Fria föredrag

The liver-alpha-cell axis during weight loss in type 2 diabetes

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Background and aims: The concept of a liver-alpha-cell axis has recently been described: increasing levels of amino acids stimulate glucagon secretion which, in turn enhances amino acid turnover in the liver by increasing ureagenesis. Thus, alpha cell function is essential for maintaining normal amino acid levels. Alanine and glutamine in particular are reported to stimulate glucagon secretion and alpha cell proliferation, respectively. We aimed to investigate the effect of weight loss by a Paleolithic diet with/without exercise on fasting amino acids, endogenous glucose production (EGP) and glucagon levels during a mixed meal to elucidate the liver-alpha-cell axis.

Materials and methods: Thirty-two overweight patients with type 2 diabetes were randomized to either a Paleolithic diet (PD) or a Paleolithic diet combined with supervised exercise (PD-EX). Subjects were served a solid mixed meal test at baseline and after 12 weeks. Glucose, insulin and glucagon were measured at 0, 30, 60, 120 and 180 min with calculation of the total area under the curve for the response. On another study day, fasting glutamine and alanine were measured with GC-MS and suppression of EGP was examined with the hyperinsulinemic euglycemic clamp technique with [6,6-2H2]glucose as a tracer and with an insulin infusion of 40 mU/m2/min.

Results: Median weight loss was 7 kg in both study groups. Fasting glucagon tended to decrease in both study groups. Postprandial glucagon decreased by 22 % in the PD-group ($P<0.01$) and by 21 % in the PD-EX group ($P=0.13$). Fasting alanine decreased in the PD group ($P<0.01$). Fasting glutamine increased non-significantly in both groups. Suppression of EGP increased by 26 % in the PD group ($P<0.05$) and by 10 % in the PD-EX group ($P=0.75$). The increased suppression of EGP during the intervention, was associated with a) reduction of postprandial glucagon levels ($rS=-0.65$, $P<0.01$), b) decreasing fasting glucagon levels ($rS=-0.51$, $P<0.05$) and c) the increasing fasting glutamine levels ($rS=0.66$, $P<0.001$).

Conclusion: Weight loss decreases glucagon levels in concert with improved suppression of endogenous glucose production of the liver/kidney. The latter is associated with increasing glutamine levels, which may be involved in the regulation of the liver-alpha-cell axis.

White matter lesions are associated with cranial radiotherapy and reduced hypothalamic volume in childhood onset craniopharyngioma

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Context: White matter lesions (WML) are pathological changes caused by obstruction of small cerebral vessels resulting in hypo-perfusion of the brain microvasculature. Adult patients with childhood onset craniopharyngioma (CP), particularly those with hypothalamic lesion (HL), have persistently increased cardiovascular (CV) risk and cerebrovascular mortality.

Objective: To analyse WML among CP patients by comparing CP patients with HL to CP patients with intact hypothalamus and matched controls. Further, possible associations with the presence of CV risk factors to WML were analysed.

Design: A cross-sectional study of childhood onset CP involving 3 Tesla MRI, was performed at median 22 years after first operation (6-49).

Setting: The South Medical Region of Sweden (2.5 million inhabitants).

Participants: Included were 41 patients (24 women, ≥17 years) surgically treated for childhood-onset CP, between 1958-2010. The median age was 35 (range: 17-56). Thirty-two controls with similar age and gender distributions were recruited. HL was found in 23 patients. After exclusions, 35 patients and 31 controls remained in the study.

Main outcome measures: A qualitative measurement of WML was performed based on the visual rating scale of Fazekas. In addition, a quantitative automated segmentation of WML was performed generating a total lesion volume. WML was explored in relation to HL and cranial radiotherapy (CRT).

Results: The CP patients had a significant increase in total WML volume compared to matched controls. Patients with CRT (n=12) had a significant increase in WML volume compared to patients without CRT (n=24). HT volume correlated negatively with WML volume only among CP patients ($r = - 0.612$, $P < 0.001$). Among patients, having CRT showed a positive correlation with WML volume and age at investigation ($r = 0.391$; $P = 0.018$). When HT volume, CRT and age at investigation where included in a linear regression model simultaneously they explained 47% of the variation in WML volume.

Conclusions: CP patients, particularly those who have a reduced HT volume and are treated with CRT have increased WML volume. Assessment of WML in CP may create an opportunity for early preventive treatment of CV diseases and stroke.

