started. When she was admitted for her third cycle, blood analysis showed an extreme low potassium level (1.8 mmol/l, lab references 3.5–5.1 mmol/l) with metabolic alkalosis (HCO₃ 42 mmol/l, lab references 21–32 mmol/l; pH 7.586 mm Hg). She had no complaints, except for some fatigue and general weakness. There were no abnormalities during the clinical examination. Further laboratory tests were ordered to determine the origin of the severe hypokalemia. A fasting blood sample showed extreme high values of ACTH (987 pg/ml, reference 7–63) and cortisol (808 ng/ml, reference 62–194). Adjuvant testing (several 24 h free urinary cortisol samples, diurnal cortisol/ACTH profiles) confirmed the status of hypercorticism. MRI scan of the pituitary gland showed no indications of an adenoma. The diagnosis of an ectopic focus of ACTH was made after performing a low-dose dexamethasone suppression test and a corticotropin-releasing hormone (CRH) stimulation test. Due to severe neutropenia and thrombocytopenia after the third cycle of chemotherapy, a sinus petrosus sampling was considered unsafe and not performed. A follow up ¹⁸F-FDG PET after 2 months showed hypermetabolic lesions of the seventh thoracic vertebra, the left scapulae, the 7th and 8th right rib and the right pubic bone, all suspected for metastatic disease, and symmetric hyperplasia of the adrenal glands. A standard 6 mCi octreotide scan showed uptake at the sites of the bone metastasis, and thus confirmed our suspicion of ectopic ACTH secreting metastases of the olfactory neuroblastoma. With the persisting hypokalemia and need for massive intravenous and peroral substitution, treatment with adrenal enzyme inhibitors was started (Ketoconazole and metyrapone) combined with oral hydrocortisone replacement to prevent iatrogenic adrenal insufficiency. This combination therapy resulted in a rapid control of serum and urinary free cortisol (serum cortisol 21, ng/ml, reference 62–194). Although this approach was well tolerated by the patient, these are only temporary measures and the multidisciplinary medical team opted to proceed to a bilateral laparoscopic adrenalectomy as a permanent solution. A concomitant biopsy of a metastatic lesion of the pubic bone was performed and confirmed a metastasis of a known esthesioneuroblastoma with positive immunohistochemical staining as an ACTH secreting metastase.

Conclusion: A patient with severe ectopic adrenocorticotrophic hormone syndrome due to an olfactory neuroblastoma is described. Treatment with ketoconazole and metyrapone led to a suppression of hypercorticism. Adrenalectomy was performed afterwards to cure the patient from hypercorticism. Hydrocortisone replacement therapy was started after bilateral adrenalectomy. The absence of any clinical sign and symptoms of hypercortisolism makes this case extremely interesting. All other cases described in the literature presented with a cushingoid appearance. The biochemical changes appearing after 2 cycles of chemotherapy although the bone metastasis were already known makes the case even more specific and special: endocrine looks can be deceiving.

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Human multipotent adult progenitor cells enhance islet function and revascularization when co-transplanted as a composite pellet in a mouse model of diabetes

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Aims of the work: Hypoxia in the initial days after islet transplantation leads to considerable loss of islet mass and contributes to the disappointing observations in the clinic. The aim of the present study was to investigate whether co-transplantation of human non-endothelial bone marrow-derived multipotent adult progenitor cells (MAPC), which are not immune-privileged and can secrete angiogenic growth factors during the initial days after implantation, could improve islet engraftment and survival.

Methods: Islets (150) were co-transplanted with or without human MAPC (250,000), as separate or composite pellets, under the kidney capsule of syngeneic alloxan-induced diabetic C57BL/6 mice. Blood glucose levels were frequently monitored and intraperitoneal glucose tolerance tests were carried out. Grafts and serum were harvested at 2 and 5 weeks after transplantation.

Main Results: Human MAPC produce high amounts of angiogenic growth factors, including vascular endothelial growth factor (VEGF), *in vitro* and *in vivo*, as demonstrated by the induction of neo-angiogenesis in the chorioallantoic membrane (CAM) assay. Islet-human MAPC co-transplantation as a composite pellet significantly improved the outcome of islet transplantation as measured by the initial glycemic control, diabetes reversal rate, glucose tolerance, and serum C-peptide concentration compared with transplantation of islets alone. Histologically, a higher blood vessel area and density in addition to a higher vessel/islet ratio were detected in recipients of islet-human MAPC composites.

Conclusions: The present data propose that co-transplantation of mouse pancreatic islets with human MAPC, which secrete high amounts of angiogenic growth factors, enhance islet graft revascularization and subsequently improve islet graft function.

Hypoglycemia due to big IGF-2

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Introduction: Hypoglycemia is most commonly iatrogenic, caused by insulin or insulin secretagogue used to treat diabetes mellitus. Diagnosis and treatment of such an event is straightforward. By contrast, spontaneous hypoglycemia in a non-diabetic patient requires a thorough investigation. Hypoglycemia is confirmed when Whipple's triad is present. Clinical evaluation and biochemical work-up with insulin, proinsulin, c-peptide, circulating oral hypoglycemic agents, insulin antibodies and cortisol is needed (1). Treatment consists of correcting the glycemic state and specific therapy for the primary disease.

Case report: A 59-year-old non-diabetic man presented on the emergency department of our hospital with confusion and impaired consciousness during a work meeting. First investigations revealed a marked hypoglycemia (36 mg/dl). After intravenous administration of glucose, consciousness and cognitive functions returned to normal. Since the resection of an intracranial solitary fibrous tumor a few months earlier, he did not feel very well with difficulties to concentrate. This improved with the ingestion of carbohydrates. His weight was thought to be stable, night sweats were reported. Further biochemical investigation showed a low insulin and undetectable c-peptide. Given these results and the history of a solitary fibrous tumor, a IGF-2 induced hypoglycemia was suspected. This was confirmed by a western immunoblot assay. Levels of growth hormone and IGF-1 were low, serum cortisol was normal. The patient tested negative for insulin antibodies. Imaging studies showed diffuse liver lesions but no primary tumor. Microscopic evaluation of a liver biopsy revealed a malignant hemangiopericytoma. Initially, there was a striking need of glucose supplementation to reach normoglycemia. Up to 900 mg intravenous glucose per 24 h was administered, on top of oral intake. This could be rapidly tapered after initiation of glucocorticoids (32 mg methylprednisolone). After reaching normoglycemia, making the diagnosis and staging, the patient was transferred to the department of oncology for initiation of chemotherapy with adriamycin.

Discussion: Tumors producing big IGF-2 are a known cause of spontaneous hypoglycemia. Big IGF-2 is an aberrant protein with a higher molecular mass, with low affinity for IGF binding proteins, and thus mainly acting on the insulin receptor causing hypoglycemia (2). These tumors are mainly benign (mostly benign solitary fibrous tumor), but a few are malignant (mostly malignant solitary fibrous tumor or hemangiopericytoma) (3). Surgical resection is

the primary treatment modality. Transarterial embolization, radiation and systemic (chemo)therapy are possibilities in selected cases (3). Glucocorticoid therapy suppresses abnormal secretion of big IGF-2 and can quickly reverse symptomatic hypoglycemia (4), as was seen in the reported case.

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How T2-weighted signal intensity of GH-secreting adenomas correlates with response to primary somatostatin analogue therapy in acromegaly

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Aim of the work: In order to ensure the best management of acromegalic patients with the varied therapeutic possibilities now available, identifying predictive factors of response to treatment is essential. In terms of imaging criteria, pituitary adenoma size and cavernous sinus invasion announce low chances of surgical cure. However, there are no recognized imaging predictive factors of somatotropinoma response to somatostatin analogue (SSA) therapy. Somatotropinomas are the only type of pituitary adenoma that often present as hypointense on T2-weighted MRI sequences. These T2-hypointense adenomas are usually smaller, more rarely invasive and correspond to higher IGF1 levels. However, an evaluation of the response, both anti-secretory, as well as anti-proliferative, of somatotropinomas to primary therapy with SSA has not been comprehensively studied and constitutes the purpose of our work.

Methods: Acromegalic patients treated with SSA as primary therapy were included in this multicentric, international study, both prospectively and retrospectively. The duration of therapy varied from 3 to 12 months. The results of biological and MRI evaluations at baseline and after treatment were recorded. T2-weighted signal of the adenoma was classified as hypointense, isointense or hyperintense compared to the normal pituitary tissue or when the latter was not visualized, to the gray matter of the temporal lobe. For a quantitative assessment, ROI measurements of the adenoma, normal pituitary tissue, and gray matter were recorded. The ratio between adenoma and pituitary tissue/gray matter ROI was used in the statistical analysis to eliminate variations between different examinations.

Main results: 106 patients were included in the study (52 male, 54 female). T2-weighted signal was hypointense for 76 adenomas (71.6%), isointense for 14 adenomas (13.2%), and hyperintense for 16 adenomas (15%). Treatment duration did not vary significantly between the T2-hypo-, iso- or hyperintense groups. However, T2-hypointense adenomas had a better biological response to SSA with a decrease in GH of 88.6% (vs 20.9% for T2-isointense and 23.8% for T2-hyperintense, $p < 0.0001$) and IGF1% of 59.6% (vs 11.7% for T2-isointense and 33.2% for T2-hyperintense, $p = 0.002$). The anti-proliferative response was also better for T2-hypointense adenomas with a decrease of adenoma volume of 38.1% (vs 7.4% for T2-isointense and 2.48% for T2-hyperintense adenomas, $p < 0.0001$). Quantitative T2-measurement validated the results of the visual assessment. Adenomas with lower T2-weighted signal intensity had more important GH, IGF1% and volume reductions under treatment.

Conclusions: T2-weighted signal intensity of pituitary adenomas assessed on the diagnostic MRIs of acromegalic patients allows the classification of somatotropinomas into different categories. T2-hypointensity appears to confirm itself as a marker of a more favorable response to primary therapy with SSA, in terms of both anti-secretory and anti-proliferative effects.

New genetic cause of gigantism and FIPA

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Context: Acromegaly and gigantism result from excessive production and secretion of growth hormone (GH), usually by a pituitary adenoma, and are considered as very rare conditions. Gigantism occurs in the period of linear growth and is poorly understood disorder. Although previous studies have identified the various alterations in predisposing genes in somatotropinomas, genetic cause in majority of cases of acromegaly and gigantism remains unclear.

Aim: We studied gigantism for genetic defects.

Methods: We conducted an international study (clinical and genetic) on the pituitary gigantism. In total 208 patients were enrolled with growth hormone excess and abnormal growth for age or final height > 2SD above country local standards. Genome-wide analyses was performed in 46 patients with gigantism and 248 patients with acromegaly.

Results: Genetic or hereditary characteristics were observed in 46% of patients and included FIPA, McCune-Albright syndrome, Carney complex, and MEN type 1. AIP mutations accounted for about one third of cases. We observed a microduplication in a region of about 500 kb on chromosome Xq26.3 in samples from 17 patients with gigantism. Four were obtained from members of two FIPA families, and 13 were sporadic cases. All sporadic cases had an original duplication, while familial cases had inherited identical duplications. In all patients, the disease appeared in infancy. None of patients with gigantism that do not bear the Xq26.3 microduplication, has grown excessively before age of 5 years. Genomic characterization of Xq26.3 region suggests that microduplications are generated during chromosome replication. Patients with X-linked infantile gigantism have a common area of overlap that involves four genes, including GPR101 gene, which encodes a receptor coupled to a G protein with seven transmembrane domains. Only this gene is strongly overexpressed in pituitary tumors from two patients with infantile gigantism.

Conclusions: A new pediatric syndrome (we called X-LAG for X-linked acrogigantism) is caused by the genomic microduplication on chromosome Xq26.3 and characterized by early onset of gigantism resulting from an excess of growth hormone. X-LAG syndrome is most likely caused by duplication of GPR101 gene.

Maternal age at childbirth is associated with glucose metabolism in adult men

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Background: Although maternal age at childbirth tends to increase worldwide, studies investigating the effects of this trend on metabolic health in the offspring are scarce.

Objective: We aimed to determine whether maternal age at childbirth is associated with adult body composition and parameters reflecting metabolic health in a cohort of young, healthy men.

Methods: This study is part of a population-based sibling pair study in healthy men aged 25 to 45 years old. 689 subjects (mean age 33.9 +/- 5.4 years) for whom maternal data were available were included in the present analyses. Data collected in the study included birth weight, adult weight, height, DXA-derived body composition, and blood pressure. Total cholesterol, glucose, and insulin levels were determined in fasting serum samples. Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR). Cross-sectional associations were investigated using linear mixed-effects modeling.

