

metabolites were determined, of which 155 were eligible for statistical analyses according to established selection criteria. To identify relevant discriminating metabolites, a series of univariate and multivariate analyses were applied. Since the distribution of the patients between the clinical entities was different according to sex ($p < 0.001$) and age ($p = 0.001$), analyses were also performed separately for each sex and age group (cut-off 50 years). Thereby, we identified 4 common metabolites (C18:1, C18:2, spermidine, ornithine) from the comparison of PHT with each endocrine hypertension subgroup (CS, PA, PPGL) separately. The ROC curve for discrimination between PHT and EHT built upon these 4 metabolites had an area under the curve (AUC) of 0.79 (95%CI 0.73-0.85). In the comparison of PHT and EHT as a common group 38 metabolites were identified. Using the top 15 metabolites from the latter comparison (C3-DC, C9, C16, C16:1, C18:1, C18:2, arginine, aspartate, glutamate, ornithine, spermidine, lysoPCaC20:4, PCaaC38:6, PCaaC40:6, PCaaC42:1) the AUC was 0.86 (95%CI 0.81-0.91). We conclude that TM is associated with distinct metabolic pattern in PHT and EHT and is a promising pre-screening tool for identifying EHT patients.

Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Metformin Attenuates Sodium Retention and Blood Pressure in Hypertensive Diabetic Mice by Reducing the Phosphorylation of Renal NCC and Its Association With the Actin Cytoskeleton

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Metformin is the first-line drug in the treatment of type 2 diabetes mellitus. The aim of this work was to evaluate the efficacy of metformin treatment in reducing blood pressure and investigate the molecular mechanism using a preclinical animal model. Adult male and female diabetic db/db mice with a blood glucose of greater than 300 mg/dl were salt-loaded (8% NaCl) for 10 days to induce hypertension. The mice were subject to metabolic cage studies for 24 hour urine collections in order to measure urinary electrolytes, albumin, and creatinine. Blood pressure was measured weekly by the tail-cuff method to assess the effect of metformin or vehicle given by oral gavage (dose of 60 mg/kg of body weight per day). At the end of the study the mice was euthanized and the left kidney was formalin-fixed and paraffin-embedded for immunohistochemistry

while the right kidney was homogenized for Western blotting. Western blotting showed attenuation of total NCC and phospho-NCC in diabetic db/db mice given an oral gavage of metformin (Pearson correlation coefficient: $0.9470 \pm 2.52e^{-3}$) compared to vehicle (Pearson correlation coefficient: $0.9800 \pm 2.86e^{-3}$). Immunohistochemical analysis showed less co-localization of the actin cytoskeleton protein filamin and phosphorylated NCC in the metformin treated group compared to the control group. Taken together, we show metformin decreases sodium retention and blood pressure by reducing the density of renal NCC at the luminal membrane and the association between NCC and the actin cytoskeleton.

Diabetes Mellitus and Glucose Metabolism

LIPIDS, OBESITY AND METABOLIC DISEASE

Regulation of ENaC by Exosomal Lipids in the Diabetic Kidney

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Effective treatment of hypertension (HTN) in patients with diabetes may help to significantly reduce the risk of those patients developing additional complications including vascular disease and diabetic nephropathy. Blockers of the renin-angiotensin system including angiotensin converting enzyme inhibitors and angiotensin receptor blockers are not always effective in treating HTN in diabetic patients. Therefore, the aim of this study was to use an animal model of type 2 diabetes to investigate a novel mechanism of diabetes associated HTN involving exosomal lipids in the upregulation of epithelial sodium channel (ENaC) activity in the kidney. We performed metabolic cages studies using male and female hypertensive (salt-loaded induced) diabetic db/db mice and healthy age-matched wild-type control mice in order to isolate and characterize urinary exosomes from each group by nanoparticle tracking analysis, Western blotting, and transmission electron microscopy. Our mass spectrometry based lipidomic studies identified key lipids that were differentially expressed in the kidney derived exosomes from the hypertensive diabetic mice compared to control mice. Sphingomyelin quantification assays showed total sphingomyelin content was elevated in the exosomes from the hypertensive diabetic mice compared to the control group. Single channel patch clamp studies showed urinary exosomes enriched in sphingomyelins from hypertensive diabetic mice compared to controls increase ENaC activity (at the level of channel density and open probability) in cultured distal tubule renal epithelial cells. Moreover, exogenous application of sphingomyelin-6 to cultured mouse cortical

collecting duct (mpkCCD) cells resulted in an increase in amiloride-sensitive transepithelial current. Taken together, our data show various lipids are enriched in exosomes from hypertensive diabetic mice compared to controls and these exosomes positively regulate ENaC activity in distal tubule and collecting duct cells.