Comorbidities in 419 patients with Cushing´s disease in remission - A Swedish Nationwide Study

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Background: Patients with Cushing´s disease (CD) in remission have increased mortality compared to the general population. To date, large cohort studies, performed to assess long-term comorbidities in patients with CD, are lacking.

Objective: To study the incidence of cardiovascular diseases, sepsis, fractures and cancer in an unselected nationwide cohort of patients with CD.

Methods: Patients with CD, diagnosed between 1987 and 2013, were identified in the Swedish National Patient Registry. Medical records were systematically reviewed to verify the diagnosis and remission status. Standardized incidence ratios (SIRs) for comorbidities after CD was diagnosed, with 95% confidence intervals (CI), were calculated by using the Swedish general population as the reference.

Patients: A total of 502 patients had confirmed diagnosis of CD. Of these, 419 (83%) patients [325 (78%) women] were in remission at the last follow-up, and thereby eligible for the analysis. The mean±SD age at diagnosis was 41±15 years and median (interquartile range) time in remission was 10 years (4-21). Out of 419 patients in remission, 315 (75%)

had been treated with pituitary surgery, 116 (28%) with radiotherapy and 102 (25%) with bilateral adrenalectomy.

Results: SIR in patients in remission was 2.6 (1.9-3.4) for stroke, 1.8 (1.1-2.6) for myocardial infarction, 4.4 (2.5-7.1) for pulmonary embolism and 3.4 (1.8-6.0) for deep vein thrombosis. The risk for sepsis was markedly elevated with a SIR of 5.8 (3.8-8.4). SIR for all fractures was 1.7 (1.3-2.1), 2.6 (1.4-4.6) for wrist fracture and 1.6 (0.9-2.6) for hip fracture. The overall incidence of cancer was not increased [SIR 1.2 (0.9-1.5)] in comparison with the background population.

Conclusions: This large nationwide study shows that patients with CD in remission have an increased risk for cardiovascular disease, thromboembolism, fractures and severe infections. The excess morbidity in these patients illustrate the importance of early identification and management of risk factors for these comorbidities during long-term follow-up.

Tre systrar med heterozygota varianter i CYP24A1, maternell hyperkalcemi, temporär hypertoni och neonatal hypoglykemi

Fredric Hedberg, Christina Pilo, Johan Wikner, Ove Törring och Jan Calissendorff

Bakgrund: En mycket ovanlig orsak till hyperkalcemi under graviditet är genetiska varianter i CYP24A1, som kodar för enzymet 24-hydroxylas. Mutationer som innebär förlorad funktion i CYP24A1 resulterar i minskad dehydroxylering av aktivt D-vitamin (calcitriol). Sekundärt till detta kan hyperkalcuri, hyperkalcemi och låga nivåer parathormon utvecklas. Dessa genetiska varianter är sällsynta och konstateras vanligen hos barn exponerade för d-vitaminprofylax. Dessa barn utvecklar nutritionssvårigheter, hyperkalcuri, nefrokalcinos och låga parathormon nivåer. Även hos vuxna med hyperkalcemi och recidiverande njursten finns de genetiska varianterna beskrivna. Nyligen beskrevs en homozygot genvariant i CYP24A1 som orsakade hyperkalcemi under graviditet. Vi beskriver här hyperkalcemi under graviditet hos två av tre systrar med kombinerade heterozygota CYP24A1 mutationer. Systrarna utvecklade också hypertoni under senare delen av graviditet och post- partum.

Metod: Vi undersökte retrospektivt journaler och registrerade calcium nivåer under och efter graviditet, hos tre systrar som tillsammans födde nio barn. Alla systrar genomgick också genetisk undersökning.

Resultat: Två av tre systrar, B och C, utvecklade hyperkalcemi under alla 7 graviditeter, och sent debuterande hypertoni. Dessa båda systrar hade två genetiska varianter i CYP24A1; c1186C>T och c443T>C. En tredje syster hade enbart c1186C>T varianten och var normokalcem. Båda systrarna utvecklade hypertoni som accentuerades post-partum för att senare normaliseras. Av sju barn till systrarna med kombinerade varianter hade fyra hyperkalcemi och fem hade också hypoglykemi som spädbarn. Kalcium normaliserades inom 5–9 månader hos mödrarna, och glukos och calcium inom veckor hos de nyfödda barnen.

