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OR08-06

Background & Objective

Patients with type-1-diabetes (T1D) are at risk of long-term micro and macrovascular complications causing significant morbidity and mortality. Overt complications are not common in childhood; however, subclinical impairments in endothelial function, may be found. Better understanding of the timeline for the appearance of diabetic complications and identifying individuals at increased risk is key for developing prevention strategies. We aimed to study endothelial function and it's determinants in adolescents with T1D at different time points from diagnosis.

Methods

Forty adolescents 11-20 years of age with T1D followed at our pediatric diabetes clinic and 18 healthy control subjects were included. Two groups of patients were recruited based on time from T1D diagnosis; 20 individuals were diagnosed 2-4 months prior to the study visit and 20 at least 7 years prior to the visit. Investigations included: i) medical and demographic data ii) anthropometrics iii) fasting blood samples iv) EndoPAT testing of endothelial function and heart rate variability (Itamar Medical Ltd., Israel) v) Carotid intima media thickness (CIMT).

Results

Mean age differed slightly between groups being 14.1±2.0years in individuals with recent-onset T1D, 16.2±2.5 in those with prolonged T1D, and 14.8±2.3 in the control group (p=0.02). There were no significant differences in pubertal stage or in BMI z-score between groups. Thirty-three (57%) females participated. No patient suffered from diabetic complications. Mean CIMT was significantly higher in individuals with prolonged T1D (0.49±0.07mm) compared to control subjects (0.43±0.05mm; p=0.013) and did not differ significantly between patients with recent-onset T1D (0.45±0.07mm) and controls. This difference remained significant when age and sex were included in the model. EndoPAT measures of endothelial function and heart rate variability did not differ significantly between groups. Mean HbA1c at the time of the visit differed between groups (6.7%±0.7, 9.6%±1.8, 5.4%±0.3, p<0.001). However, the average of HbA1c reflecting the 6-7 months prior to the visit did not differ significantly between subjects with recent onset T1D (9.8%±1.3) and those with prolonged T1D (9.5%±1.7). LDL was higher in subjects with prolonged T1D (114±28mg/dl) compared to either controls (93±26mg/dl) or recent onset T1D (88±19mg/dl),p=0.002. Diastolic blood pressure was higher in subjects with prolonged T1D (70±6mmHg) than in controls (61±6, p=0.007).

Conclusions

Our results demonstrate disease duration to be an important factor in the development of subclinical arterial damage in the pediatric age group. Early in the course of T1D, CIMT results were similar in patients and control subjects, suggesting an important window for prevention. Larger studies could shed light on the precise timeline of endothelial impairment.

Adrenal

TRANSLATIONAL STUDIES ON ADRENOCORTICAL FUNCTION IN HEALTH AND DISEASE

Metformin Inhibits Activation of the Melanocortin Receptor 2 and 3 in Vitro, a Possible Mechanism for Its Anti-Androgenic and Weight Balancing Effects in Vivo

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OR19-07

Metformin is recommended as one of the first-line drugs for the treatment of type 2 diabetes and the metabolic syndrome. In addition to its insulin sensitizing effects, it has been shown to attenuate androgen excess in women with polycystic ovary syndrome (PCOS) or congenital adrenal hyperplasia (CAH), as well as to ameliorate obesity. The mechanisms of metformin action seem manifold. Preclinical studies suggest that it inhibits the cellular stress response at the level of the mitochondrial OXPHOS system and through AMPK dependent and independent mechanisms. Recent studies have shown that metformin decreases ACTH secretion from pituitary and reduces ACTH-stimulated adrenal secretion. In this study we investigated the effect of metformin through its specific melanocortin receptor 2 (MC2R) on signaling targeting adrenal steroidogenesis. To assess this effect, we used mouse adrenal OS3 cells, which do not express the MC2R. Cells were transfected with the human melanocortin receptor 2 and stimulated by ACTH. Downstream cyclic AMP production was then assessed by a co-transfected cAMP-responsive vector producing luciferase that was measured by a dual luciferase assay. The amount of luciferase produced in this assay corresponds to the amount of receptor activation with varying amount of ACTH. The effect of metformin was then tested in this system. We found a significant inhibition of ACTH induced MC2R activation and signaling with 10 mM metformin. The ACTH concentration response curve (CRC) was half-log shifted indicating antagonism. This effect was dose dependent with an IC_{50} of 4.2 mM. Metformin did not affect cell viability and basal cAMP level under used conditions. We also tested the effect of metformin on homologous receptors (MCRs). No significant effect was found on MC1R and MC4R activity. However, a 2-log shift in ACTH EC_{50} was observed with MC3R. In conclusion, metformin seems to act on MC2R and MC3R signaling directly. The role of MC2R for steroidogenesis is well established. MC3R is involved in energy balance and seems to act as a rheostat when the metabolism is challenged. Our study may explain how metformin attenuates the excess response to ACTH and helps in weight loss and improving androgen excess in PCOS and CAH.

