Reproductive Endocrinology

BASIC MECHANISMS IN REPRODUCTION: FROM BEGINNING TO END

Transcriptional Changes in Lipid Metabolism of Adipocytes Derived from Subcutaneous Abdominal Adipose Stem Cells of Normal-Weight Polycystic Ovary Syndrome Women

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Normal-weight polycystic ovary syndrome (PCOS) women exhibit increased adipose insulin resistance *in vivo* (1) accompanying enhanced subcutaneous (SC) abdominal adipose stem cell (ASC) development to adipocytes with greater lipid accumulation per cell *in vitro* (2). To determine whether this phenomenon is associated with abnormal adipogenic gene transcription during ASC differentiation into adipocytes, SC abdominal ASCs isolated from three non-Hispanic Caucasian normal-weight PCOS women and three age- and BMI-matched controls were cultured in adipogenic differentiation medium for 3–12 days. After RNA isolation, gene expression levels were determined by RNA sequencing at days 3, 7, and 12. Differentially expressed genes were filtered for significance (p_{adj}<0.05) and fold change (>2-fold); upstream regulator genes and gene ontology (GO) functions were determined using Ingenuity Pathway Analysis. Gene set enrichment analysis (GSEA) also was used to identify enriched cellular processes (3). Differentially expressed genes in PCOS vs. control cells were either upregulated (466, 768 and 441 genes on days 3, 7 and 12, respectively) or downregulated (742, 974 and 605 genes on days 3, 7 and 12, respectively) over time, with critical genes governing adipocyte cell differentiation in PCOS cells increased 2–6 fold at days 3, 7 and 12 (*PPARγ, CEBPα, ADIPOQ, AGPAT2, FABP4, LPL, PLIN1*). The predicted upstream regulator genes *TGFβ1* (an adipogenic inhibitor) and *TNF* (a pro-inflammatory adipokine) were significantly reduced in PCOS relative to control cells at all time points. The GO functions lipid oxidation and free fatty acid (FFA) beta-oxidation were enriched amongst upregulated genes in PCOS cells across all time points, while acylglycerol synthesis was increased at days 7 and 12 alone (z>2, p<0.05, all GO functions). In parallel, GSEA showed in PCOS cells significantly increased transcripts related to oxidative phosphorylation, peroxisome activity and adipogenesis at all time points (p<0.05). Thus, adipocytes derived from SC abdominal ASCs of normal-weight PCOS women exhibit early activation of adipogenic genes, potentially underlying their exaggerated lipid accumulation *in vitro*, as previously described (2). These PCOS-related changes in gene expression involve an increase in both oxidative phosphorylation and FFA beta oxidation, which could disrupt the balance between energy production and lipid storage, particularly when caloric intake exceeds energy utilization. **References**: (1) Dumesic DA, et al JCEM 2019;104(6):2171–83; (2) Leung KL, et al. JES 2019;3:Supplement 1, SUN-107 (3) Subhramanian A, et al. PNAS 2005;102:43

Thyroid

THYROID DISORDERS CASE REPORTS I

Successful Surgical Management of Graves' Disease in Pregnancy

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Background: Total thyroidectomy in pregnancy is not a widely used approach for management of Graves' disease (GD) but is indicated when thyrotoxicosis persists in spite of efforts to optimise thyroid status.

Clinical case: A 27-year-old lady with history of GD, presented at the 9th week of her second pregnancy. She had been counselled about anti-thyroid medications but was on carbimazole (CBZ) 30 mg tds and propranolol LA 80 mg od at presentation. She complained of palpitations, heat intolerance, irritability, weight loss and difficulty swallowing. On clinical examination, she had a heart rate of > 100/min and diffusely enlarged goiter with a bruit. Thyroid Ultrasound showed a right lobe of 6.5 x 2.8 x 2.7 cm and left lobe 5.3 x 2.6 x 2.4 cm. Free thyroxine (FT4) was 42.3 pmol/L (12–22), free triiodothyronine (FT3) 9.09 nmol/L (1.3–3.1), and TSH < 0.01 mIU/L (0.27–4.2). TRAB titer was >40 IU/L (0.0–1.75). She was advised to switch to propylthiouracil (PTU) and labetalol to minimize fetal adverse outcomes. She reported that she was unable to afford PTU and requested a switch back to CBZ.

During her course of therapy, she had recurrent admissions with thyrotoxicosis, tachycardia, panic attacks and difficulty in swallowing. A decision was made to manage her with total thyroidectomy in the second trimester. She was treated with Lugol's iodine, beta blockers and CBZ 2 weeks prior to her surgery and there were no immediate post-operative adverse events. Histology was consistent with GD. Her post-op TRAB titer remained >40 IU/L until present.

She delivered at 28 weeks of gestation due to threatened premature labor a baby boy who had neonatal thyrotoxicosis, required admission to the neonatal ICU and therapy with flecanide and CBZ. His TSH was 0.09 mIU/L, (FT4) 68.7 pmol/L and TRAB 19.4 IU/L. He is currently 18 months old, well and not on any medications.

Conclusion: Poor control of thyrotoxicosis is associated with pregnancy loss, prematurity, stillbirth, thyroid storm, and maternal congestive heart failure. Therefore, pre-pregnancy counseling is crucial to establish Euthyroid state for the safety of mother and fetus.

Reference: (1) Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol. 1989;160:63–70. doi: 10.1016/0002-9378(89)90088-4. (2) Vini L, Hyer S, Pratt B, et al. Management of differentiated thyroid cancer diagnosed during pregnancy. Eur J Endocrinol. 1999;140:404–406.