Results: Maternal age at childbirth was 27.0 ± 4.7 years (range 15–48) and was positively associated with birth weight ($\beta = 0.13$; $p = 0.001$). In their adult sons, maternal age at childbirth was inversely associated with fasting glucose levels ($\beta = -0.12$; $p = 0.001$) and HOMA-IR values ($\beta = -0.07$; $p = 0.050$) after adjustment for adult age and BMI. After further adjustment for birth weight, the associations between maternal age and glucose levels remained significant ($\beta = -0.12$; $p = 0.003$), whereas the association between maternal age and HOMA-IR weakened ($p = 0.092$) and birth weight became an independent inverse predictor of HOMA-IR ($\beta = -0.07$; $p = 0.039$). No associations were found between maternal age and body composition, blood pressure or cholesterol levels. When subjects were divided into 4 groups according to maternal age at birth (<25, 25–29, 30–34 and ≥ 35 years), sons of mothers aged 30 to 34 at childbirth had significantly lower HOMA-IR values and fasting insulin levels compared to sons of mothers in the other age groups ($p = 0.007$ – 0.015 for HOMA-IR, $p = 0.007$ – 0.028 for insulin), whereas sons of mothers aged < 25 had higher fasting glucose levels compared to sons of mothers aged 30–34 ($p = 0.010$) and sons of mothers aged ≥ 35 ($p = 0.042$). These associations were independent of adult age, BMI, and birth weight.

Conclusion: Maternal age at childbirth is associated with birth weight and glucose metabolism in adulthood. Part of the association between maternal age and insulin resistance might be mediated through birth weight.

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Impact of thyroid autoimmunity on cumulative delivery rates in IVF /ICSI patients

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Context: Since the first publication in 1978 of the first baby born after *in vitro* fertilization (IVF) multiple papers have been published to investigate and improve success rates after IVF. Thyroid autoimmunity may be an important factor determining fertility treatment outcome.

Objective: To predict the impact of thyroid autoimmunity (TAI) on the probability of delivery after a defined number of treatment cycles, using analysis of cumulative delivery rates in patients with and without TAI.

Design: The Brussels thyroid autoimmunity IVF study started in 2010. A two armed study design was performed: patients with TAI and patients without TAI (control group). All patients who started their first IVF/ICSI cycle in our fertility center between 01 January 2010 and 31 December 2011 were included. A follow-up until 31 December 2013 was carried out.

Setting: All patients were recruited in the Brussels IVF Centre in a university setting. Live birth delivery after 25 weeks of gestation was taken as the primary endpoint of our study. Cumulative delivery rates were calculated for both groups until 6 treatment cycles.

Patients: In total 2406 women who consulted our center were included. We included 333 patients with TAI and 2019 patients without TAI. Baseline patient characteristics in both groups at the time of the first oocyte retrieval were analyzed and summarized.

Intervention(s): All patients (in both groups) received the usual IVF treatment protocols, i.e. antagonist or agonist protocol.

Main outcome measure: Impact of TAI on cumulative delivery rates after IVF/ICSI was investigated. The hypothesis being tested was formulated before the data collection. As secondary endpoint we analyzed the influence of thyroid function (TSH, fT4), age, smoking, BMI, and ovarian reserve (AMH and FSH) on obstetrical outcome in anti-TPO positive patients

Results: In the TAI group 333 women underwent a total of 802 ICSI cycles. Overall 156 deliveries were recorded until the sixth cycle. In the first cycle, the average delivery rate was 25%. The crude cumulative delivery rate after six cycles was 47% while the expected cumulative delivery rate was 64%. In our control group, 2019 women underwent a total of 3937 ICSI cycles. Overall 948 deliveries were recorded until the sixth cycle. In the first cycle, the average delivery rate was 26%. The delivery rate per cycle remained stable until the sixth cycle. The crude cumulative delivery rate after six cycles was 47% while the expected cumulative delivery rate was 76%.

Conclusion: Our study did not confirm an influence of TAI status in patients undergoing fertility treatment on cumulative delivery rates after six IVF/ICSI cycles. Age was the only independent parameter to determine the outcome of IVF/ICSI in TAI positive patients.

An unusual cause of central diabetes insipidus

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In February 2014, a previously healthy 23-year-old woman presented with polydipsia and polyuria. A diagnosis of central diabetes insipidus (DI) was made based on the results of a water deprivation test. Magnetic resonance imaging (MRI) of the pituitary gland showed thickening of the pituitary stalk and loss of normal hyperintense T1-weighted signal of the posterior pituitary gland. Circulating levels of anterior pituitary hormones were normal. Cytological examination and tumor markers in serum and cerebrospinal fluid, including alpha-fetoprotein and beta-human chorionic gonadotropin, were normal. Serum angiotensin-converting enzyme was not elevated and anti-pituitary antibodies were negative. Chest X-ray was unremarkable. The tuberculin skin test and *in vitro* gamma interferon release assay were also negative.

Skin biopsy of macular lesions on the back showed non-specific chronic inflammatory changes with no argument for histiocytosis.

¹⁸F-FDG PET/CT revealed hypermetabolism of the pituitary stalk but also of the maxillary sinus as well as a tumor-like lesion in the right kidney. Renal contrast-enhanced ultrasonography (CEUS) confirmed the presence of the latter, measuring 2 cm in diameter.

As anti-MPO ANCA were positive, granulomatous with polyangiitis (GPA) was suspected. However, sinus biopsy showed neither granulomatous inflammation nor vasculitis. Moreover, urine analysis and renal function were normal.

At this time, renal mass was not easily accessible to percutaneous US-guided biopsy.

Close clinical and radiological follow-up was proposed.

Six months later, CEUS showed progression of the right renal mass which had doubled in size (4.3 cm) and suspected new lesions in the left kidney. This was confirmed by ¹⁸F-FDG PET/CT.

The enlargement of the right renal tumor allowed safe percutaneous biopsy. Histopathological examination of the biopsy specimen revealed severe necrotizing granulomatous tubulointerstitial nephritis and extracapillary glomerulonephritis, confirming a diagnosis of GPA.

In order to avoid cyclophosphamide-induced ovarian failure, treatment with rituximab and prednisolone was initiated. Ultrasonographic controls performed 5 and 13 weeks after the last rituximab administration demonstrated disappearance of renal tumors. Additionally MRI imaging control 5 months later showed a return to normal pituitary size and stalk width but a persistent loss of the normal posterior lobe T1 hyperintensity. Central DI persisted. The case described here is unique in many respects.

Pituitary involvement is an uncommon complication of GPA with about 30 patients reported in literature^{1,2}. When it occurs, central DI usually follows rather than precedes lung and kidney involvement. In a recent monocentric series on GPA-related pituitary diseases, the most frequent endocrine dysfunctions were secondary hypogonadism and DI. All patients had abnormal pituitary imaging³.

Granulomatous renal inflammatory pseudotumor (IPT) is even rarer with only 16 cases described. These pseudotumoral lesions have only exceptionally been identified by ¹⁸F-FDG PET/CT⁵ and never by CEUS.

Most of the reported cases of GPA-associated renal IPT have been treated surgically or less frequently by classical immunosuppression (cyclophosphamide and steroids)⁴.

Our patient experienced rapid and complete renal response to rituximab.

The persistence of DI could be related to irreversible damage, although longer follow-up is required considering the positive evolution of pituitary imaging. In the Mayo clinic series reversibility of DI was noted in 67% of cases³.

