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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MON-334

Introduction: The diagnosis and management of hypercalcemia in hospitalized patients can be challenging. Hypercalcemia is often associated with significant morbidity and end-organ damage which may delay a patient's recovery. **Case report:** A 63-years-old female presented for evaluation of left hip pain and was found to have an infection of the prosthetic joint. Past medical history was significant for type 2 diabetes and atrial fibrillation. No known history of malignancy or excess calcium, vitamins A or D intake. Past surgical history was significant for multiple left hip fixation surgeries and a left hip arthroplasty 4 months prior. Patient's serum calcium on admission was 8.4 mg/dL (corrected 9.5 mg/dL, range 9.5-10.5 mg/dL), serum creatinine 1.2 mg/dL (range, 0.5 - 1.2 mg/dL). Three days later, she underwent surgical irrigation and debridement of the left hip with placement of 30 cc STIMULAN® antibiotic beads with vancomycin. On postoperative day (POD) 5, patient was found to be confused. Laboratory workup revealed serum calcium 13 mg/dL, ionized calcium 1.91 mmol/L (range, 1.12-1.32 mmol/L), serum creatinine 1.6 mg/dL, intact PTH 10 (range, 15- 65 pg/mL), PTH-rp 15 pg/mL (range, 14-27 pg/mL), 25-OH-vitamin D 18 ng/mL (range, 30-60 ng/mL), 1,25-OH2-vitamin D <8 ng/mL (range, 18-72 ng/mL). **Clinical challenge:** The differential diagnosis of non-PTH mediated hypercalcemia includes malignancy, granulomatosis and/or excess calcium intake. The patient's history and laboratory data were not consistent with these etiologies. The temporal nature of the hypercalcemia in relation to implantation of antibiotic beads suggest causality of exogenous calcium sulfate and development of the patient's hypercalcemia. Mild renal insufficiency, as well as immobilization in the setting of surgery, were likely also contributory. **Treatment and outcome:** This patient was first treated with aggressive intravenous saline and calcitonin. Serum calcium rose to 13.7 mg/dL and pamidronate 30 mg was administered. Hypercalcemia resolved on POD 11 with improvement in patient functional status. **Discussion:** Hypercalcemia due to implanted calcium sulfate antibiotic beads is not well described outside of case reports. Kallala found hypercalcemia in less than 0.01% of patients who underwent bead implantation, with all the affected patients presenting with preoperative renal failure. **Conclusion:** Hypercalcemia in the setting of calcium sulfate antibiotic beads implantation may contribute to a patient's confusion and increase length-of-stay. We recommend serum calcium and creatinine to be closely monitored during the perioperative period in patients who receive calcium sulfate antibiotic beads. Risk factors for the development of hypercalcemia require additional study, though patients with pre-existing renal insufficiency may not be good candidates for the mechanism of antibiotic administration.

Thyroid

THYROID DISORDERS CASE REPORTS III

Rebel Nodule or Reluctant Gland? the Challenge Presented by Heterophile Antibodies

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MON-462

Introduction:

Interpretation of thyroid function tests (TFTs) in background of non-specific symptoms concerning for hypothyroidism, has become challenging with assay interference. Heterophile antibody interferences are both test and laboratory platform dependent. We present a case of a toxic nodule erroneously diagnosed as isolated central hypothyroidism due to heterophile antibody interference.

Case:

A 38 year old lady was referred to Endocrinology for possible central hypothyroidism with symptoms of progressive fatigue, 40lb unintentional weight loss, poor appetite, nausea, intermittent diarrhea/constipation, occasional cold intolerance and intermittent lightheadedness. TFTs suggested low TSH 0.175 mcIU/ml (N 0.35-3.8 mcIU/ml) and low FT4 0.74 ng/dl (N 0.8-1.8 ng/dl). Pituitary hormone evaluation revealed normal ACTH, AM cortisol, IGF-1, prolactin and FSH. A pituitary MRI was normal.

Two months later, she had worsening fatigue, anxiety with palpitations and tremors, and 14lb weight gain. TFTs again confirmed low TSH (0.575 mcIU/ml) and lower FT4 (0.70 ng/dl). Empirical weight-based levothyroxine (LT4) supplementation was initiated for central hypothyroidism. Six weeks later, TFTs showed hyperthyroidism (TSH <0.005 mcIU/ml, FT4 1.57 ng/dl). The patient endorsed worsening lightheadedness and palpitations on LT4, which resolved on LT4 discontinuation. One month later, TFTs were abnormal again (TSH 0.047 mcIU/ml, FT4 0.74 ng/dl).

Due to persistent discordance in symptoms and biochemical tests, TFTs were evaluated for heterophile antibody interference. While HAMA-treated TSH remained low (0.04 mIU/l), FT4 by equilibrium dialysis (FT4 ED) was normal (1.1 ng/dl, regular assay 0.74 ng/dl), suggesting subclinical hyperthyroidism. A thyroid uptake scan confirmed an autonomous toxic right thyroid nodule with suppressed remaining gland. Patient ultimately underwent 15 mCi RAI ablation of the nodule. TFTs done 1 month post-RAI suggested normal TSH (1.2 mcIU/ml) and normal FT4 ED (1 ng/dl). Previous symptoms have since resolved.

Conclusion:

Current methods of TFTs are generally reliable in diagnosing and monitoring thyroid disease. Rarely, medications, supplements, and endogenous antibodies can bind to TSH, T4 or lab reagent, resulting in inaccurate values. This has become increasingly common with use of high dose biotin. TSH with HAMA/heterophile antibodies and FT4 ED are more accurate forms of diagnostic testing. When approaching patients with symptoms not consistent with typical hypo- or hyperthyroidism and are not responding as expected to therapy, it is important to consider more accurate testing to rule out assay errors.

References: