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**MON-160**

**Background:** Adrenal insufficiency (AI) is a chronic disorder necessitating life-long replacement. Patients' quality of life and health outcomes depend on knowledge and comfort level with self-management.

**Objective:** To determine patients' knowledge in regards to diagnosis and management, estimate burden of disease and to identify predictors of adverse outcomes in patients with AI

**Methods:** Survey study of patients with AI evaluated at two tertiary medical centers between 2015 and 2019. Collected variables included data on circumstances of AI diagnosis, symptoms, management, burden of disease, and overall well-being.

**Results:** Among 785 patients (mean age at diagnosis 44.2 ± 18.0, 64% women, and 92% Caucasian), 310 (40%) had primary AI (PAI), 255 (33%) had secondary AI (SAI) not related to glucocorticoid use, and 211 (27%) had steroid-induced AI (SIAI). Patients were diagnosed with AI after presenting with symptoms for a median of 1 year (0-6), 28% with symptoms lasting >2 years, 44% visiting emergency room (ER) at least once prior to diagnosis. A third of patients reported a discordant diagnosis from their medical record.

Baseline glucocorticoid replacement therapy included hydrocortisone (HC) in 447 (59%), median of 20 mg (IQR 15 - 25mg), prednisone in 190 (25%), median of 5 mg (IQR 4 - 7.5mg), other regimens in 38 (5%), and no steroids in the remainder (85, 11%); 197 (26%) patients reported daily equivalent HC dose of >25 mg. Overall, 549 (73%) of patients reported use of stress dose steroids at least once per year, higher in patients taking HC >25 mg/day (3.2 vs 2.7 times per year if HC<25mg/day, p=0.01). Improper use of stress steroids was reported in 193, 25% patients. Patients taking HC>25 mg /day reported a higher number of adrenal crises (1.6 vs 1.3 in patients on HC<25 mg/day, p=0.04). Among 314 (41%) patients who reported ER visits due to adrenal crisis, only a third received prompt glucocorticoids.

One third of patients described their general health as fair or poor. Predictors of negative perceptions of overall health included SIAI (OR 6.2 and 2.5, vs PAI and SAI respectively), poor understanding of diagnosis (OR 2.6), daily HC>25 mg (OR 2.1), and presence of at least one adrenal crisis (OR 2.3) (p<0.001 for all).

**Conclusion:** Patients with AI experience delay in diagnosis, and a third do not fully understand their diagnosis. In addition to patient education, interventions to improve general health and outcomes may include selecting a physiological glucocorticoid replacement therapy, prevention of adrenal crisis, and improving ER care.

# Adipose Tissue, Appetite, and Obesity

## ADIPOSE TISSUE BIOLOGY AND OBESITY II

### *27-Hydroxycholesterol Triggers the Whitening of Brown Adipose Tissue*

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**SUN-590**

27-Hydroxycholesterol (27HC) is the most abundant oxysterol in circulation and metabolized by a P450 enzyme CYP7B1. Its levels closely correspond to those of cholesterol in the body. In addition, previously it was found that 27HC is an endogenous selective estrogen receptor modulator (SERM), which links cholesterol metabolism to estrogen receptor actions (1). Brown adipose tissue (BAT) is the primary source of energy expenditure and energy homeostasis, as well as body temperature maintenance. While previously it was believed that BAT activity is limited to neonates and young children, it is now recognized that BAT is also active in adult humans and its function is impaired by metabolic diseases such as obesity. BAT is also a secretory organ and produces brown adipokines, although the exact function of BAT and adipokines from this tissue in obesity has not been completely understood. Recently, it was reported that 27HC plays an important role in obesity and augments body weight gain in response to a high fat, high cholesterol (HFHC) diet by increasing pre-adipocyte population in the white adipose tissue. 27HC mimics the effects by HFHC diet-feeding on white adipose tissue, such as promoting the inflammation and macrophage infiltration (2). In this study, we explored the effect of 27HC on BAT morphology and function. First, we compared the morphology of BAT from wild-type mice and *Cyp7b1*$^{-/-}$ mice that have elevated levels of 27HC using H&E staining. Interestingly, brown adipocytes from *Cyp7b1*$^{-/-}$ mice were larger in cell size than those from wild-type mice, and the cells were mostly unilocular compared to the multilocular cells from wild-type mice, indicating the transition toward a "whitening" phenotype. Next, We treated mice fed a normal chow or a HFHC diet with 27HC or vehicle control for 8 weeks to examine the direct effect by 27HC on BAT. Similar to the phenotype in *Cyp7b1*$^{-/-}$mice, 27HC increased the "whitening" of BAT regardless of the diet. We also determined the gene expression of brown adipocyte markers such as UCP1, PGC1a, and DIO2, and found that 27HC significantly decreased the expression of the BAT markers regardless of the diet, confirming the "whitening" observed in the morphology. Moreover, the energy expenditure in mice treated with 27HC was decreased compared to the vehicle control on a HFHC diet, suggesting that 27HC also alters BAT function. These results show that 27HC causes the whitening of BAT, and shed light on the important role of 27HC in brown adipose tissue function. Future experiments will be warranted toward further understanding of the role of 27HC in BAT function. **Reference:**(1) Umetani, Michihisa, et al. *Nature medicine* 13.10 (2007): 1185. (2) Asghari, Arvand, et al. *Endocrinology* 160.10 (2019): 2485-2494.

# Reproductive Endocrinology

## CLINICAL STUDIES IN FEMALE REPRODUCTION I

### *A New Concept for the Endocrinology of Pre-Eclampsia: The Role of Spiral Steroids*

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**SAT-006**

**Background**: In 1987, Graves observed that during the 3rd trimester, some patients with pre-eclampsia had high levels of unknown materials that could be detected with

assays for digoxin (DLM). In 2018, we characterized a new candidate for the DLM, Ionotropin. It is a phosphocholine (PC) ester of a novel steroid with 23 carbon atoms. As Ionotropin shares structural features (a) with spironolactone (both have spiral lactones in the E-ring) and (b) with digoxin (E-ring lactone and 3α-5β configuration), we have proposed that Ionotropin may function as a potassium (K+) sparing diuretic. This suggestion is supported by the observations that [1] patients who cannot make Ionotropin (7-dehydrosterol reductase deficiency) are K+ wasting and [2] breast cyst fluids with high K+ levels also have high Ionotropin levels.

**Hypothesis**: During the 3rd trimester, fetal requirements for K+ reach a maximum, fetal blood pressure increases and aldosterone signaling is blocked. This blockage leads to fetal sodium (Na+) wasting and is essential for formation of amniotic fluid. These events are consistent with a normal role for an unknown endogenous K+ sparing hormone and would be the basis for a modest elevation of maternal DLM during the 3rd trimester. Our hypothesis is that if any of the functions were inadequate, then the fetal-placental unit would synthesize excess PC-spiral steroids; the woman would exhibit symptoms of K+ sparing hormone excess (hypertension and proteinuria) and would be diagnosed with pre-eclampsia.

**Experimental Results**: We have just reported a pilot study associating elevated PC esters of spiral steroids in women with pre-eclampsia. In brief, 12 of 19 women had elevated levels of at least one of the PC steroids (Z-score > 2) when compared to the levels in 20 pregnant women matched for gestational age and fetal sex. There are two basic mechanisms for this dichotomy: (a) there may be episodic secretion with of a DLM with a short half-life or (b) there may be two different underlying biochemical causes. In prior studies, there has been no indication of episodic secretion of DLM similar to that observed with glucocorticoids, Ionotropin or other PC spiral steroids.

**Discussion**: There are two basic types of K+ sparing diuretics. Type A: Spironolactone functions by regulating the NaK-ATPase. Type B: Triamterene functions by blocking synthesis of epithelial Na+ channels. Thus, Type A would have high levels of spiral steroids and Type B would have low levels of spiral steroids. Type A patients would be expected to have higher risk of long-term consequences when compared to the Type B patients.