Konklusion: Kombinerade varianter i CYP24A1 orsakade långvarig gestationell hyperkcalcemi och sent debuterande hypertoni. En konsekvens hos nyfödda till mödrar med dessa varianter kan bli hyperkalcemi och hypoglykemi som kräver omgående behandling. CYP24A1 mutationer ska övervägas vid oförklarlig hyperkalcemi bland annat under graviditet. De sammantagna effekterna under graviditet är en ny observation.

Posters

P1
Kortisolsvikt hos patienter som genomgått hypofyskirurgi pga icke- hormonproducerande hypofysadenom, nationell uppföljning i Svenska Hypofysregistret.

Nasrin Al-Shamkhi, Katarina Berinder, Henrik Borg, Per Dahlqvist, Bertil Ekman, Daniel S Olsson, Oskar Ragnarsson, Eva Rask, Britt Edén Engström

Icke- hormonproducerande hypofysadenom (NFPA) är svårdiagnosticerade då symtomen ofta är diffusa och utvecklas långsamt. NFPA upptäcks inte sällan som ett bifynd vid röntgenundersökningar (1). NFPA orsakar ofta brist på ett eller flera av hypofyshormonerna vilket kan leda till en försämrad livskvalitet. Det är mycket viktigt att identifiera en eventuell ACTH- och därmed kortisolsvikt och initiera substitution. Tidigare studier är motstridiga gällande postoperativ återhämtning av preoperativ hypofyssvikt (2, 3). Vårt syfte var att studera ACTH-svikt hos patienter med NFPA före och efter transsfenoidal operation. Studiepopulationen har erhållits genom utdrag från Svenska Hypofysregistret (från 2018-02-26) och består av 1 322 icke- strålbehandlade patienter med NFPA som opererats transsfenoidalt mellan åren 1991–2014, varav 908 hade någon form av postoperativ uppföljning.

Preoperativt hade 28% (370/1 322) av patienterna ACTH-svikt, 61% hade ej svikt och för 11% saknades uppgift eller så var de ej bedömbara. Bland de 590 patienterna med både preoperativa data och 1-års uppföljning hade 33% (194/590) ACTH-svikt preoperativt och 42% (248/590) postoperativt. Nytillkommen ACTH-svikt 1 år postoperativt rapporterades för 17% (103/590) av patienterna medan 8% (49/590) hade återhämtat sig från en preoperativ svikt. Validering av registerdata genom journalgenomgång bekräftade att 27 av dessa 49 patienter hade en säkerställd svikt preoperativt, två var kliniskt misstänkta och i fyra fall var det osäkert om det förelåg en preoperativ svikt. Två patienter hade ingen svikt preoperativt och för resterande 14 patienter har ännu ingen eftergranskning genomförts. Bland 348 patienter med preoperativ, 1-års och 5-års postoperativ data hade 24% (84/348) ACTH-svikt preoperativt och även postoperativt. 44% utvecklade ingen svikt under uppföljningstiden och 17% drabbades av en nytillkommen svikt 1 år postoperativt. 9% (31) sviktade preoperativt men ej 1 år postoperativt. Ingen verifierad ACTH-svikt utvecklades eller återhämtade sig mellan 1 år och 5 år postoperativt.

Sammanfattningsvis rapporterades preoperativ ACTH-svikt hos 28% av patienterna med NFPA. Hos en mindre andel av dessa patienter sker en återhämtning av ACTH/kortisolaxeln. Frekvensen av återhämtning förefaller dock lägre än vad vissa tidigare studier visat och talar inte för att återhämtning av ACTH/kortisolaxeln skulle vara en operationsindikation.

P2
GH-pattern with high troughs found after daily sc rhGH-injections in children.

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Background: Endogenous GH pattern is characterized by high peaks (i.e. the growth signal) and low troughs (i.e. the metabolic signal). Exogenous GH given by subcutaneous

injections (scGH-injection) daily at bedtime was studied in children that were longitudinally followed.

Objective and hypotheses: To study pharmacokinetics, i.e. the pattern of the serum concentration of the injected GH and the factors influencing intra-/interindividual variation of the pharmacokinetics.

Method: 128 subjects were followed yearly ≤8yrs with GH-curves after deep sc injections using 12 mm needles, with GH doses GH33/GH67µg/kg. The EXPerimental setting consisted of 59 GH-curves from 15 patients with multiple pituitary hormone deficiency (MPHD) while the CLINical setting consisted of 429 GH-curves from 117 patients with isolated growth hormone deficiency (IGHD) or non-GHD short stature. Tmax (h) at maximal GH-concentration Cmax (mU/L), area under the curve (AUC) mU/L and GHpeakwidth were estimated.

