reported in patients with fibromyalgia, potentially related to hypothalamus-pituitary dysfunction.[1,2] Superimposed adrenal insufficiency (AI) may contribute to some fibromyalgia symptoms or delay improvement in patients enrolled in fibromyalgia treatment programs. We hypothesized that a subset of patients with fibromyalgia have: 1) partial secondary AI and concomitant growth hormone (GH) deficiency 2) a discordance in Cosyntropin stimulation test and 3) improvement in fibromyalgia symptoms with initiation of glucocorticoid and/or GH replacement.

Design: This was a retrospective study of patients with fibromyalgia diagnosed with partial secondary AI based on abnormal insulin tolerance test (peak cortisol < 18 mcg/dL) at our institution from June 2002 to August 2019. Patients were excluded if they had other reasons for adrenal insufficiency, including steroid exposure and opioid use.

Results: We identified 22 patients (18 women, 82%) diagnosed with partial AI at a median age of 38 years (range 19-65). The fibromyalgia symptoms included fatigue (n=22, 100%), pain (n=22, 100%), sleep disturbance (n=15, 68%), and bowel changes (n=13, 59%). The median morning cortisol concentration was 8.6 mcg/dL (range 1.1-11); 9 patients (41%) had a morning cortisol concentration below the normal range (7 mcg/dL). The median ACTH level was 15.5 pg/mL (range 7.7-54). Nineteen patients had baseline IGF1 levels, with a median z-score of -0.94 (range -1.96 to 1.70). MRI pituitary imaging was performed in 20 patients and showed no significant pituitary pathology.

All patients achieved hypoglycemia <=40 mg/dL during the insulin tolerance test. Peak median cortisol level was 11 mcg/dL (range 5.4-17). Nineteen patients (86%) also had partial GH deficiency (defined as a peak GH < 4 ng/mL) with a median GH level of 0.36 ng/mL (range 0.03-3.83). Cosyntropin stimulation test was performed in 13 patients (59%) with a 1 mcg dose in 2 patients and 250 mcg dose in 11 patients. The peak cortisol was >=18 mcg/dL in 10 (77%) patients. All patients were started on physiologic glucocorticoid replacement, and 12 patients were started on GH replacement. Endocrinology follow-up information was available for 13 patients, and 8 (62%) reported symptom improvement after starting treatment.

Conclusions: Patients with fibromyalgia can have co-existing partial secondary AI and GH deficiency as defined by insulin-induced hypoglycemia. Cosyntropin stimulation test can be used in patients with fibromyalgia, but a normal test does not rule out partial secondary AI. Replacing the underlying deficiency improved symptoms in some patients demonstrating certain fibromyalgia symptoms may overlap with AI and GH deficiency.

[1]Gur et al. Ann Rheum Dis. 2004. 63(11):1504-1506.
[2]Kirnap et al. Clin Endocrinol (Oxf). 2001. 55(4):455-459.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Disrupted ACTH-Cortisol Temporal Coupling in Healthy Men After an Overnight Fast, and the Modulatory Role of Orally Ingested Macronutrients

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MON-184

While long term fasting is reported to augment the corticotropic function, effect of short term (overnight) fasting on ACTH-cortisol coordinated release pattern and potential effect(s) of nutrient intake is not fully defined. Eleven healthy men (age: 33-70 yrs, BMI 20.4-31.5 kg-m^2) were studied after overnight fast on 4 separate days, involving oral ingestion of 300 ml of either water, dextrose, protein, or lipid solutions. Test meals were isocaloric (400 kcal). Sessions were 6.5 h long, starting at 0800-0900 hrs. Blood was collected at 10-min intervals for ACTH (pg per mL), and cortisol (µg per dL) measurements. Linear regression, cross-correlation, deconvolution, and ApEn were used for data analyses. ACTH and cortisol concentration time series during short-term fast (water day) were found not to be chronologically coupled per linear regression (r^2= 0.0014, P=0.82), and cross-correlation (r= - 0.156, lag=150 min) statistics. Oral intake of the 3 macronutrients improved the temporal relationship between ACTH and cortisol concentrations, verified by linear regression (r^2:P- dextrose 0.54:0.0001, protein 0.65: 0.0001, lipid 0.42:0.0001), and cross-correlation (r:lag in min- dextrose 0.8:10, protein 0.77:10, lipid 0.78:20). Oral ingestion of either macronutrient did not significantly alter mean ACTH and cortisol concentrations and their respective secretion pattern (total, pulsatile, basal) over the period of 6.5 hr. However compared to the control (water) session, dextrose ingestion evoked less frequent and larger ACTH secretory bursts, and more regular ACTH and cortisol secretory patterns. In this study, we have observed lack of concordance between ACTH and cortisol after overnight fasting, which is restored with oral intake of macronutrients. This effect appears to be uniform among the 3 macronutrients, except for less frequent and lager ACTH bursts and more regular ACTH and cortisol release events after dextrose intake. These findings and the specific role of nutrients being direct or via physiologic nutrient-induced hormonal adaptation warrants future investigation.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

Characterizing DNA Methylation Signatures in Adipose Tissue from Metabolic Impaired Asymptomatic Individuals

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MON-708

Obesity remains as a global epidemic characterized by progressive metabolic dysregulation in glucose homeostasis.

Along with a genetic association in the development of T2D, epigenetic regulation has been suggested as a significant contributor in altered gene expression. Recent studies have described DNA methylation changes in insulin-sensitive tissues involved in T2D pathogenesis, however epigenetic dynamics on early stages to metabolic alterations is still unclear.