**Conclusion**: The recognition of the division of pre-eclampsia into two separate diseases might be the key observation for developing Type-specific diagnosis and therapy. For example, a Type A patient might benefit from a low salt diet but that diet would not be expected to benefit a patient with Type B disease.

# Adipose Tissue, Appetite, and Obesity

## RARE CAUSES AND CONDITIONS OF OBESITY: PRADER WILLI SYNDROME, LIPODYSTROPHY

### *Iron Parameters in Patients with Partial Lipodystrophy and Impact of Metreleptin Therapy*

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**SUN-607**

**Introduction** Intriguing rodent studies and epidemiological data suggest that iron metabolism and adipocytokines crosstalk to regulate glucose metabolism and fuel storage. Iron parameters have not been previously studied in patients with lipodystrophy whereas increased iron stores have been associated with type 2 diabetes. In this study, we sought to investigate the status of iron parameters in patients with partial lipodystrophy (PL) and to interrogate whether the adipocyte hormone leptin can modulate iron metabolism. **Methods** Serum samples of 19 patients with PL (age: 42, IQR: 34-57, M/F: 3/16) were used from an open-label study previously performed at the University of Michigan evaluating the efficacy of metreleptin in nonalcoholic steatohepatitis (NCT01679197) to measure ferritin, hepcidin, iron, and transferrin soluble receptor levels. High-sensitivity C-reactive protein (hs-CRP) levels were also determined as broader changes in inflammatory pathways may potentially impact circulating ferritin levels. Results were integrated into an existing database of metabolic parameters. Data are presented as median, IQR. **Results** At baseline, ferritin levels were positively correlated with fasting glucose (r = 0.533; p = 0.023) and HbA1c (r = 0.510; p = 0.031). During the 6 months of therapy period, HbA1c (9.2%, 7.3-10.3 vs. month-3: 8.6%, 7.7-9.6; p = 0.099; and month-6: 8.5%, 6.8-9.5; p = 0.264), triglyceride levels (346 mg/dL, 240-1771 vs. month-3: 346 mg/dl, 237-479; p = 0.047; and month-6: 295 mg/dl, 207-495; p = 0.091), and hepatic fat (12.7%, 9.8-20.6 vs. month-6: 8.9%, 7.0-11.0; p = 0.031)} decreased. Reductions were observed in serum ferritin after metreleptin treatment (83.23 ng/mL, 76.43-178.97 vs. month-3: 73.79 ng/ml, 68.30-78.59; p = 0.007; and month-6: 61.03 ng/mL, 46.45-157.74; p = 0.004). There was a tendency for hepcidin and iron to be decreased, but this did not reach statistical significance. On the other hand, there were notable reductions in hs-CRP levels at 6 months compared to baseline (2.94 mg/L, 1.30-4.80 vs. 1.6 mg/L, 1.00-6.30; p = 0.012). Baseline leptin level was inversely correlated with percent reduction in hs-CRP at month-6 (r = -0.685; p = 0.001). Also, modest correlations were observed between changes in serum iron and triglycerides (r = 0.491, p = 0.033) and hepatic fat (r = 0.412, p = 0.079). **Conclusions** We observed a significant relationship between ferritin and glucose control in a group of patients with PL. Metreleptin therapy was associated with improvements in triglycerides and hepatic fat and there were also significant decreases in ferritin and hs-CRP levels. These results raise the possibility that metreleptin therapy influences iron metabolism. However, whether the decrease in ferritin indicates a decrease in iron stores or is mediated by an effect on inflammation remains unknown.

# Thyroid

## THYROID DISORDERS CASE REPORTS II

### *Atypical Presentation of Recurrent Cardiac Tamponade Following Pericardial Window in the Setting of Uncontrolled Hypothyroidism*

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