Results: Interindividual variability, median (coefficient of variance, %), was for Cmax 71(44), AUC 534(42); intra-individual variability was for Cmax 71(38), AUC 534(36). A positive GH-concentration dependency 16 vs 4 IU/ml, p=0.025 and a GHinj time dependency, evening vs morning (p=0.0014) was found. There was a dose-dependency with Cmax 63(51) vs 103(46), p<0.001, and AUC 464(45) vs 865(37), p<0.001, GH33 vs GH67 respectively. 43% of both Cmax and AUC-variation could be explained by the GH-dose and indirect measurements of the injection depth, i.e. GHpeakwidth and BMISDS . 15% of the EXP-GHcurves and 60% of the CLIN-GHcurves had not returned to zero-level before the next injection.

Conclusion: More than half of all the GH-curves have an extended time to return to undetectable GH-level before the next injection, which was unexpected. The importance of that persistent GH-level has been shown to promote IGF-I and metabolism, whereas it is less effective to promote growth. The GH pattern of the scGHinj was characterized by a peak after approximately around 3h (signal for growth), higher after a deep evening injection with the higher GH dose and the higher GH concentration with great intra-/interindividual variability that was mainly explained by injection depth.

P3
Vitamin D levels in thyrotoxicosis; data from the Uppsala Prospective Thyrotoxicosis Study (ProThyr)

Selwan Khamisi, Britt Edén Engström, Östen Ljunggren.

Background: Thyrotoxicosis is one of the most common endocrine disorders. The condition can be divided into Graves disease, toxic nodular goitres and acute phases of thyroiditis. Of these the autoimmune disorder is of central importance.
Previous studies have shown effects of vitamin D on cell proliferation, apoptosis, differentiation, immune regulation and neurogenesis. Many studies also showed association between D-vitamin deficiency and cardiovascular diseases, cancer, diabetes, infectious diseases, autoimmune diseases, etc. However, it is difficult to be sure whether vitamin D deficiency is the cause or only the consequence of various chronic diseases.
In this report we present the structure of the “Uppsala Prospective Thyrotoxicosis Study (ProThyr) and initial data on the relation between vitamin D status and thyrotoxicosis.

Aims: To create a prospective study with patients newly diagnosed with thyrotoxicosis in order to investigate the pathophysiology, and outcome of current treatment.
To prospectively follow up vitamin D levels in newly diagnosed patients with thyrotoxicosis.

Methods: Thirty nine patients with thyrotoxicosis were recruited at the Uppsala University

Hospital. 25(HO)D measured at diagnosis and 3-6 respective 6-12m after diagnosis and treatment start. Of 39 patients with newly diagnosed thyrotoxicosis, 31 patients have Graves´ disease with positive TRAb, 1 Graves´ disease without TRAb, 5 patients with TNG and 2 patients with thyroiditis. TNG, thyroiditis and patients with D-vitamin supplement have been excluded.
Results: On the first visit, this group had a mean of 25(HO) D at 68.2 nmol/L ,+/-19,23. In follow-up, the mean was 56.99 nmol/L ,+/-17.36 and 57.87 nmol/L ,+/- 19.14, after 3-6 months respective 6-12 months. No D-vitamin deficiency was observed at diagnosis. Furthermore the 25(HO)D levels at 3-6 months were significantly lower compared to levels at the first visit.
Conclusion: No D-vitamin deficiency was observed at time of diagnosis of Graves´ disease and 25(HO) D was significantly lower 3-12 months after diagnosis of thyrotoxicosis. Lower 25(HO) D are likely to occur secondary to chronic disease nature more than triggering factor of thyrotoxicosis.