Finally, GPA should be considered in the differential diagnosis of central DI. The key role of ¹⁸F-FDG PET/CT in the diagnosis work-up presented here is consistent with emerging data on the potential benefit of this exam in the assessment of central DI⁵. Rapid recognition of GPA as the cause of DI and initiation of treatment could minimize the risk of irreversible damage. In renal mass-like lesions, establishing the diagnosis of GPA could prevent unnecessary nephrectomy. To our knowledge this is the first case combining central DI and subsequent bilateral renal pseudotumors in the setting of GPA.

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Low free testosterone is associated with hypogonadal symptoms in men with normal total testosterone levels: results from the European male ageing study

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Background: During aging, total testosterone (TT) declines and SHBG increases, resulting in a greater decline of free testosterone (FT) compared to TT. However, guidelines suggest using TT to diagnose androgen deficiency and to reserve FT only for men with borderline TT. We investigated if isolated low FT or isolated low TT was associated with androgen-related endpoints in healthy men.

Methods: 3369 community-dwelling men, aged 40–79, were included. We assessed differences between men with both normal TT (≥ 10.5 nmol/L) and calculated FT (≥ 220 pmol/L) (referent), men with normal TT/low FT (group 1) and men with low TT/normal FT (group 2) by descriptive statistics and ordinal logistic regression adjusted for age, center, BMI, and comorbidities.

Results: 2540 men had normal TT (18.4 ± 5.5 [mean \pm SD] nmol/L) and FT (326 ± 75 pmol/L). There were 261 men in group 1 (normal TT (14.2 ± 3.7 nmol/L), low FT (195 ± 22 pmol/L)) and 92 men in group 2 (low TT (9.6 ± 0.7 nmol/L), normal FT (247 ± 20 pmol/L)). Compared to referent, men in group 1 were older and had higher SHBG, whereas group 2 was younger and had lower SHBG. BMI was higher in both groups. Men

in group 1, but not group 2, were in poorer health and had lower hemoglobin. Regression analysis showed that men in group 1 had less frequent morning erections ($p = 0.012$), more erectile dysfunction ($p < 0.001$) and more physical symptoms (limited vigorous activity ($p = 0.011$), walking 1 km ($p = 0.026$) and bending ($p = 0.005$)). Compared to referent, sexual and physical symptoms did not differ in group 2.

Conclusions: Independent of age, BMI, and comorbidities, men with isolated low FT, but normal TT, have more androgen deficiency-related symptoms than men with normal TT and FT levels; whereas symptoms do not differ in men with isolated low TT. Not only total, but also FT levels should therefore be assessed in men with hypogonadal symptoms.

RNA-based MAFA overexpression is sufficient to drive human pancreatic duct-derived cells toward a β -cell-like phenotype

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Aim of the Work: Pancreatic epithelial cells represent an attractive cell source for replacement therapy of type 1 diabetes. Previously, we designed a protocol for expansion of human pancreatic duct-derived cells (HDDCs) and showed their β -cell engineering potential. In this study, we reprogrammed HDDCs into β -cell-like lineage by overexpressing mRNAs of key pancreatic transcription factors (TFs).

Methods: Pancreatic duct cells ($n = 6$) were purified and propagated into endothelial growth-promoting media. Synthetic modified (sm) RNAs were manufactured by unidirectional subcloning of PDX1, NGN3, and MAFA into a plasmid containing 5' and 3' UTR regions. The UTR-flanked inserts were excised and poly(A)-tailed. The final smRNAs were synthesized through *in vitro* transcription followed by phosphatase and DNase treatments, before being daily transfected in HDDCs.

Results: In all donors, transfection of PDX1, NGN3 or MAFA led to upregulation of endogenous target (ex: NGN3) and β -cell marker (ex: INS, synaptophysin, SLC2A2, GCK) genes, with the highest expression levels being reached after MAFA transfection. Co-transfection of TFs did not significantly improve β -cell differentiation. After 7 consecutive daily smRNA transfections, we noticed acceptable impact on cell viability and innate immune response in HDDCs based, respectively, on annexin-V/PI staining and on low IFNA and RIG-1 gene expression. After MAFA transfection, HDDCs immunostained positive for MAFA, insulin ($19.3 \pm 3.3\%$) and PDX1, and C-peptide content and release (21.45 ± 2.42 pg/mL/106 cells) were shown by ELISA under basal conditions.

Conclusions: We showed that MAFA RNA overexpression is sufficient to efficiently reprogram HDDCs toward β -cell-like phenotype in a timely manner. Further research will be needed to demonstrate a controlled insulin secretion capacity after differentiation.

International meeting presentations of the work: Oral presentations at 75th Scientific Sessions of the American Diabetes Association, Boston, 2015, and ISPAD Meeting, Toronto, 2014.

Hospitalization cost and length of stay associated with ophthalmological surgery depending on the diabetic status

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Objectives: Ophthalmological complications (glaucoma, retinopathy, cataract) are frequent in patients with type I or type II diabetes and often require surgical treatment. This study aimed at assessing the impact of diabetes on the hospitalization costs and the length of stay associated with these surgical treatments in Belgium, using retrospective data.

Methods: The average hospitalization cost and the average length of stay (LOS) among patients hospitalized for ophthalmological surgery were estimated using the longitudinal IMS Hospital Disease Database (year 2013), including data (diagnoses, procedures, costs) on 24% of Belgian hospital beds. Stays were searched based on ICD-9-CM procedure codes corresponding to surgery for glaucoma (12.1–12.7), vitrectomy (14.71–14.74), and cataract extraction (13.19, 13.6). Patients were identified as diabetic if at least one diagnostic of diabetes (ICD-9-CM: 249–250) had been documented during the calendar year. The impact of diabetes on LOS/cost was assessed through Wilcoxon non-parametrical tests.

Results: 671 stays with surgery for glaucoma, 1,438 stays with vitrectomy and 204 stays with cataract extraction were retrieved in the database (with diabetic patients accounting for 56, 202 and 24 of these stays, respectively). Patients with Type I diabetes ($n = 16$, split between glaucoma surgery and vitrectomy) were significantly younger than Type 2 diabetes or non-diabetic patients (50.3 years, vs. 69.5 and 66.6 years, respectively) at the time of surgery. The average cost of diabetic patients (both types) was more than twice the cost of non-diabetics in both glaucoma surgery (€7,972 vs. €3,278; $p < 0.001$) and cataract extractions (€10,668 vs. €3,935; $p = 0.031$) and about 30% higher in vitrectomies (€3,755 vs. €2,869; $p < 0.001$). LOS was also systematically higher in diabetic patients (glaucoma surgery: 5.8 vs. 2.4 days; vitrectomy: 2.3 vs. 1.7 days; cataract extraction: 14.7 vs. 3.0 days).

