Concern for a possible ectopic ACTH secretion prompted further investigation with imaging studies such as an abdominal Cat scan which showed no adrenal pathology. Pituitary MRI was ultimately performed which showed no evidence of pituitary lesions.
These were following by an 8mg Dexamethasone suppression test which adequately decreased the ACTH level. However re-check of ACTH levels, after weeks of being on her physiological hydrocortisone dosing, showed that her ACTH levels had started to rise again. Given she had also had multiple admissions for adrenal crises, the concern was raised for possible malabsorption.
Given her risk for auto-antibody development, there was concern for another autoimmune process such as Celiac disease, as a potential cause for malabsorption. Her TTG IgA antibodies were checked, however they were absent.
At this point, the decision was made to use prednisone as a means of suppression of ACTH, and she was given three days of 40mg Prednisone daily, followed by ACTH level testing, which showed a decrease from 2009 to 708. These results prompted us to change her hydrocortisone to prednisone daily dosing instead, and we converted her to a slightly higher dose of Prednisone.
In the setting of underlying DM, this may pose an additional challenge with glycemic control, but we plan for close clinic follow up and repeat ACTH levels a few weeks after she has been on the new prednisone regimen.
Conclusion: This is a rare case of a patient with polyglandular autoimmune syndrome, type 2, with a persistently elevated ACTH level, requiring Prednisone, instead of hydrocortisone for treatment of primary adrenal insufficiency in efforts to reduce ACTH levels.
References: Neufeld M, Maclaren NK, Blizzard RM, Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. Medicine (Baltimore). 1981;60(5):355.

Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

A1AT: Novel Inhibitor of Active PCSK9

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SUN-574

Heart disease is the principal cause of death and disability for both men and women in the US, accounting for 40% of all annual deaths. African American populations are disproportionately burdened with metabolic diseases, due in part to cholesterol metabolism deficiencies. Elevated low density lipoprotein (LDL) cholesterol levels and inflammation promote atherogenic conditions which lead to heart disease. Proprotein convertase subtilisin/kexin-9 (PCSK9) is a biomarker which enhances athrogenic progression by controlling the number of LDL receptor molecules expressed at the plasma membrane. PCSK9 indirectly regulates LDL-cholesterol levels. Previous reports show some patients do not respond well to general anti-cholesterolemic treatments. We believe this is due to altered PCSK9 activity, which is currently not being evaluated. We have developed a novel assay to detect active PCSK9. A1AT is a SERPIN family member whose primary objective is inhibition of proteases. Specific levels of A1AT are required to maintain metabolic homeostasis. Based on this, we hypothesized that a specific ratio between A1AT serum levels and PCSK9 activity levels would eliminate statin intolerance/resistance, regulating LDL-cholesterol metabolism congruently. Using this novel active PCSK9 detection assay, we provide evidence that A1AT interacts with PCSK9 in the medium of C3A hepatic-like cells, preventing the formation of PCSK9/LDL receptor complexes *in vitro*. There was an approximate 20% inhibition in PCSK9-LDL receptor complex formation when liver cells were treated with recombinant A1AT (rA1AT). A dose dependent response analysis proved 200ng/ml of rA1AT had an 46% reduction in PCSK9 activity. We determined PCSK9 activty and A1AT levels correlate with key diabetic factors in humans, suggesting that A1AT could effect diabetes progression.

Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

Subclinical Alpha-1 Antitrypsin Deficiency Is Associated with Increased Free Cortisol Fraction in Plasma and Altered Glucocorticoid Delivery to Tissues

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SUN-221

Background
Corticosteroid Binding Globulin (CBG) binds >85% of plasma cortisol and controls the circulating free cortisol pool. Proteolytic cleavage by neutrophil elastase is proposed to reduce CBG binding affinity and increase free cortisol availability to inflamed tissues. The CORtisol NETwork (CORNET) consortium found that genetic variation at a locus spanning *SERPINA1* (encoding alpha-1 antitrypsin, A1AT, the endogenous inhibitor of neutrophil elastase) and *SERPINA6* (CBG) contributes to morning total plasma cortisol variation. We hypothesised that A1AT deficiency increases CBG cleavage and hence free plasma cortisol, resulting in increased tissue cortisol delivery in adipose and in HPA axis negative feedback. We tested this in recall-by-genotype studies of people who are heterozygous for inactivating mutations in *SERPINA1*.
Methods
16 healthy carriers of one of the two most common A1AT-deficiency single nucleotide polymorphisms (rs17580 &