P4
Camel Milk Rescued Boy from Seizures and Hypoalbuminemia in Undiagnosed 22q11-Deletion Syndrome with Partial Hypoparathyroidism and Proteinlosing Enteropathy

Kristina Linder Ekberg

Background: 22q11.2 deletion syndrome (earlier called DiGeorge or CATCH22) is a congenital disorder caused when a small part of chromosome 22 is missing. This deletion results in the poor development of several body systems including parathyroid hypoplasia

Clinical Case: This Egyptian 18 year old boy was referred to us due to hypocalcemia and severe D-vitamin deficiency. Since childhood he has a proteinlosing enteropathy due to lymphangioectasies in duodenum with severe hypoalbuminemia and a need for albumin transfusions daily. He also has immune deficiency, a cleft palate, speech problems and a cognitive mental retardation. He was from childrens department prescribed 6 g daily of calcium and ergocalciferol mixture as well as albumin transfusions. He also had an epilepsy diagnosis due to minor and major seizures. For an endocrinologist the di George syndrome (22q11.2 deletion) was strongly suspected and soon verified by genetic analysis.

Very interesting is the observation of the father that fresh camel milk could substitute both calcium and albumin-medication and in periods with regular camel milk he had no seizures and normalized albumin. Unfortunately he could not afford to import regularly.

Diagnostic evaluation First visit 2015: Ca++ 0.84 (1.13-1.33 mmol/L), phosphate 1.4 (0.7-1.6 mmol/L), PTH 4.5 (1.1-6.9 pmol/L), 25OHvit D 17 nmol/L (50-250 nmol/L), Albumin 16 (36-48 g/L)

Treatment Hypoparathyroidism is now treated with Alfacalcidiol 4.5 ug,1.5 g Calcium and 500 mg Magnesiumhydroxide daily. Parenteral treatment of the D-vitamin deficiency with 100000 U of cholecalciferol every second month. Daily MCT-oil is recommended. 120g Albumin is given nightly i-v.

Follow-up With abovementioned substitution calciumlevels are stabilised around lower reference limit (free calcium 1.15 mmol/L) and vitamin D normalised, the patient has no or seldom minor seizures.

Clinical Lesson Partial hypoparathyroidism is often missed due to the belief that normal PTH-levels excludes hypoparathyroidism. In this situation with both a severe D-vitamin

deficiency and a severe hypocalcemia PTH should have been high, a value in the normal range proves hypoparathyroidism. This is known by most endocrinologists but other specialities needs reminding, this boy would probably have had his syndrome diagnosed much earlier if the hypopara-diagnosis had been there.

The reported positive effects of fresh camel milk on calcium levels and even more interestingly on albumin levels needs further studies. There are reports of anti-inflammatory properties of camel milk and possibly there might also be an PTH-RP effect since best effect was observed by milk from a mother to her first newborn camel.

P5
Sjuksköterskebaserad binjureincidentalom-mottagning.

Linda Viborg och Jeanette Wahlberg-Hughes

Introduktion
Undersökningar har visat att 1-5 % av den vuxna befolkningen har förändringar i ena eller båda binjurarna. Med adrenalt incidentalom (AI) avses accidentellt upptäckt expansivitet i binjuren hos patient utan känd malignitet.

Syfte
Att efter 18 månader utvärdera en sjuksköterskebaserad mottagning för adrenala incidentalom definierad från nationella och internationella rekommendationer.

Metod
Patienter med binjureincidenatalom som remitterats till endokrinklinik bokas till sjuksköterskemottagning.

Sjuksköterskan genomför en strukturerad anamnes och rutinstatus med fokus på symptom på hormonstörning, malignitet och hypertoni. Mätning av Na, K, kreatinin, dexametasontest (över natt, 1 mg), fraktionerade metoxykatekolaminer i plasma (”plasmametanefriner”) alternativt metoxykatekolaminer i dygnsurin. Vid hypertoni eller hypokalemi analyseras p-aldosteron/renin.

Resultat
Totalt 48 individer (23 kvinnor och 25 män; medianålder 69 år (range 30-86 år)) undersöktes. Medelstorleken på binjuretumören (vid bilateral tumör räknas på största tumör) var 2,2 cm ± SD, (range 0,9-4,8 cm). Tjugo procent (n=10) var bilaterala incidentalom. Tumörernas täthet angavs som Houndsfield Units: HU < 10 (61 %); HU 10-20 (30 %) och HU >20 (9 %). Sammanlagt 13 patienter bedömdes ha förhöjda hormonvärden i olika kombinationer och av dessa hade 11 hypertoni (varav 2 diagnostiserades vid besöket). Tio patienter hade P-kortisol 51-138 nmol/L vilket bedömdes som möjlig autonom kortisolproduktion. En patient diagnostiserades med overt adrenalt cushingsyndrom (P-kortisol 462 nmol/L) och en patient med misstänkt cushing syndrom (194 nmo/L) efter 1 mg dexametason hämning. Fyra individer hade förhöjd aldosteron/reninkvot varav 3 av dessa patienter även hade patologiskt dexametasonhämningstest (73, 194, 462 nmol/L). Ingen patient hade signifikant förhöjda metoxykatekolaminer. S-Kortisol efter dexametasonhämning korrelerade signifikant med systoliskt blodtryck, r=0,54, p=0.0001 och tumörstorlek r=0.33, p=0.038. Hittills har 38 (79%) av de 48 patienterna kunnat avskrivas. Mediantiden från att remissen inkommit till avskrivning var 3,1 månader (range 1,1-14,8).