Conclusions: The presence of diabetes increases dramatically both LOS and hospitalization costs in patients undergoing ophthalmological surgery.

Diabetes mellitus: one train may hide another

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A 26-year-old Chinese male, known with autism spectrum disorder and moderate mental retardation, was referred to start insulin therapy for uncontrolled diabetes mellitus (HbA1c: 88 mmol/mol; C-peptide: 1.75 ng/ml; anti-GAD AB: negative) treated with oral antidiabetic drugs (metformin and DDP4-inhibitor) since 2012. He is the first child of healthy unrelated parents. His only sister is in good health.

Clinical examination reveals a tall man with overweight and truncal obesity in light of his ethnicity (height: 180 cm; weight: 80 kg, BMI 24.7 kg/m², waist circumference (WC): 94 cm (cutoff values Chinese males: BMI > 24 kg/m²: overweight; WC > 90 cm: truncal obesity). On further inspection, we withhold facial dysmorphism with hypertelorism, scarce facial hair and some signs of alopecia. Furthermore, he has a true gynecomastia (Tanner stage III) and acanthosis nigricans. Tanner genital stage is IV, however testicular volume is smaller than 4 ml. Further clinical examination shows clinodactyly, pes planus, and thin enamel of the teeth. A cardiac and abdominal sonography was performed, no abnormalities were found.

Blood results show hypergonadotropic hypogonadism (LH: 14.1 U/L, FSH:25.3 U/L, testosterone: 195 ng/dl, free testosterone: 5.71 ng/dl, SHBG:0.41 µg/dl). There was no history of testicular pathology. Bone densitometry shows osteopenia at the lumbar spine (T-score lumbar spine: -1.4). Genetic testing shows the presence of an 48 XYYY karyotype.

48, XYYY syndrome, was first described by Muldal and Ockey (1962) as a genetic variant of Klinefelter syndrome and has an incidence of 1:17,000 – 1:50,000 male births (1). Most cases are thought to result from the fertilization of a normal female oocyte with aneuploidy sperm produced through non-disjunction events during meiosis I and meiosis II of the spermatogenesis (2). Clinical characteristics are similar to Klinefelter syndrome, however in 48 XYYY males prevalence and severity of mental retardation and behavioral problems is higher. Moreover, 48 XYYY are more prone to have epilepsy and intention tremor. Renal and cardiac congenital malformations are described in patients with 48 XYYY syndrome as renal dysplasia, atrial or ventricular septal defects and tetralogy of Fallot. Little data on diabetes mellitus in 48 XYYY are available. One study described a frequency of 18% based on medical questionnaires, however without biochemical data confirming diagnosis (3). Diabetes mellitus in Klinefelter disease is classified as 'other genetic syndromes sometimes associated with diabetes' (WHO classification). As 48 XYYY often is defined as a variant of Klinefelter syndrome, it will be classified in the same way. There are almost no data on possible pathophysiological mechanism of diabetes mellitus in 48 XYYY. The following mechanism is sometimes proposed: low total and free testosterone levels are associated with truncal obesity leading to metabolic syndrome, insulin resistance, and type 2 diabetes (4). Abdominal obesity and high C-peptide levels in our patient are arguments in favor of insulin resistance as a possible etiological factor. Based on the suggested pathophysiological mechanism, metformin and testosterone could be considered as possible treatment options of diabetes mellitus in 48 XYYY. It seems reasonable to use metformin to enhance insulin sensitivity. Testosterone treatment might also improve metabolic control by increasing skeletal muscle mass at the expense of fat mass and decreasing abdominal obesity and non-esterified fatty acids, through inhibition of lipoprotein lipase activity thereby improving insulin sensitivity (5). Little data are available on androgen substitution in 48 XYYY. Positive effects on well-being, metabolic parameters, and bone mineral density have been described. There is however some concern about possible negative effects of testosterone treatment on behavioral problems. We decided to treat our patient with basal-bolus insulin therapy in combination with metformin. Testosterone treatment was suggested to the patient for general well-being and possible positive metabolic effects.

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Diagnosis of a growth hormone insensitivity syndrome in a Flemish adolescent

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Background: Growth hormone (GH) insensitivity syndrome (GHIS) is defined by a growth failure due to resistance to the actions of GH. GHIS has several underlying causes, including GH receptor (GHR) mutations. Diagnosis is complicated by a wide phenotype-genotype variability and a wide variability in biological severity (1, 2). A detailed hormonal and genetic investigation for growth failure in an adolescent with severe growth retardation and normal GH but low normal IGF-1/IGFBP3 serum values, who was initially diagnosed with idiopathic familial short stature (ISS), led to the diagnosis of a GHR mutation.

Case report: A 15-year-old boy was referred for progressive growth failure. His mother measured 172 cm and had menarche at age 12. His father was short (height 157 cm) despite some residual height gain of 30 cm after age 18. Paternal grandparents were 167 cm (grandfather) and 150 cm. He was born by vaginal delivery in normal position after an uneventful twin gestation of 38 weeks as first born. No prolonged icterus or episodes of hypoglycemia were noticed during the neonatal period. His birth weight was 2830 g and birth length 50 cm. He had a bilateral orchidopexia for inguinal testes. He suffered from nocturnal enuresis until the age of 10, while his neurodevelopment was normal. Investigation at age 10 for progressive growth failure since the age of 4 years, resulting in a very short stature (height z-score of -3.4) but normal body proportions, showed a delay in bone maturation of 1.8 years, repetitively low serum IGF-1 values, normal basal GH levels (0.8 ng/ml), and a glucagon stimulated GH peak value of > 40 ng/ml. Karyotype and SHOX gene copy number variation screening were normal. Diagnosis of ISS was made at that time. At physical examination, his body weight was 28.7 kg, standing height 135.5 cm, sitting height 71 cm, and arm span 132 cm. Midfacial hypoplasia, slight frontal bossing, and poor musculature were present. Pubertal staging (Tanner) was A1P1G1 with a testes volume of 3 ml. Repeated laboratory evaluation showed a borderline low IGF-1 (41 ng/ml) and IGFBP3 (1859 µg/l) concentration, unchanged after 7 days of GH administration at a dose of 0.05 mg/kg/day. Thyroid function tests, prolactin, DHEAS, and cortisol concentrations were normal. Bone age (Greulich and Pyle) was 12.5 yr. Sequencing of the IGFALS gene was normal. A heterozygous c.876G > T (p.Arg292Ser) mutation was found in exon 7 of the GHR gene by Sanger sequencing. This mutation is known to weaken the usual acceptor splice site of intron 8, leading to a frameshift (3). Treatment with recombinant IGF1 (Increlex) was recently started (4).

