bilateral adrenalectomy for CS as she had virilization, hirsutism, hypertension and cardiac hypertrophy 9 weeks old. Adrenalectomy revealed that she had iMAD. She also presented with hemihypertrophy of the right leg, labia and mild newborn hypoglycemia, however she was negative for Beckwith-Wiedemann mutation. Gene analysis of *PRKAR1A* did not reveal any mutations. After whole exome sequencing (WES), we found a novel heterozygous *USP8* variant (c.1387_1393delinsT, p.Ala463_Ile465delinsPhe) at germline level and loss of heterozygosity (LOH) at tumor level. Immunohistochemistry showed significantly lower expression of USP8 protein in both of her adrenals compared to a control tissue.

The second case is a 59-year old female with osteoporosis who failed to suppress cortisol levels after low dose dexamethasone administration. MRI revealed an adenoma on the right adrenal (2.6cm). She underwent right adrenalectomy and was found to have PMAH. We performed WES in germline level and we detected a novel heterozygous missense *USP8* variant (c.287A>G, p.Lys96Arg) that is present also at tumor level. Immunohistochemistry showed significantly lower expression of USP8 protein in her adrenal tumor compared to the control tissue. No LOH was identified.

Conclusion: This is the first report of the association of *USP8* in ACTH-independent CS and the preliminary findings support UPS8 involvement in the development of adrenocortical disease. We are currently performing further in vitro studies to evaluate the effect of these two *USP8* variants into the canonical Wnt pathway which is commonly involved in adrenocortical disorders.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

CXCR2 Repression by Glucocorticoids in Adipose Tissue

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Obesity-induced type 2 diabetes (T2D) is a significant risk factor of cardiovascular disease (CVD), which affects 28.1 million adults in the United States. Adipose tissue chronic inflammation is one of the main factors that drive obesity-induced insulin resistance (IR) and T2D. Despite several studies that have shown a link between obesity, adipose tissue inflammation, and IR/T2D, the mechanisms underlying this association are not well understood. Synthetic glucocorticoids are widely used for their potent anti-inflammatory actions; however, their use is hampered due to off-target side effects. Glucocorticoids exert profound effects on adipose tissue, including the regulation of adipocyte metabolism and immune functions. However, whether their effects on adipose tissue are positive or negative it is still a controversial topic. Genome-wide microarray data obtained from adipocyte-specific glucocorticoid receptor (GR) knockout (AdipoGRKO) mice showed that lack of GR leads to a significant increase in the expression of pro-inflammatory genes in white adipose tissue (WAT). Moreover, WAT isolated from adipoGRKO mice demonstrated significant increase in immune cell infiltration, which correlates with our gene expression data. Among the most up-regulated genes, we found the C-X-C Motif Chemokine Receptor 2 (CXCR2), which is a critical mediator of chemotaxis to the sites of inflammation. Although studies have shown the presence of CXCR2 in adipocytes and suggested the contribution of CXCR2 signaling in adipocyte development, its role in obesity-driven adipose tissue inflammation is unknown. This led us to hypothesize that adipocyte specific administration of glucocorticoids can reduce obesity-induced adipocyte inflammation by inhibiting CXCR2 gene transcription and signaling. Our in vitro studies using 3T3-L1 cells derived adipocytes showed that treatment with the synthetic glucocorticoid, Dexamethasone (Dex) led to a significant repression of CXCR2 mRNA and protein levels. Correlating with these results, Dex treatment significantly inhibited macrophage migration to adipocytes in a mechanism dependent on GR activation and repression of CXCR2. Furthermore, these results were recapitulated in vivo. Together our findings suggest that local delivery of glucocorticoids to adipose tissue could ameliorate inflammation and reduce the risk of developing IR and T2D.

Neuroendocrinology and Pituitary

PITUITARY TUMORS: TRIALS AND STUDIES

Is the Improved Glucose Homeostasis in Patients with Acromegaly Treated with Pegvisomant Caused by Improved Glucagon Secretion?

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Context: Active acromegaly is associated with impaired glucose metabolism, which improves upon treatment. Treatment with first generation somatostatin analogues (SSA) has a detrimental effect on insulin secretion, but the effect on glucose homeostasis is neutralized by the reduction in growth hormone (GH) and Insulin-like growth factor-1 (IGF-1). Treatment with GH receptor antagonists has a more favorable effect on glucose homeostasis.

Objective: To describe the secretion of glucose, insulin, glucagon, glucagon-like peptide-1 (GLP1), and glucose-dependent insulinotropic polypeptide (GIP) in surgically treated patients with acromegaly treated or not with somatostatin analogues, either as monotherapy (SSA) or in co-treatment with pegvisomant (SSA+PEG), respectively, compared to healthy controls.

Methods: Descriptive study of data from 23 surgically treated, non-diabetic patients with acromegaly and 6 healthy controls. After an overnight fast, all participants

underwent a three-hour 75 g oral glucose tolerance test (OGTT) and subsequently a three-hour isoglycaemic intravenous glucose infusion on a separate day. *Analysis:* Baseline hormone concentrations, time to peak and area under the curve (AUC) on the OGTT-day, and the incretin effect in the patient groups and controls were compared using analysis of variance with *post-hoc* analysis.