Diskussion
Sammanlagt fann vi avvikande hormonprover hos 27 % (13/48) av undersökta patienter. Hypertoni var vanligt och är en behandlingsbar komplikation hos patienter med autonom kortisolproduktion och /eller aldosteronproduktion. En sjuksköterskebaserad strukturerad mottagning förbättrar kontinuiteten och leder till hög specificitet och sensitivitet för utredningen avseende hormonöverproduktion och associerade symptom vid binjureincidentalom.

P6
Adrenal Incidentaloma: Clinical Assessment of 483 Patients Evaluated Between 2014-2018.

Fatema Jabarkhel and Oskar Ragnarsson

Introduction: In the West Gotaland County in Sweden, adrenal incidentaloma (AI) was found in 4.5% of all abdominal CT performed between 2002-2004. Of patients with AI, 22% were treated surgically, where half of the patients had a benign non-functioning adenoma.

Aim: The aim of this study was to see how common AIs are in the modern era and to describe the characteristics as well as management.

Methods: This was a retrospective study, performed at the Sahlgrenska University Hospital in Gothenburg. Clinical, radiological, biochemical and histopathological data of all AI referred to the departments of endocrinology and endocrine surgery, between 2014 to 2018, were reviewed.

Results: A total of 483 patients with AI were identified, 289 (60%) women and 194 (40%) men. The median age was 69 years (range 70; IQR 17). The AI was detected by a CT-scan in 456 (94%) patients. Additional imaging was performed in 340 (70%) patients. Four hundred fifty-seven (95%) patients underwent biochemical screening. Benign and inactive lesions were detected in 422 (89%) of the cases. Sixty-nine of these (14% of the whole cohort) had bilateral lesions. Malignant tumours were found in 16 (3%) patients; 8 (1.7%) adrenal metastases, 4 (0.8%) adrenocortical carcinoma and 2 (0.4%) primary adrenal leiomyosarcoma. Hormonally active tumours were found in 38 (8%) patients; 21 (4.3%) pheochromocytoma, 13 (2.7%) primary aldosteronism and 4 (0.8%) Cushing's syndrome. Adrenalectomy was performed in 49 (10%) patients. Ten (20%) of these had a benign non-functioning adenoma.

Conclusion: The majority of AIs are benign and inactive lesions where surgical treatment and unnecessary and extensive follow-up should be avoided. A small but significant number of AIs are either hormone-producing or malignant tumours that need thorough management. The proportion of patients with a benign non-functioning adenoma who are treated surgically has decreased dramatically.

Keywords: Adrenal incidentaloma, pheochromocytoma, primary aldosteronism, Cushing's syndrome, adrenocortical carcinoma.

P7
Effect of Licorice on Late-night Salivary Cortisol

Marcus Imamovic, Nils Bäcklund, Staffan Lundstedt, Göran Brattsand, Elisabeth Aardal-Eriksson, Tommy Olsson and Per Dahlqvist

Context
Late-night salivary cortisol testing is a recommended screening method for suspected Cushing's syndrome. However, the licorice component glycyrrhizic acid inhibits the enzymatic conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase in the salivary glands. Hence, salivary cortisol levels may be falsely elevated after licorice consumption, but further details of this effect need to be established.

Objective
To determine if licorice significantly increases late-night salivary cortisol levels, and if so, what dose yields this effect and how long wash-out period is required for salivary cortisol levels to normalize.

Design
30 healthy volunteers refrained from licorice for four weeks prior to the start of the study. Participants were randomized to a low, medium or high dose of licorice, corresponding to a glycyrrhizic acid dose of 1.5, 3.0 or 6.0 mg/kg body weight. Saliva samples were collected during one week of baseline sampling, one week of daily licorice consumption and four weeks of wash-out. Salivary cortisol and cortisone were analyzed with LC-MS/MS.

