Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Intermediate Hyperglycemia and Type 2 Diabetes in Women with Polycystic Ovary Syndrome: Findings from Large Caucasian Cohort.

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MON-030

Background: Insulin secretory defects and insulin resistance exists in women with polycystic ovary syndrome (PCOS) and are prerequisites for the development of type 2 diabetes (T2D). Objective: To determine the prevalence of T2D, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), as well as the factors associated with these dysglycemic conditions. Participants: 1614 women with PCOS of Caucasian origin (Rotterdam criteria) with a mean age 25.14±5.56 years and BMI 27.34±7.09 kg/m^2 comprised the study group, whereas 359 normally ovulating, not hyperandrogenic women of comparable age and BMI, served as controls. Design: Observational study. Setting: Outpatient clinics of tertiary hospitals. Main Outcome and Measures: Clinical, biochemical, hormonal and ovarian ultrasound as well oral glucose tolerance test were performed in all subjects participating in the study. Diabetes and intermediate hypeglycemia was categorised according to WHO criteria and PCOS subgroups was based on the Rotterdam criteria. Results: In the PCOS group 2.2%, 9.5% and 12,4% of subjects had T2D, IGT and IFG, respectively. In control group 1,11%, 7.5% and 8.9% had T2D, IGT and IFG, respectively. When the existence of T2D was stratified according to age and BMI, no difference was found among age and BMI subgroups or PCOS subgroups. Namely in patients aged 17-22 years, T2D was detected in 3 lean and 2 obese subjects. The corresponding distribution for patients aged 22-30 years was 4 lean, one overweight and 2 obese, whereas in those older than 31 years, 2 overweight and 5 obese suffered from T2D. Free Androgen Index (FAI), waist to hip ratio (WHR) and LDL levels were significantly higher in T2D subjects in comparison to PCOS women with normal glucose metabolism. Diagnosis of T2D was significantly associated with Free Androgen Index (r: 0.469, p<0.05), while subjects with either IFG and IGT had positive association with BMI, WHR, FAI and HOMA-IR. In controls, T2D, IGT and IFG were positively associated with BMI and androgen concentrations. Conclusions: The prevalence of T2D and IGT is significantly higher in our large cohort of PCOS women in comparison to controls. The existence of T2D is irrespective of age and BMI, and seems to be inherent for PCOS women. Hence, the evaluation of glycemic status in women with PCOS using OGTT is supported.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

Nuclear Corepressor; SMRT Acts as an Important Regulator for Both Beta-Oxidation and the Maturation of Myogenesis in Mouse C2C12 Cell

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MON-713

Background: Silencing Mediator of Retinoid and Thyroid hormone receptors (SMRT; NCoR2) is a transcriptional corepressor which has been recognized as an important player in the regulation of hepatic lipogenesis and the somatic development in mouse embryo. SMRT protein is also widely expressed in the mouse connective tissues, for example adipocyte and skeletal muscle, and we recently reported that the mouse of global deletion of SMRT causes significant obesity which is independent from thyroid hormone signaling and thermogenesis. However, the tissue specific role of SMRT in skeletal muscle is still unelucidated. **Methods:** To clarify this, we took the gene targeting strategy for SMRT using CRISPR Cas9, and made the myogenic C2C12 clone which lacks SMRT protein (C2C12-SMRTKO; SKO). For this study, wild type C2C12 cell (WT) and SKO cell were cultured in differentiation medium (DMEM+2% horse serum) for 5-6 days, and analyses for gene expression compared two cell types were performed. **Results:** We found the significant up-regulations of muscle specific beta-oxidation related genes (ex. *Ppar delta*, *Ampk2*), and higher protein level of PGC-1A in the SKO cell, suggesting that SKO cell had similar gene profile to that of rodent skeletal muscle in the exercise test. On the other hand, confocal microscopic analysis showed SKO cell had decreased cell-fusion and loss of myotube, indicating that the morphology was similar to immature mouse myoblasts. Further gene analyses compared between WT and SKO cell demonstrated that SKO cell had higher expressions of myogenic markers;

MyoD and *Myogenin*. However, interestingly, the lower expressions of muscle constitutive genes; *MHC*, *Actin*, and *Alpha-dystrobrevin* were found in the SKO cell. These data indicate that the SKO cell has incomplete muscle fiber formation. **Conclusion:** Taken together, we demonstrate that SMRT works as a pivotal transcriptional mediator for both beta-oxidation and the process of myotube formation in C2C12 cell. Further inquiry for the cause of sarcopenia-like phenotype manifested in the SKO cell will be needed.