Adrenal

ADRENAL CASE REPORTS III

Cushing's Syndrome and Illegal Receptors

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Cushing's syndrome and Illegal Receptors

Case presentation:A 48-year-old female with HTN presented to the endocrinology clinic for the evaluation of incidental bilateral adrenal masses noted on chest CT for dyspnea workup. At the time of the presentation, she reported generalized fatigue, significant weight gain in the past year and shortness of breath. Her physical exam was remarkable for central obesity. Lab work showed elevated cortisol after 1 mg dexamethasone suppression test x 2 and elevated 24-hour urine cortisol. Plasma free metanephrine levels and aldosterone/renin ratio were normal. MRI abdomen was done and showed bilateral adrenal masses (left: 5.6 cm, right: 3.2 cm). Patient was diagnosed with Cushing's syndrome secondary to primary bilateral adrenal hyperplasia and was referred to endocrine surgery who recommended unilateral adrenalectomy. The decision was made to remove the larger left side adrenal mass. On post-operative day one her am cortisol decreased to 2.1 and she was started on hydrocortisone 20 mg in the morning and 10 mg in the evening.

Discussion:Primary bilateral adrenal hyperplasia is a rare cause (< 2 %) of endogenous Cushing's syndrome, usually occurs in a bimodal age distribution, in childhood and in the fifth- sixth decades. Presentation is variable with most patients having no symptoms or subclinical Cushing's. The theory is the larger nodule size correlates with the higher cortisol production. Studies have shown between 60-70% of cases has aberrant ectopic hormone receptors which leads to increased cortisol production not only from ACTH but also from other ligands such as serotonin and vasopressin. Aberrant receptor testing examines whether cortisol or other steroid production increases in response to either physiologic or pharmacologic stimulus. Multiple genetic mutations have been associated, the most frequent is mutations in the Armadillo repeat-containing 5 gene identified in 2013. Treatment can either be medical or surgical. Medical therapy can be initiated if testing for an aberrant receptor is positive. In recent years there has been a trend towards doing unilateral adrenalectomy instead of bilateral, with initial remission of symptoms reported in about 84% of

cases after unilateral adrenalectomy although there is a small risk of recurrence. Post operatively after unilateral adrenalectomy patients should be monitored for adrenal insufficiency. Our patient declined aberrant receptor testing and opted for surgery and is doing well post operatively.

Conclusion:Primary bilateral adrenal hyperplasia is a rare cause of endogenous Cushing's syndrome which can be treated either medically or surgically.

Thyroid

THYROID DISORDERS CASE REPORTS II

Recurrent Dysphagia Due to an Esophageal Stricture in a Patient With Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED).

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Background:Chronic Mucocutaneous Candidiasis is one of the hallmark features of Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED). Untreated esophageal candidiasis may lead to complications such as esophageal stricture, rupture and or fistula formation^{1,2}.

Case Presentation:A 31-year-old man with a past medical history significant for APECED with involvement including hypoparathyroidism, hypothyroidism and adrenal insufficiency presented to the Emergency Department with dysphagia and globus sensation after eating. This was the fourth time in the last 2 years that the patient had presented with this chief complaint. The patient underwent emergent esophagogastroduodenoscopy (EGD) where a large meat bolus was identified at approximately 20 cm and removed. A discrete esophageal tear at 19-20 cm was identified and clipped. The esophagus was noted to be diffusely narrowed with mild corrugation, and biopsies showed evidence of esophageal candidiasis. A chest CT scan demonstrated diffuse pneumomediastinum and soft tissue emphysema throughout the esophagus, suspicious for a tear. Fluoroscopic Esophagogram showed mild narrowing of the upper third of the esophagus without evidence of gross extravasation. The patient was placed on NPO (nothing by mouth) diet, started total parenteral nutrition, and treated with IV Fluconazole, administered for 10 days and then transitioned to oral Fluconazole for a total of 21 days, with improvement. A subsequent repeat fluoroscopic esophagogram showed absence of extravasation at the previously identified level of the esophagus. The patient is currently scheduled for a repeat EGD in 3 months.

Conclusion:This case demonstrates a significant complication of APECED involving esophageal candidiasis. Timely diagnosis and treatment of esophageal candidiasis in APECED may prevent life-threatening esophageal pathology.

References:1)Kim, Byung-Wook et al. Esophagomediastinal fistula and esophageal stricture as a complication of esophageal candidiasis: A case report. *Gastrointestinal Endoscopy*, Volume 52, Issue 6, 772 – 775.2)Hyun J, Chun H, Keum B et al. *Candida esophagitis complicated by esophageal stricture. Endoscopy* 2010; 42(S02): 180 - 181. doi:10.1055/s-0029-1244014.