Results
Significant increases of salivary cortisol levels were observed during seven days of licorice intake in the medium and high dose groups with a mean increase of 85% and 106% respectively. Significant increases were also seen for the cortisol:cortisone ratio with a mean increase of 104% in the medium dose group and 141% in the high dose group. The salivary cortisol levels returned to baseline three days after licorice withdrawal in both the medium and high dose groups. The cortisol:cortisone ratio returned to baseline levels at the second day after stopping licorice intake in the medium dose group and at the fourth day in the high dose group.

Conclusion
Licorice intake corresponding to a glycyrrhizic acid dose of 3.0 mg/kg body weight leads to a significant increase in late-night salivary cortisol levels. This effect of licorice intake wears off after four days.

P8
Hormonellt inaktiva neuroendokrina pankreastumörer som transformeras till maligna insulinom, beskrivning av fyra fall

C. Christofer Juhlin, Sissela Skoglund, Lisa Juntti-Berggren, Mia Karlberg och Jan Calissendorff

Bakgrund: Funktionella och hormonellt inaktiva neuroendokrina pankreastumörer (Pan-NETs) är ovanliga, men är bland de vanligaste neuroendokrina tumörerna. De är oftast långsamt växande med kapacitet att metastasera, och de-differentiera, vilket kan leda till en mer aggressiv tumör. Mycket sällan kan hormonellt inaktiva tumörer blir hormonellt aktiva. Vi beskriver här fyra patienter med initialt hormonellt inaktiva Pan-NETs som med tiden började producera insulin eller dess förstadier, och orsaka svår hypoglykemi.

Metod: Vi granskade medicinska journaler, biokemi och radiologiska undersökningar. Patienternas vävnadsprover eftergranskades av patolog, och som tillägg utfördes immunhistokemiska analyser.

Resultat: Fyra patienter; tre kvinnor och en man, 51, 61, 65 respektive 68 år gamla vid diagnos, utvecklade maligna insulinom 2, 5, 6 och 7 år efter initial diagnos av hormonellt inaktiva Pan-NETs. Ki-67 var initialt 2, 5 och 6% och steg till 6, 17 respektive 50%. En patient initiala Ki-67 var 5% men kompletterande vävnad analyserades inte. Alla fyra patienter avled till följd av sin cancersjukdom inom 12, 6, 19 och 29 månader efter att behandling för hypoglykemi påbörjats. Klinisk undersökning och/eller eftergranskning av histopatologi bekräftade initial diagnostik av hormonellt inaktiva Pan-NETs med senare transformering till insulin-producerande tumörer.

Konklusion: Hormonellt inaktiva Pan-NETs kan transformeras till insulin-producerande tumörer, vilket försämrar prognos. Kontinuerlig uppföljning krävs av dessa patienter, inte bara klinisk bedömning och radiologi, utan också med biokemi. I fall med mer aggressiv sjukdom föreslås histopatologisk bedömning avseende proliferation och hormonproduktion, för att klarlägga eventuella förändringar i tumörkarakteristika som möjliggör förbättrad terapi och omhändertagande.

P9
The autoimmune targets in IPEX are dominated by gut epithelial proteins

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Regulatory T cells (Tregs) play a key role in immune system homeostasis by suppressing detrimental immune responses against self-proteins. Patients with mutations in the gene FOXP3 display a severe defect of Treg function that results in IPEX syndrome, characterized by multi-organ autoimmunity, particularly enteropathy, type 1 diabetes, and dermatitis. We sought to determine the repertoire of autoantigens in IPEX, to better understand the autoimmune manifestations of this syndrome and to gain new insight to the role of FOXP3-dependent Tregs in peripheral tolerance. To this end, we used a panel of more than 9000 human proteins to characterize autoantibody targets in 14 IPEX patients and 24 healthy controls. Candidate autoantigens were verified using radio-ligand binding assays in an extended group of IPEX patients and additional control groups. The identified autoantigens, which included all previously described autoantigens in the panel and multiple new immune targets, were predominantly expressed in tissues typically affected in IPEX patients – dominated by the intestinal epithelial cell. Our comprehensive investigation of autoantigens in IPEX point to a specific role of T regulatory cells in maintaining the immune tolerance to enterocyte self-antigens.