Pediatric Endocrinology

PEDIATRIC SEXUAL DIFFERENTIATION, PUBERTY, AND BONE BIOLOGY

High Throughput Genetic Analysis Revealed Novel Genomic Loci and Candidate Genes Involved in Central Precocious Puberty Associated with Complex Phenotypes

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SUN-081

Background: Central precocious puberty (CPP) is mostly described as an isolated entity. Few studies have shown an association of CPP with complex cases or genetic syndromes, but without making inferences on molecular causalities.
Objective: To genetically investigate a cohort of patients with CPP associated with complex phenotypes using high throughput methodologies.
Patients and methods: From a large cohort of patients with idiopathic CPP followed at a university hospital outpatient clinic, thirty-eight patients were selected for high throughput genetic investigation for presenting at least 3 additional clinical features and conditions, characterizing complex phenotypes. All had normal brain MRI. Pathogenic allelic variants in CPP known genes were initially excluded. All patients were submitted to genomic microarray (SNP or CGH arrays). A subset of patients was also submitted to whole-exome sequencing (11 cases) or target panel sequencing (18 cases).
Results: Among the group of 38 patients (35 girls, 4 boys; 21 sporadic, 17 familial), mean age at puberty onset was 5.8 ±2.1 and 8.3 ±3.0 yr in girls and boys, respectively. The more prevalent clinical features described included metabolic, growth and neurocognitive phenotypes; less prevalent features included dysmorphic features and congenital anomalies. Pathogenic or probably pathogenic genetic defects were identified in 9 cases: 5 sporadic (all identified as *de novo*) and 4 familial. Defects in sporadic cases were as follows: three cases with 7q11.23 deletion (Williams syndrome); one girl with ventricular arrhythmia presenting a rare 1p31.3 duplication, involving *NFIA* gene coding a transcription factor of NFI family with hypothalamic expression; and one girl with imperforate anus and learning difficulties with rare frameshift variants in *AREL1* gene (p.Ser229Aspfs*3) coding an ubiquitin ligase, and *TNRC6B* gene (p.Gly665Leufs*35) coding a regulator of translational inhibition. In the four familial cases, the genetic defects segregated with CPP in a dominant inheritance mode. Three cases from unrelated families presented growth phenotypes and Xp22.33 deletions, including *SHOX* gene and other elements. One boy with maternal familial CPP and autism had two rare potentially pathogenic variants: a frameshift deletion in *MKKS* gene (p.Phe144Leufs*14); and a missense variant (p.Pro267Leu) in *UGT2B4* gene. Interestingly, the later gene encodes a protein involved in estrogen hydroxylation and is associated to menarche timing in GWAS.
Conclusion: Novel genetic defects were identified in 23% cases of CPP associated with complex phenotypes. Three chromosomal regions represented *loci* potentially implicated in CPP: Xp22.33, 7q11.23 and 1p31.3. Five genes were identified as candidate genes associated with CPP: *NFIA*, *AREL1*, *TNRC6B*, *MKKS* and *UGT2B4*.

Thyroid

THYROID DISORDERS CASE REPORTS III

Evaluating Conflicting Thyroid Function Tests in New Admissions: Discordance of TSH, FreeT4 and Clinical Status: A Clinical Challenge!

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MON-473

Background: It is not uncommon to encounter patients whose thyroid function tests (TFTs) seem mutually inconsistent or inconsistent with a patient's clinical status, At times, the simplest reconciliation of the findings invokes a rare disorder that we are hesitant to accept. In this case, a clinically euthyroid patient presents with elevated TSH and Free T4 (FT4) suggestive of a TSH-producing tumor or of Thyroid Hormone Resistance.
Clinical Case: A 72 yr-old man with cardiomyopathy on amiodarone is admitted to the Medical Service for treatment of anasarca. He had no symptoms or signs of thyroid dysfunction and was not taking L-T4, amphetamines or propranolol. Findings on exam included normal VS, runs of atrial tachycardia, and edema from feet to scrotum. Thyroid exam was normal. Serum creatinine was 2.24 mg/dl (NL: 0.67-1.17). Bili was 2.7 mg/dl (NL: 0.67-1.17); AST and ALT were normal, Chest x-ray revealed cardiomegaly with clear lung fields. Thyroid ultrasound revealed a normal size gland containing a few sub-centimetric nodules. On ***Day 2*** The serum FT4, by analog assay, was elevated at 1.66 ng/dl (NL: 0.76-1.46) and TSH was elevated at 9.06 mIU/L (NL: 0.35-3.74), Anti-peroxidase and anti-thyroglobulin antibodies were negative. The Medical Service' diagnosis was "amiodarone-induced thyroiditis." The amiodarone was discontinued and diuresis was induced with bumetanide, Endocrinology consultation was requested On ***Day 4*** the FT4 and TSH were still elevated at 1.62 and 10.1, respectively. FT4 by dialysis was *not elevated* at 1.62 ng/dl (NL: 0.9-2.2). The FT3 was 2.34 pg/ml (NL: 2.18-3.98). **On *Day 5*** Anti-thyroxine antibodies and Thyroid Stimulating Immunoglobulins (TSI) were negative. Paired TSH samples with and without neutralization of Human Anti-Mouse Antibodies (HAMA) were identical: both elevated at 8.30 mIU/L (NL: 0.4-4.50). Serum Iodine was markedly elevated at 2288 mcg/L (NL: 52-109).
The FT4 levels by analog assay therefore appear to have been falsely elevated (as indicated by the dialysis assay) though not by recognized factors such as thyroxine antibodies, amphetamines or propranolol. Continued