

genes and play a crucial role in the implementation of sex hormones function.

The aim of the study was to assess the vitamin D level in women of reproductive age, depending on the presence of signs of PCOS and waist circumference (WC).

71 women from 19 to 44 years old were examined of these, 41 patients were diagnosed with PCOS and impaired ovulatory function, in 30 patients the ovulatory cycle was preserved, and signs of PCOS were not detected. The level of vitamin 25 (OH) D3 in the serum of the subjects was evaluated by tandem chromato-mass spectrometry at the ArchiMed clinic of new medical technologies, Moscow.

In the recommendations of the Canadian "The Vitamin D society", 40-60 ng/ml the optimal level of serum vitamin D, a concentration of 20-40 ng/ml insufficiency, <20 ng/ml as a deficiency.

Vitamin D deficiency was detected in 57% of women in both groups, with a pronounced deficiency (<10 ng/ml) in 17%, insufficiency was observed in 43% of cases, a sufficient level was not detected in any of the subjects. The average level of vitamin D in patients with PCOS was 18.2 (2 to 32.3) ng/ml, the value in patients without signs of PCOS was 18.5 (6.8 to 31) ng/ml.

Comparison of the vitamin D value with WC showed that in women with PCOS with an WC <80 cm the value of this indicator was 18.8 ng/ml, and for WC ≥ 80 cm it was statistically significantly lower - 13.3 ng/ml (p<0.05).

Conclusion. High prevalence of vitamin D deficiency among patients of reproductive age, with no differences in the magnitude of this indicator depending on the presence of signs of PCOS and persistent ovulation.

Difference was established between the levels of vitamin D in patients with PCOS depending on the waist circumference - its insufficiency increases with an increase in WC.

The results of the study suggest that the deficiency of vitamin D in the body increases with the aggravation of hormonal dysfunction in PCOS, which should be taken into account by specialists during the management of this category of patients and the treatment of infertility.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Endogenous Expression of TCF21 by CRISPR/dCas9 System Results in Different Biological Responses in Adrenocortical Carcinoma and Hepatocarcinoma

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Transcription factor 21 (TCF21/POD-1/Epicardin) inhibits the expression of SF-1 (NR5A1) by binding to the promoter E-box site in adrenocortical carcinoma (ACC). In contrast, TCF21 promotes increased expression of LRH-1 in hepatocarcinoma cell line, HepG2 cells, by binding to the Small Heterodimer Partner (SHP/NROB2) promoter region, an LRH-1 negative regulator. Epigenetic alteration induced TCF21 loss of function and has been associated with increased of cellular migration and invasion. In ACC, TCF21 promoter is hypermethylated and less expressed.

Our aim was to evaluate the effect of TCF21 by expressing or silencing TCF21 in adrenocortical pediatric adenoma, ACA-T7 cells, in ACC cell lines SW-13 and H295R cell line, and in HepG2 cell line. Were used CRISPR/dCas9/TCF21 and pCMVMycPOD1 or siRNATCF21 to express and silence TCF21, respectively. Increased expression of TCF21 in H295R/pCMVMycPOD1 and SW-13/CRISPR/dCas9/TCF21 cells resulted in significantly decreased cell migration and invasion (53.2±36.1%/70.8±26.5% and 82.6±4.2%/100%, respectively). In ACA-T7/siRNATCF21 cells, the inhibition of TCF21 resulted in significant increase migration and invasion capacity (45.0±12.7%/33.1±17.4%) compared with ACA-T7 cells. Higher TCF21 expression in HepG2/CRISPR/dCas9/TCF21 increased invasion [147.08±16.54% (p<0.0001)]. Analysis of metalloproteinase genes expression showed that TCF21 significantly (p<0.01) increased MMP8 expression in SW-13/CRISPR/dCas9/TCF21 and H295R/pCMVMycPod-1 whereas decreased MMP9 and MMP2 (p< 0.0001). The opposite effect was observed in ACA-T7/siRNATCF21. Moreover, in HepG2/CRISPR/dCas9/TCF21 cells was observed an increase of MMP2 and MMP9 expression (p<0.001). These results suggest that TCF21 regulate epithelial mesenchymal transition and vice versa (EMT/MET) in tumors depending on cellular context. Supported by Fapesp and Capes.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Pattern and Predictors of Thyroid Dysfunction Among Paediatric Endocrine Referrals at Tertiary Care Centre: A Longitudinal Study

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Background Post iodisation era has experienced gradual change in pattern of thyroid disorders among paediatric population with autoimmunity taking precedence over iodine deficiency disorders and subclinical hypothyroidism (SCH) now more frequently diagnosed but inappropriately managed. **Aims** This study was conducted to evaluate pattern of abnormal thyroid function among children referred to our tertiary care centre, to ascertain characteristics that influence treatment decisions and to follow them for various outcome measures. **Design** It was an observational longitudinal follow up study where all children less than 18 years, referred to our outpatient clinic for suspected thyroid disorder were recruited. Demographic data, personal and family history, clinical features were noted and laboratory tests including TT4, TT3, TSH, anti-thyroid peroxidase(antiTPO) and anti-thyroglobulin(antiTG) antibody were conducted in study subjects. Management was based on the clinical judgment of the attending endocrinologist. Patients were followed at 6 week, 3 months, 6 months and one year with clinical and laboratory work up at each visit. **Results** A total of 241 subjects aged 18 days to 17 years were included out of which 62.25% were females. Initial evaluation revealed SCH in 40% of referred

subjects, overt hypothyroidism (OH) in 33%, congenital hypothyroidism (CH) in 18% and overt thyrotoxicosis in 5%. Autoimmune thyroiditis constituted the major cause of hypothyroidism in the OH group with significantly higher prevalence of anti-TPO and antiTG antibody in comparison of SCH group (61% vs 31%; 45% vs 21.9%, $p < 0.05$) respectively. All subjects in OH group were treated whereas 76% subjects in SCH group were treated and the mean dose of L thyroxine required to treat OH was significantly higher ($2.31 \pm 1.1 \mu\text{g}/\text{kg}/\text{day}$ vs $1.76 \pm 1.07 \mu\text{g}/\text{kg}/\text{day}$; $p < 0.001$) in comparison of SCH group. A major independent predictor of treatment in SCH was initial TSH which was significantly higher in the treated group ($11.65 \pm 3.80 \text{ uIU}/\text{ml}$ vs $9.24 \pm 1.31 \text{ uIU}/\text{ml}$; $p < 0.001$). Subjects with congenital hypothyroid presented at a mean age of 6 months (18 days to 2 years) with most common aetiology being thyroid hypoplasia and dyshormonogenesis (20% each). Graves' disease was diagnosed in 11 out of 12 subjects with thyrotoxicosis and were treated with antithyroid drugs. Overall 85.5% of referred subjects were treated and after one-year follow up management was found to be adequate in 81% subjects. **Conclusions** The evolving trend of diagnosing children having nonspecific symptoms with SCH is a matter of concern as many are subjected to the burden of unwanted prolonged treatment and frequent testing as highlighted in our study. Delayed presentation of CH in our study warrants active surveillance of children at birth for thyroid disorders to avoid long term adverse effects on mental development.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Female Mice Lacking Brain Insulin Production Exhibit Learning Deficits, Anxiety, and Reduced Hippocampal Cyclin D1 Expression

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Insulin dysregulation independently underlies diabetes and Alzheimer's Disease (AD) pathology. However, the former has also been shown to be a risk factor for the latter. The ancestral insulin gene (*Ins2*), but not the pancreas-specific *Ins1* gene, is transcribed locally within the brain in mice. We confirmed that neuronal expression of *Ins2* is most prominent within the hippocampus, a brain region with established roles in learning and memory, and that it was reduced by a diet known to promote neuronal dysfunction. It is not yet clear, however, how insulin produced locally within the brain influences hippocampal function, learning and memory. To eliminate brain-derived insulin, we used young and old mice with germline *Ins2* knockout (*Ins2*^{-/-}) and their normal

complement of wildtype *Ins1* alleles, which had equivalent pancreatic insulin and normal glucose homeostasis. Using the Morris water maze, we found that learning and memory performance of female *Ins2*^{-/-} mice was significantly impaired relative to wild-type mice, whereas the performance of male *Ins2*^{-/-} and wild-type mice did not differ. During acquisition training, the swim-speed in female *Ins2*^{-/-} was faster than wild-type mice, suggesting increased stress reactivity and motivation to escape from water. Indeed, anxiety-like behavior was increased in female mice as assessed by the open-field test. Using RNA sequencing to profile isolated hippocampi, we found that female *Ins2*^{-/-} mice had a significant reduction in Cyclin D1 (*Ccnd1*) compared with littermate controls. This observation points to a possible defect in hippocampal neurogenesis, a physiological hallmark of impaired memory and emotionality implicated in both, diabetes and AD. Together these data suggest that *Ins2* plays sex- and brain region-specific roles in neuronal function and perhaps adult neurogenesis.

Adrenal

ADRENAL CASE REPORTS I

When Acne, Hirsutism and Menstrual Irregularities Are More Than PCOS

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SAT-210

Background: Polycystic ovarian syndrome (PCOS) mimics non-classic congenital hyperplasia (NCCAH), presenting with hyperandrogenic symptoms. NCCAH is usually diagnosed later in life, where 21-hydroxylase (21OHD) is the most common deficiency. There are more than 300 mutations in 21OHD, being V281L one of the described mutations.

Clinical Case: 23 y/o female patient G0P0 comes to the office complaining of irregular periods, frontal hair loss, weight gain, acne and hirsutism. She has had noticed these changes since menarche; however, her acne was getting worse. Was seen 2 months prior to presentation by her gynecologist who order a free Testosterone that was elevated (6.4 pg/mL, $n < 4.2 \text{ pg}/\text{mL}$), with normal TSH (1.1 uIU/mL, $n, 0.45-4.5$). She was not taking any medication. Her mother has history of 2 spontaneous abortions and her sister has acne and hirsutism as well. On physical exam BMI was 26, it was noticed comedones and papules on her face, back and shoulders. Ferriman-Gallwey scale was > 8 . At the initial visit due to the clinical scenario, it was thought that she had hyperandrogenic syndrome, probably secondary to PCOS. Serum blood test were ordered and showed an elevated total testosterone (71 ng/dL, $n, 8-48 \text{ ng}/\text{dL}$), free testosterone (8.4 pg/mL, $n < 4.2 \text{ pg}/\text{mL}$), 17-OH pregnenolone performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) was (429 ng/dL, $n, 35-290 \text{ ng}/\text{dL}$ luteal phase) and androstenedione LC-MS/MS (1941 ng/dL, $n, 41-262 \text{ ng}/\text{dL}$) which confirmed NCCAH diagnosis due to 21OHD. She had no desire to become pregnant at the time of evaluation; however, was concern about fertility and genetics. Was started on OCPs and genetic testing was positive for V281L mutation in the CYP21A2 gene, being homozygous for this