rs28929474) and 16 age-, gender- and BMI-matched controls were recruited from the Generation Scotland Biobank. Participants underwent combined receptor antagonist stimulation of the HPA axis ('CRASH') testing using RU486 400mg and spironolactone 200mg, or placebo in a double blind randomised crossover design. Plasma free cortisol was measured by isotopic dilution and ultrafiltration, total cortisol by LC-MS/MS, total CBG by ELISA, CBG binding capacity by radioligand displacement assay, and ACTH by immunoassay. Serum A1AT was measured by ELISA. Tissue cortisol (LC-MS/MS) and expression of glucocorticoid dependent transcripts (qPCR) were measured in subcutaneous adipose samples collected by needle biopsy.
Results
Serum A1AT was confirmed lower in those with heterozygous mutations vs wild type controls (411.3 +/- 27.44 vs 565.1 +/- 23.38 mg/dL, p=0.0002). No measurable differences in total CBG or CBG binding capacity were observed. However, plasma free cortisol fraction was higher in those carrying A1AT mutations (16.13 +/- 0.2 vs 13.88 +/- 0.04 %, p<0.0001). Adipose cortisol concentrations were not significantly different but expression of glucocorticoid responsive genes e.g. *PER1* was 54% higher (p=0.014) in A1AT-deficient subjects. Plasma cortisol was elevated during CRASH testing in both groups, with the increment versus placebo tending to be lower in A1AT-deficient subjects (82.5 +/- 6.7 vs 126.7 +/- 6.8 nM).
Conclusion
Alpha-1 antitrypsin mutation heterozygosity, common in the general population, is associated with higher free cortisol fraction, consistent with enhanced cleavage of CBG. This is associated with evidence of enhanced delivery of glucocorticoid to adipose tissues but reduced HPA negative feedback, suggesting tissue-specific control of cortisol delivery by CBG.

Thyroid

THYROID DISORDERS CASE REPORTS III

Anti-Streptavidin Interference in Multiple Hormones Immunoassays: Case Report

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MON-477

Automated immunoassays are the most commonly current methods used in clinicial laboratory to hormone tests, due short turnaround time and high specificity and sensibility. However immunoassays are not free from interferences. Several immunoassays use biotin-streptavidin interaction to anchor antigen-antibody complexes in solid phase and so are susceptible to biotine intake or anti-streptavidin antibody. In sample with these interferents, the results in competitive assays are falsely high and in non-competitive assays are falsely low. OBJECTIVE: To report a case of multiple hormones immunoassay interference by an anti-streptavidin antibody. MATERIAL AND METHODS: A 11-years-old boy with child obesity, and no other symptoms, had discordant laboratory results with markedly elevated free T4, total T4 and total T3 with normal TSH. Repeated measurements in the same sample and in a new collected sample confirmed the initial results and revealed low PTH and high TRAb without hypocalcemia or hyperthiroidism clinical pictures. All the parameters were measured on the automated Cobas e602, Roche plataform.The patient and your family denied biotin ingestion, so anti-streptavidin interference could explain the multiple interference.The serum was pre-incubated with streptavidin microparticles during an hour and centrifuged for 10min (3000 rpm) to removed the analytical interference. RESULTS: The results of post-incubation with microparticles were all in the normal range. Three control samples were not affected by the incubation. Since luminescence is inversely proportional to analyte concentration in competitive assays, low signals lead to falsely high levels (like in free T4, total T4, Total T3 and TRAb in our patient). The reverse occurs with immunometric assays, in which low signals result in falsely reduced values (like in PTH in our patient). CONCLUSION: In literature, streptavidin antibodies seem to be a rare occurrence. In samples with biotin or anti-streptavidin suspection, pre-incubation with streptavidin microparticles is a simple and effective procedure to remove this interference.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

ACVR1 Activation in Primary and iPS-Derived Human Skeletal Muscle Stem Cells Impairs Myogenic Transcriptional Signature and Function

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MON-710

Developing optimal strategies for skeletal muscle regeneration and repair requires a detailed understanding of how these processes are regulated. The number of primary human satellite cells that can be obtained is usually extremely low, and may be impaired in disease of impaired skeletal muscle repair. One such condition is fibrodysplasia ossificans progressiva (FOP), a progressive disease characterized by massive heterotopic ossification in skeletal muscles and aberrant skeletal muscle repair after injury. FOP patients have activating mutations in the Activin A Type I receptor (ACVR1), a bone morphogenetic protein (BMP) receptor. Our overall hypothesis is that activated ACVR1 signaling caused by the ACVR1 R206H mutation incites inappropriate activation of human muscle stem cells (satellite cells, PAX7 expressing cells), causing loss of muscle cell fate and aberrant muscle repair. Since human satellite cells are difficult to obtain from live tissue donors, and injury can trigger heterotopic ossification, we created human induced pluripotent stem cell (iPSC)-derived muscle stem cells (iMuSCs) from FOP and control iPSC lines. We found that control and FOP iPSCs can