Discussion: GHR gene mutations, responsible for the Laron Syndrome, which is characterized by severe growth failure, facial signs, and elevated basal GH concentration, have been mainly found in consanguineous families from Mediterranean, Middle Eastern, and South Asian regions (5). The growth pattern with a gradually decreasing height SDS and midfacial hypoplasia in the presented adolescent were consistent with GHIS. On the other hand, birth data and linear growth in the first years of life were normal, serum IGF-1 values were not severely decreased and no consanguinity was present. In addition, basal GH concentration was normal. However, no increase in IGF-1 and IGFBP3 were documented during the IGF1 generation test, pointing to a GHR abnormality.

Conclusion: In children with ISS and low serum IGF-1 and IGFBP3 concentrations, an IGF-1 generation test is helpful in detecting GHIS. Patients with GHR gene mutations do not always present elevated basal GH levels, while early growth deficit and facial signs might be minimal.

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Clinical characteristics of children with congenital combined growth hormone deficiency without associated syndrome in Belgium

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Background: Despite the fact that pituitary stalk interruption syndrome (PSIS) is a frequent finding in children with combined growth hormone (GH) deficiency (CGHD), clinical data are still limited and the growth response to GH treatment has not been evaluated in comparison with CGHD with a normal stalk.

Objective and hypotheses: To report the clinical and hormonal findings and evaluate the short-term growth response to GH in Belgian children with congenital non-syndromic form of CGHD presenting with and without PSIS at MRI.

Method: This retrospective study includes 59 children with a congenital form of CGHD without additional cerebral anomalies, who were started on GH treatment between January 1996 and December 2011. MRI, hormonal, and growth data at start and in the first year of GH therapy, which were recorded in the national GH database of the BESPEED, were analyzed. The patients were divided into two groups: one with and the other without pituitary stalk abnormalities.

Results: In 36 (61%) of the 59 patients with GH deficiency and another pituitary hormone deficiency at start of GH therapy PSIS was diagnosed on MRI. The median peak of GH level after pharmacological stimulation was similar (1.6 and 1.5 ng/ml, respectively) between PSIS and non-PSIS patients. The mean age at start of GH was 6.1 years (6.7 years for patients with PSIS and 5.3 years for patients without stalk involvement). In patients with and without stalk involvement, TSH deficiency was present in, respectively, 97% and 83% of cases, ACTH deficiency in 78% and 52% ($p = 0.04$), and LH/FSH deficiency in 55% and 35% ($p = 0.04$). During follow-up, 75% of PSIS patients developed additional deficiencies, compared to 48% of patients without stalk involvement. The height gain in the first year of GH therapy was similar, respectively, 11.6 cm (4.2 cm; range 5.7 – 29.4 cm) or 1.2 SDS and 11.1 cm (5.8 cm, range 1.5 – 29.8 cm) or 0.8 SDS.

Conclusion: Pituitary stalk anomalies are a frequent finding in patients with congenital non-syndromic CGHD. Compared to congenital CGHD patients with a normal pituitary stalk, PSIS patients are diagnosed at a similar age, but have a higher risk of developing additional pituitary hormone deficiencies

(ACTH and LH/FSH deficiencies) during GH therapy. A similar degree of GH deficiency at pharmacological stimulation tests as well as a similar initial height gain in response to GH treatment was evidenced.

Low serum FT₄ and cortisol concentrations in early onset hyperphagic obesity: a clue to SIM1 deficiency

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Introduction: Although hypothyroidism, leptin deficiency or resistance, and POMC deficiency are rare causes of infantile obesity, thyroid function tests, leptin and cortisol determinations are routinely performed in the work up of infantile obesity. The finding of low serum FT₄ and cortisol concentrations should suggest beside a POMC deficiency, a hypothalamic disorder, including single minded 1 (SIM1) gene deficiency. We report the clinical and hormonal findings in a girl with a 6q16 deletion, including the SIM 1 gene.

Case report: A 10-year-old girl with early onset obesity, hyperphagia, and mental retardation, was seen in our obesity clinic for additional endocrine investigations. Her parents were not consanguineous. Her father was known with persistent enuresis nocturna and his BMI was 35.9 kg/m². Her mother had a gastric bypass, decreasing her BMI from 53.9 kg/m² to 25 kg/m². Her only brother and paternal grandparents had severe overweight as well. She was born at 40 weeks of gestation with a normal birthweight and birthlength. Her psychomotor development was delayed and behavioral problems increased with age. Because of learning difficulties, she received special education type 8. She presented with hyperphagia and increasing body weight from the first year of life. From the age of four years, she had polydipsia (drinking 4 liter a day) with polyuria and enuresis nocturna. Previous hormonal and metabolic investigations had shown a partial urinary concentration deficit during a water deprivation test, a low FT₄ with normal TSH concentration, an elevated leptin concentration for age, but normal for degree of obesity, and insulin resistance on OGTT. Genetic studies included a normal karyotype and a negative screening for Prader-Willi syndrome (PWS) and for MRC4 gene mutation. Brain MRI imaging was normal. Primary familial obesity had been diagnosed. Dietary counseling was given, but her overweight increased further. Low FT₄ and cortisol concentrations were found at repeated laboratory examinations. At physical presentation at our clinic at the age of 10 years, her body weight was 96 kg, height 161 cm, head circumference 56 cm, BMI 38.0 kg/m², blood pressure 147/96 mm Hg, pulse 75 per minute, and Tanner stage A1P1M1. Facial dysmorphic features including a coarse and flat face, small upper lip, pointed chin, and low implanted ears were present. She had bilateral genu valgus, short hands, and global hypotonia. Additional laboratory investigations showed an increased uric acid and confirmed the low FT₄ (7.4 ng/L) and low basal cortisol (45 µg/L) concentration. A TRH test showed a high TSH reserve and a CRH test showed an exaggerated ACTH response. A microarray revealed a deletion on chromosome 6 (arr [hg 19] 6q16.1q16.3 (96,037,310–102,931,814)x1).

Discussion: A 6q16 deletion syndrome, which is a contiguous gene-deletion syndrome including the SIM1 gene, was diagnosed in this girl presenting with unexpected thyroxine and cortisol levels for primary obesity (1). Diagnosis of this genetic syndrome was missed during earlier investigations for diabetes insipidus, hyperphagic infantile onset obesity and behavioral problems. In mice, postnatally induced Sim1 deficiency causes hyperphagic obesity and defective hypothalamic TRH, CRH, oxytocin, and ADH expression (3,4). In humans, loss of function SIM1 variants may cause human obesity with or without PWS-like features (2).

Conclusion: 6q16 deletion syndrome should be excluded in hyperphagic children with early onset obesity, developmental delay, learning difficulties, and behavioral problems.