Results: The total group of patients treated with somatostatin analogues (*N*=15) had numerically impaired glucose, insulin, GLP1 and glucagon responses (AUC, P>0.05 respectively), and an impaired GIP-response (AUC, P=0.007) during OGTT as compared to patients not treated with somatostatin analogues and healthy controls. Similarly, the incretin effect was numerically impaired.

Patients co-treated with pegvisomant (SSA+PEG, *N*=4) had a numerically increased secretion of insulin and glucagon compared to patients on SSA (*N*=11) during OGTT (insulin AUC mean (SEM), SSA+PEG 49 nmol/l*min (8.3) vs SSA 25 (3.4), P>0.05) [*healthy controls 62 (13.6)*]; glucagon AUC, SSA+PEG 823 pmol/l*min (194) vs SSA 332 (69), P>0.05) [*healthy controls 946 (233)*]). GIP secretion remained significantly impaired, whereas GLP1 secretion was numerically increased with PEG (SSA+PEG 3088 pmol/l*min (366) vs SSA 2401 (239), P>0.05) [*healthy controls 3972 (451)*] but remained without a glucose-dependant increase as in SSA. The incretin effect numerically increased in SSA+PEG compared to SSA (SSA+PEG 49.9% (13.9) vs SSA 33.6% (47.4), P>0.05) [*healthy controls 55.5% (7.7)*].

Conclusion: Somatostatin analogues impaired the secretion of both insulin, glucagon and incretin hormones secretion. Co-treatment with pegvisomant seemed to counteract the somatostatinergic inhibition of the glucagon secretion and improved the insulin response to OGTT. We speculate that pegvisomant exerts its action via GH-receptors on pancreatic δ-cells.

Thyroid

THYROID DISORDERS CASE REPORTS III

A Rare Case of Hypocalcemia-Induced Intractable Vomiting Requiring PEG Tube Placement

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Introduction: Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia secondary to inadequate PTH secretion. Clinical manifestations are carpopedal spasm, perioral paresthesia, and seizures. Herein, we present a case of hypoparathyroid-induced hypocalcemia requiring PEG tube placement.

Case Presentation: Patient is a 41-year-old female who presents with intractable nausea, continuous vomiting, abdominal pain, and perioral paresthesia for the past 4 days. Patient has a past medical history significant for hypoparathyroidism, severe hypocalcemia, hypomagnesemia, hyperphosphatemia, and iron deficiency anemia. Patient was diagnosed with hypoparathyroidism at the age of 16 when her son was born with congenital abnormalities due to severe maternal hypocalcemia. She has 4 children, 1 son passed away in infancy from severe hypocalcemia. Out of the remaining 3 children, 2 daughters have hypoparathyroidism. Patient has had multiple recurrent admissions for severe hypocalcemia presenting as angina, syncope, and left-sided weakness. Both cardiology work up and neurology workup have been negative. MRI of the brain shows basal ganglia calcifications. Labs are significant for corrected calcium 6.72 mg/dL (n 8 to 10 mg/dL), magnesium 1.4 mg/dL (n 1.7 to 2.2 mg/dL), phosphorus 7.4 mg/dL (n 2.4 to 4.5 mg/dL), Vitamin D 14.9 ng/mL (n 30 to 100 ng/mL), and PTH level 9.8 pg/mL (n 18.5 to 88 pg/mL). Prior ACTH stimulation test was within normal limits excluding adrenal insufficiency. EGD biopsy on prior admission was positive for H. Pylori, however patient left against medical advice and did not receive triple therapy. Patient was admitted for hypocalcemic crisis and placed on a calcium gluconate drip, oral calcium, magnesium, calcitriol, and Vitamin D, in addition to H. pylori triple therapy. During the hospitalization, she was unable to tolerate oral medications for greater than 2 weeks resulting in PEG placement. The patient's electrolytes were successfully repleted via PEG tube and she was discharged.

Discussion: Spontaneous hypoparathyroidism is a rare metabolic disorder characterized by parathyroid glands that do not produce or secrete enough PTH to maintain normal levels of calcium and phosphorous in the blood. Though GI consequences such as steatorrhea may occur, to our knowledge, this is the first reported case of hypocalcemia-induced intractable vomiting requiring PEG tube. Before PEG placement, the patient had 12 admissions in 1 year. After PEG placement, the number dropped significantly to 4 admissions in 1 year. Due to the unique presentation of hypoparathyroid hypocalcemia, we would like to raise awareness regarding such a presentation which can be challenging for clinicians.

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Adrenal

PROGRESS IN ADRENAL CORTEX AND MEDULLA RESEARCH

New Insights into the Functional Human Adrenal Cortex Zonation

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The zonation of the human adrenal cortex has long been established morphologically and histologically as three distinct layers of cells. The outer zona glomerulosa (ZG) comprises densely packed cells arranged in clusters that produce aldosterone; the zona fasciculata (ZF) is composed of cells with large cytoplasm, containing lipid droplets arranged in radial columns that synthetize cortisol; and the zona reticularis is composed of compact and pigmented cells producing androgens. The main purpose of this