We investigated potential DNA methylation signatures in 34 asymptomatic individuals from the GEMM family study. We compared differentially methylated CpG sites (DMC: B value>0 and delta Beta >|10%|; Infinium EPIC array) from subcutaneous adipose tissue (SCAT) in different groups of individuals according to BMI (kg/m^2) and HbA1c (%) levels as follow: Group A Control (C): n=9, 22.0±1.9 kg/m^2, 4.8±0.3%; Group B Overweight (OW) with normal HbA1c: n=6, 27.8±1.6 kg/m^2, 5±0.2%; Group C Obese (OB) with normal HbA1c: n=6, 34.6±4.2 kg/m^2, 5.2±0.2%; Group D Prediabetes (PD): n=7, 31.1±5.7 kg/m^2, 5.9±0.2% and Group E T2D: n=6, 30.6±7.3 kg/m^2, 7.2±0.9%.

We found 43 overlapping genes with shared pathways in all groups, mainly those related to metabolism and adipogenesis. We also documented particular altered methylated genes, in each group (OW: 386, OB:1005, PD:76 and T2D:189). Pathway enrichment analysis in OB and T2D was mainly related to glucose metabolism, while in OW and PD was NOTCH signaling. All groups displayed a consistent hypermethylation in *RARA*, *ESR1* and *NCOR2*, well known genes involved in lipid metabolism. Additionally, we describe for the first time, a progression toward hypomethylation in *ARHGAP15* and *MTAP*, related with an impaired metabolic status. Otherwise, analysis of overlapping CpG sites revealed a consistently hypermethylated state in OW (86.42%), OB (86.48%) and PD (51.72%), in contrast with the hypomethylation state (56.3%) observed in the T2D group, previously observed elsewhere (1).

In conclusion, comparison of methylation in SCAT obtained from OW, OB, PD and T2D individuals, display potential pathways and DMC signatures specific in each group. Common novel overlapping genes in global DNA methylation profiles of SCAT, were also observed.

Reference: (1) Barajas-Olmos et al., *BMC Med Genet*. 2018 Feb 21;19(1):1-8.

Nothing to Disclose: FE, FB, AM, EH, GEMM, ER, RB, LO.

Diabetes Mellitus and Glucose Metabolism

ISLETS, LIVERS, PLACENTA, AND VASCULATURE — THE MULTITISSUE IMPACT OF DIABETES

Association Between Placental Glucose Uptake and Protein O-Glcnacylation and Birth Outcomes in Obese Non-Diabetic Mothers

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OR14-07

Increased transport of nutrients such as glucose, across the placenta, has been linked to abnormal fetal growth and pregnancy complications in obese non-diabetic mothers (1); however, the underlying mechanisms are poorly understood. We hypothesized that in placenta, the metabolic and nutrient sensor O-GlcNAc transferase (OGT), highly sensitive to glucose flux through the hexosamine biosynthetic pathway (HBP), responds to maternal obesogenic environment by increasing O-GlcNAc post-translational modification of nucleocytoplasmic proteins in the placenta altering fetal growth trajectories. Tissue biopsies were isolated from placentas collected at term from 26 non-diabetic mothers alongside routine biochemistry and anthropometric data (maternal fasting glucose, glycated hemoglobin (HbA1c), early pregnancy body weight (BMI) and birth weight). OGT and glucose transporter 1 (GLUT1) protein expression as well as tissue levels of O-GlcNAcylation were determined by immunoblotting using specific antibodies. The BeWo choriocarcinoma cell line was also used as an *in vitro* model of trophoblast to test the effect of high glucose and GLUT1 silencing on the OGT activity by immunoblotting. Maternal BMI was positively correlated to birth weight centile (BWC) (p=0.0130, R^2=0.231), maternal fasting glucose (p=0.0177, R^2=0.221) and HbA1c levels (p= 0.0156, R^2=0.229) as well as placental OGT protein expression (p=0.0294, R^2=0.183). The latter was positively associated to the levels of protein O-GlcNAcylation (p=0.0023, R^2=0.326). Interestingly, GLUT1 protein levels were positively correlated to BWC (p=0.0056, R^2=0.279) and strongly correlated to protein O-GlcNAcylation (p<0.0001, R^2=0.507), suggesting an increase in the placental flux of glucose. In agreement with findings in placenta biopsies, in BeWo cells total protein O-GlcNAcylation levels were altered by cell exposure to different glucose levels (5 mM vs 15 mM, p<0.01). This was prevented by downregulating OGT or GLUT1 expression (p<0.001) using gene silencing. In addition, OGT protein levels were negatively associated to AMP-activated protein kinase (AMPK) activation (p=0.0005, R^2=0.402) in placenta biopsies identifying a novel cross-talk between two placental nutrient sensors, OGT and AMPK, previously shown in other tissues (2). Accordingly, the silencing of OGT promoted the activation of AMPK (p<0.01) and its downstream target acetyl-CoA carboxylase (ACC) (p<0.01) in BeWo cells, as demonstrated by increased phosphorylation of residues Thr172 and Ser79 for AMPK and ACC respectively. Such obesity-associated cross talk between metabolic and nutrient sensors might disrupt multiple cellular pathways involved in fetal development and growth.

***References**: (1) Acosta et al. Am J Obstet Gynecol. 2015 Feb;212(2):227. (2) Bullen et al. J Biol Chem. 2014 Apr 11;289(15):10592-606.*

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Severe Hypercalcemia Following Hip Joint Implantation of Stimulan® Calcium Sulfate Antibiotic Beads

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