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Incidence and predisposing factors for the development of disturbed glucose metabolism and diabetes mellitus after intensive care admission: the DIAFIC study

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Introduction: Stress hyperglycemia (SH) is commonly observed during hospitalization in the intensive care unit and adversely influences outcomes [1]. When SH occurs in previously non-diabetic patients, this might reflect a latent disturbance of glucose metabolism and predict future risk of diabetes.

We wanted to assess the incidence of disturbed glucose metabolism (DGM) and identify predictors for future diabetes risk. This could support timely diagnosis, prevention, and early treatment of impending diabetes mellitus (DM).

Methods: In this prospective observational study, we enrolled 338 patients without known DM, who were admitted for at least 36 h to the ICU of the Antwerp University Hospital between September 2011 and March 2013. A 75 g oral glucose tolerance test was performed six to nine months post-ICU admission to screen for disturbed glucose metabolism. Furthermore, we examined whether post-discharge glucose disturbances could be predicted by the FINDRISC questionnaire [2], patient demographics, comorbidities, HbA1c at ICU admission, and by parameters related to ICU stay (glucose parameters, insulin need, caloric intake, disease severity).

Results: In total, 246 patients (73%) experienced SH during ICU stay. Eight months post-ICU admission, glucose metabolism was disturbed in 119 (35%) subjects. Of these, 27 (8%) had impaired fasting glucose, 43 (13%) had impaired glucose tolerance, 25 (7%) had impaired fasting glucose and impaired glucose tolerance, and 24 (7%) were diagnosed with DM. A disturbed glucose metabolism tended to be more prevalent in subjects who experienced SH during ICU stay as compared to those without SH (38% vs. 28%, $p = 0.065$). HbA1c on admission correlated with the degree of SH ($r = 0.308$, $p < 0.001$). The FINDRISC score (9.5 vs. 11, $p = 0.001$), SAPS3 score (median of 42 in both groups, $p = 0.003$), and daily caloric intake during ICU stay (222 vs 197, $p = 0.011$) were associated with a DGM.

Conclusions: Stress hyperglycemia is frequent in non-diabetic patients and has a tendency toward future disturbances in glucose metabolism and diabetes mellitus. Glucose metabolism was disturbed in 35% of subjects eight months post-ICU-admission, of whom 7% was diagnosed with diabetes mellitus. Predictors of elevated risk included a high FINDRISC score, high SAPS3 score, and a lower daily caloric intake during ICU stay.

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The Findrisc score, visceral adiposity, insulin sensitivity and secretion estimates are independent predictors of type 2 diabetes in obese and overweight subjects

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Aim: The Findrisc score is a valuable tool to screen for patients at risk of developing diabetes, but it was never used in an exclusively overweight or obese population. The aim of this study was to evaluate the Findrisc score in an apparently healthy overweight and obese population without a history of diabetes in Belgium.

Methods: 651 overweight and obese subjects (M/F: 193/458, BMI 38.2 ± 6.1 kg/m², age 43 ± 13 y) were tested for glucose status using OGTT and HbA1c. Anthropometry (CT visceral fat), Findrisc score, HOMA-S, and HOMA-B were determined.

Results: Exactly 50.4% were found to have prediabetes and 11.1% were newly diagnosed with type 2 diabetes, (M/F = 22.2/8.8%). Subjects without diabetes had a Findrisc score of 11 ± 3 , those with prediabetes 13 ± 4 and subjects with *de novo* diabetes 15 ± 5 ($p < 0.001$). The sensitivity of the Findrisc when using 12 as cutoff value was 80.6%, the specificity was 47.8%. Subjects with a Findrisc score ≥ 12 had more visceral fat [203(146–272) vs. 158.5(105–210) cm², $p < 0.001$], higher HbA1c [5.6(5.4–5.9) vs. 5.4(5.2–5.6)%, $p < 0.001$], higher triglycerides [150(107–200) vs. 117(86–168) mg/dl, $p < 0.001$], and higher HOMA-S [3.8(2.4–5.9) vs. 2.8(1.8–4.5), $p < 0.001$] compared to those with a Findrisc score < 12 . Fasting [89(82–98) vs. 83(78–90) mg/dl, $p < 0.001$] and 2 h post-OGTT glycaemia [152(126–181) vs. 130(111–148) mg/dl, $p < 0.001$] also differed. Exactly 81% of the subjects with diabetes had a risk score ≥ 12 . Logistic regression analysis with diabetes status as dependent variable identified the FINDRISC score (OR = 1.102 (95% CI: 1.017–1.195), $p = 0.018$), HOMA-S (OR = 1.690 (95% CI 1.455–1.964), $p < 0.001$), HOMA-B (OR = 0.989 (95% CI 0.986–0.993), $p < 0.001$), and visceral fat (OR = 1.102 (95% CI 1.017–1.195), $p = 0.027$) as an independent risk factor. From the risk factors which are included in the Findrisc model, age [OR = 1.048 (95% CI 1.024–1.074), $p < 0.001$], waist [OR = 1.029 (95% CI 1.010–1.049), $p = 0.004$], history of high blood glucose [OR = 2.471 (95% CI 1.380–4.435), $p = 0.002$], and the use of blood pressure medication and/or hypertension [OR = 2.702 (95% CI 1.164–6.272), $p = 0.021$] were identified as independent risk factors for diabetes, but not BMI, physical activity, eating habits, nor familial diabetes in this exclusively overweight and obese population.

Conclusion: In an exclusively overweight and obese population, 50.4% of the subjects were found to have prediabetes and 11.1% were newly diagnosed with type 2 diabetes. The Findrisc score increased with worsening of glucose tolerance status and proved to be an independent predictor of diabetes status, as did HOMA-B, HOMA-S, and visceral fat. The results of this study were presented at the 75th Scientific Sessions of the ADA (American Diabetes Association), Boston, USA, June 2015.

A rare ovarian cause of hyperandrogenism in a hirsute adolescent girl

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Background: In girls the abrupt onset and rapid progression of hirsutism as well as additional signs of virilization are suggestive for an androgen secreting tumor from the adrenal gland or the ovary. Ovarian tumors pose a diagnostic challenge, since they are uncommon, sometimes small and difficult to detect at imaging and/or by venous sampling and may have a variable secretion pattern.