Bone and Mineral Metabolism
CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Diagnostically Significant Relationship Between the Results of Determination of Vitamin D3 and Its Metabolites by the EIA Method and Pure Vitamin D3 by the LC-MS Method.

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MON-379

Diagnostically significant relationship between the results of determination of vitamin D3 and its metabolites by the EIA method and pure vitamin D3 by the LC-MS method.

Introduction: Vitamin D is an important hormone in the human body. He is involved in many physiological body processes. Measuring the level of vitamin D in the patient's blood is important, diagnostic criteria for identifying and confirming a number of diseases: obesity, hypogonadism, sarcopenia, autoimmune pathologies.

Two methods currently prevail in the laboratory diagnostic market measurement of the level of vitamin D3 in blood plasma: EIA and LC-MS (with its variety - LC-MS / MS). Fundamental differences in the physicochemical nature of these methods are the basis for differing results determined in the same sample.

Objective: In this paper, we set the goal of determining how the results correlate for determining vitamin D3 and its metabolites using the EIA method with the results of determination Pure Vitamin D3 through LC-MS / MS.

Materials and methods: The study was conducted at the clinic of Professor Kalinchenko. Have been selected patients with a clinical picture of vitamin D deficiency. These patients were referred to determination of the level of vitamin D3 using the above methods, subject to preparation rules before analysis. EIA was performed using LC-MS / MS was done using AB SCIEX QTRAP 4500 apparatus connected to Waters Acquity UPLC system. The results were combined for subsequent statistical processing. For a pair of EIA / LC-MS methods, we determined the reliability value of the approximation r^2 and the linear regression equation.

Results: For the presented data, the level of vitamin D3 and its metabolites determined by EIA, and pure vitamin D3, determined by LC-MS, r^2 was 0.9638 (very strong dependence), and the linear regression equation was as follows: LC-MS [nm / ml] = 1.2808 * (EIA) [nmol / ml] + 6.9731.

Discussion: Despite studies by foreign colleagues showing a high level bias and low correlation of results between the EIA and LC-MS methods, our data show a very strong relationship between the two values. By our assumptions, the cause of the various findings is monoclonal antibodies, differing in the global market for reagents for determining the level of hormones derived our linear regression equation allows a practicing endocrinologist to quickly and accurately determine the level of true vitamin D3 in the patient.

Diabetes Mellitus and Glucose Metabolism
TYPE 2 DIABETES MELLITUS

HNF4A Mutation in Siblings with Diazoxide Responsive Congenital Hyperinsulinism

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SUN-690

Background: Congenital hyperinsulinism (HI) is the leading cause of severe, persistent hypoglycemia in infants. Transient HI seen at risk neonates due to prenatal stress and some of the congenital HI cases due to mutations in K-ATPase channel are responsive to diazoxide. It is not a common practice to obtain genetic evaluation for diazoxide responsive HI. However, children with dominant inactivating variants in HNF4A gene may present with diazoxide-responsive HI and mimic transient HI in infancy. **Objective:** To describe two siblings with diazoxide responsive HI with HNF4A mutation associated with maturity onset diabetes of youth type 1 (MODY1). **Clinical Case:** Case 1, term female with macrosomia and Case 2, preterm male appropriate for gestational age were born to same mother without gestational diabetes and with no perinatal stress. Siblings were non-dysmorphic and both presented with hypoglycemia during first week of life. Diagnosis of HI is confirmed based on inappropriately suppressed β-hydroxybutyrate at the time of hypoglycemia and inappropriate glycemic response to glucagon consistent with increased insulin action. Both siblings responded to diazoxide therapy. Family history was significant for late-onset diabetes in paternal extended family. Case 1 required very low dose diazoxide (2 mg/kg/day) during first year of life to sustain normoglycemia. She came off of diazoxide at 19 months of age. Case 2 is normoglycemic on 5mg/kg/day diazoxide at 4 months of age. Genetic evaluation through whole exome sequencing pursued upon diagnosis of Case 2 revealed paternally inherited heterozygous pathogenic start loss variant in HNF4A gene *(c.3G>T)* in both siblings. Father was completely asymptomatic without any history of hypo- or hyperglycemia.