Case presentation: A 13 7/12-year-old girl was referred for unexplained hyperandrogenemia. Since her menarche at the age of 12 10/12 years, she noticed a more rapid hair growth over her chest, abdomen, back, arms, and legs, but also new hair growth at the chin and upper lip. In addition some voice deepening and irregularity as well as prolongation of her menses appeared. No excessive weight gain, galactorrhea or other symptoms were present. No medication, dermal products or nutritional supplements were used. Family history was negative for consanguinity, infertility, rare tumors, and multinodular goiter. Laboratory evaluation showed a borderline high DHEA sulfate (297 µg/dl), a mildly elevated androstenedion (4,35 ng/ml) and 17 Hydroxy progesteron (4.6 ng/mL), but a markedly elevated testosterone (425 ng /dl), while cortisol (12 µg/dl), SHBG (27 nmol/l), LH (7 U/L), FSH (4.9 U/L), and estradiol (40 ng/ml) were normal. ACTH testing showed a normal androgen response. Ultrasound and CT scanning of the adrenals were normal. Pelvic Ultrasound showed normal sized ovaries with small cysts. At referral, body weight was 63.2 kg, height 168.2 cm. Pubertal status was A3P6M4. Blood pressure was 113/80 mm Hg. Excessive hair growth was present on the upper lip, chin, cheek, chest, back, sacral area, abdomen, legs, and arms. (Ferryman Galway score 26). A muscular build, slight acne, no acanthosis nigricans, no male pattern baldness, and cliteromegaly were noticed. Hormonal analysis confirmed the elevated testosterone by LC MSMS (222 ng/dL), showed normal 17 OH progesterone, DHEAS, and androstenedion concentrations. A search for ovarian tumor markers showed an elevated AMH 17.4 mcg/L and markedly elevated Alfa fetoprotein (268 mcg/L), but a normal Inhibin B and normal b hCG. A FDG PET CT scan showed an oval mass with sharp borders (3.1x 2.4 cm) with high peripheral FDG uptake of the right ovary. The mass was confirmed at MRI. An unilateral right oophorectomy was performed laparoscopically. Macroscopic evaluation revealed a solid right ovarian mass of size 4 x 3 x 2.5 cm. Tubular structures, with slightly atypical cells, including clusters of Leydig cells without atypia were seen at microscopy. Histopathological and histochemically the diagnosis of Sertoli-Leydig Cell Tumor (SLCT) was made.

Discussion: The initial elevation of both adrenal androgens and testosterone led to the suspicion of a late onset adrenal hyperplasia or an adrenal tumor. These adrenal causes were excluded by dynamic testing and imaging. The high/normal gonadotropin levels were against the exogenous administration or cutaneous contact with testosterone. On the other hand, normal gonadotropin levels have been observed in adolescents with testosterone producing tumors and are explained by a low degree of aromatization to estradiol. There are three ovarian tumors that can cause hirsutism and virilization: SLCT's, lipid cell tumors, and hilus cell tumors. SLCT's account only for 1% of all ovarian neoplasia, occur more commonly in the second or third decade and seldom secrete alpha-fetoprotein. The experience with fluorodeoxyglucose-PET scanning is limited, but was helpful for tumor localization in our case.

Conclusions: Ovarian malignancy should be suspected in case of severe clinical features of hyperandrogenism and a very high (> 200 ng/dl) serum testosterone in hirsute adolescent girls. Ovarian tumor markers as well as FDG -PET scanning might be helpful in diagnosing ovarian malignancy.

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Total thyroidectomy: a clue to understand the metabolic changes induced by subclinical hyperthyroidism?

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Aim of the work: The effects of subclinical hyperthyroidism on bone and heart have been well documented. Effects on other parameters like lipids metabolism and weight regulation have also been reported but mainly in cross-sectional studies. The impact of treatment of endogenous subclinical hyperthyroidism is more controversial as few large controlled studies showing benefit in clinical outcomes have been performed. The aim of our work was to evaluate changes in body weight and lipids parameters following total thyroidectomy in patients with subclinical hyperthyroidism and with euthyroidism. Any potential differences between both groups regarding changes in weight gain or in lipids parameters will suggest a direct effect of the correction of subclinical hyperthyroidism

Methods: All of the 422 files of patients who underwent total thyroidectomy between 2006 and 2010 and who had a follow-up in Erasme Hospital were retrospectively reviewed and separated into two groups according to their preoperative thyroid status: one group with preoperative euthyroidism (EUT), one group with preoperative subclinical hyperthyroidism (SCH). 226 patients were excluded from the study. The causes of exclusion were: overt hyperthyroidism or treatment with anti-thyroid drugs ($n = 57$), overt or subclinical hypothyroidism ($n = 12$), treatment with L-thyroxine ($n = 37$), cancer including thyroid cancer ($n = 90$), any condition likely to affect weight changes during follow-up such as pregnancy ($n = 15$), or bariatric surgery ($n = 7$), other causes ($n = 8$). TSH levels, evolution in weight, and serum lipids values were recorded up to 3 years after surgery. Patients were included in the study if at least one body weight was reported in their file during the 6 months 3 years follow-up. Results are expressed as means \pm SEM

Results: Out of the 196 eligible patients, 120 had at least one body weight reported in their file during the 6 months 3 years follow-up period and were included in the study: 77 (64,2%) had preoperative EUT and 43 (35,8%) had pre-operative SCH. Preoperative median TSH was 1,00 U/L in the EUT group and 0,18 U/L in the SCH group ($p < 0.01$) Mean follow-up time was 26,2 \pm 0,8 months and did not significantly differ between the two groups. Before surgery, BMI of patients with euthyroidism and subclinical hyperthyroidism were 27,33 \pm 0,45 kg/m² and 25,88 \pm 0,95 kg/m², respectively (NS). Post-surgery median TSH levels were similar in the two groups. Maximal weight gain (defined by the difference between preoperative weight and the maximal weight observed during the 6 months 3 years follow-up) was significantly higher in the SCH group (+ 5,07 \pm 0,70 kg) than in the EUT

group ($+ 2,38 \pm 0,48$ kg); $p < 0,01$. Increase in BMI was also higher in the SCH group (from $25,88 \pm 0,95$ kg/m² to $27,79 \pm 1,09$ kg/m²) than in the EUT group (from $27,33 \pm 0,45$ kg/m² to $28,18 \pm 0,52$ kg/m²); $p < 0,01$. Most of the weight gain was already observed within the first 18 months of follow-up. After surgery, a significant increase in LDL cholesterol values of $13,3 \pm 5,7$ mg/dl ($n = 20$, $p < 0,05$) was observed in the SCH group and not in the EUT group ($4,3 \pm 4,5$ mg/dl, $n = 40$, $p = 0,34$).

Conclusion: In the follow-up of patients undergoing thyroidectomy for multinodular goiter, weight gain, and raise in serum cholesterol were significantly higher in the group with preoperative subclinical hyperthyroidism than in the euthyroid group. As postoperative TSH values were similar in both groups, this observation is probably only due the correction of subclinical hyperthyroidism. Ours results strongly suggest that alteration in body weight regulation and lipid metabolism caused by subclinical hyperthyroidism are reversible after normalization of thyroid function.