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OR30-07

Background: The duodenum is a key metabolic signaling center and regulator of metabolic homeostasis. Duodenal mucosal hyperplasia is therefore a potential therapeutic target for metabolic diseases related to insulin-resistance. Previous reports demonstrated that DMR, a minimally invasive, endoscopic mucosal ablative procedure, safely improves hepatic and glycemic parameters. Primary endpoints from REVITA-2, the first randomized, sham-controlled, double-blind, prospective, multicenter study of DMR safety and efficacy in patients with T2D, were met and previously reported. Here we further explore mechanisms underlying the beneficial effects of DMR on hepatic and glucose metabolism by analyzing mixed meal tolerance test (MMTT) data from the REVITA-2 study. **Methods:** Eligible patients (HbA1c 7.5–10%, BMI ≥ 24 to ≤ 40 kg/m^2, on stable treatment with ≥1 oral anti-diabetic medication) received DMR or sham procedure (1:1). Exploratory endpoints included median change in fasting plasma glucose (FPG), MMTT glucose area under the curve (AUC) over 2 hours, and change in MMTT C-peptide and glucagon over 2 hours, from baseline to 12 weeks post-DMR. One-sided *P* value based on ANCOVA model on ranks without imputation assessed treatment difference at the 0.05 significance level. The modified intent to treat primary analysis population included randomized patients in whom study procedure was attempted. **Results:** A total of 70 patients (DMR, N = 35; sham, N = 35) were included in the analysis, of which 57% and 54% (DMR, n = 20; sham, n = 19) had baseline FPG ≥ 180 mg/dL. Median MMTT AUC for glucose was significantly reduced post-DMR (-36.38 mg/dL) compared with sham (-4.94 mg/dL; *P* = 0.009), driven by a significant decrease in FPG (DMR, -41.0 mg/dL; sham, -15.0 mg/dL; *P* = 0.003) rather than median MMTT postprandial glucose excursion (DMR, -4.63 mg/dL; sham, 5.34 mg/dL; *P* = 0.209). AUC glucose reductions were more pronounced in patients with baseline FPG ≥ 180 (DMR, -63.03 mg/dL; sham, -20.31 mg/dL; *P* = 0.007) compared with baseline FPG < 180 (DMR, -26.81 mg/dL; sham, 13.81 mg/dL; *P* = 0.271). In patients with baseline FPG ≥ 180, postprandial C-peptide excursion was significantly increased (DMR, 0.41 ng/mL; sham, 0.02 ng/mL; *P* = 0.012) and postprandial glucagon excursion was significantly decreased (DMR, -8.03 pg/mL; sham, 2.13 pg/mL; *P* = 0.027). **Conclusion:** DMR markedly improves glucose responses to a mixed meal challenge, primarily driven by a decrease in FPG, suggesting a primary effect on insulin resistance. Increases in C-peptide and reductions in glucagon levels suggest improvement in beta cell function in addition to improvements in hepatic insulin sensitivity, and ratifies the position of the duodenum as both a culprit endocrine organ and therapeutic target for patients with T2D.

Cardiovascular Endocrinology

PREVALENCE, DIAGNOSIS, AND MECHANISMS OF HYPERALDOSTERONISM

Somatic Transmembrane Domain Mutations of a Cell Adhesion Molecule, CADM1, Cause Primary Aldosteronism by Preventing Gap Junction Communication Between Adrenocortical Cells

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OR34-02

Primary Aldosteronism (PA) is the commonest curable cause of hypertension. Whole exome sequencing (WES) in 2011 and 2013 identified common somatic mutations in genes regulating membrane polarisation in 60–80% of aldosterone-producing adenomas (APA). We undertook WES on 39 consecutive APAs in search of further variants. 1 APA revealed a somatic mutation (Val380Asp) within the single transmembrane domain of *Cell Adhesion Molecule 1* (*CADM1*). An adjacent mutation (Gly379Asp) was discovered on WES from a PA patient in Munich.

Both short and long isoforms (442 & 453 residues) of wild-type (WT) and both mutant *CADM1* genes were cloned into lentivirus vectors and each transduced into adrenocortical (H295R) cells to assess its effect on aldosterone secretion and other parameters. Previous studies in pancreatic islet cells suggested a role of CADM1 in regulating gap junction (GJ) communication. To assess this we microinjected single WT or mutant H295R cells with the GJ permeable dye calceinAM and counted the dye-positive cells after 1 hour. The effect of inhibiting or silencing GJs in H295R cells using peptide gap27 or a Dharmacon smartpool was assessed. H295R cells were also co-transfected with WT or mutant *CADM1* and the GJ protein CX43, tagged with the mApple fluorophore. These were mixed with cells transfected with CX43-Venus, allowing confocal visualisation of GJ formation. Protein modelling was undertaken to determine whether Asp in the intramembranous domain changes angulation of CADM1.

All mutant isoforms had consistently different effects, shown as a range compared to WT. Cells transduced with mutant *CADM1* showed 3-6-fold increase in aldosterone secretion ($p<0.01$) and 10-20-fold increase in *CYP11B2* expression ($p<0.001$) compared to WT. Dye transfer assays showed paucity of dye transfer between neighbouring mutant *CADM1* cells, while calcein passed easily through GJs in WT cells. CX43 inhibition increased aldosterone secretion 2-fold ($p<0.01$), and *CYP11B2* expression 3 to 8-fold (<0.001). Knock-down of GJ proteins increased aldosterone

secretion 1.5-fold (p<0.01) and *CYP11B2* expression 1.7-fold (p<0.001).
Protein modelling showed mutations to increase the angle of ectodomains to cell membrane, from 49° in WT cells, to 62° and 90° in Gly379Asp and Val380Asp respectively; increasing inter-cell distance from 21.2nm to 24.7 and 27.9nm. Mixing of Venus and mApple-tagged CX43 transfected cells showed fewer intact GJ channels in cells co-transfected with mutant compared to WT *CADM1* [mutant 42/291 (14.4%) VS WT 68/212 (32.1%) p<0.001].
The *CADM1* mutations shows the importance of membrane proteins in aldosterone regulation to extend beyond ion channels and transporters. A key role may be to bring opposing CX43 hemichannels close enough to form GJ channels, permitting the oscillating Ca^{2+} currents which regulate aldosterone in intact adrenal slices.

Thyroid

THYROID DISORDERS CASE REPORTS II

Unusual Case of Hypothyroidism Possibly Due to Dialysis Leading to Van Wyk Grumbach Syndrome (VWGS)

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SAT-520

Background: Van Wyk Grumbach Syndrome (VWGS) is characterized by precocious central puberty in the setting of juvenile chronic primary hypothyroidism with symptom regression following thyroxine replacement.
Clinical Case: A 2 year old girl with dysplastic kidneys and chronic renal disease had been treated by her nephrologist with growth hormone for poor growth. She was referred to Endocrinology for evaluation of bloody dialysate thought to be retrograde menstrual flow. Pelvic US showed bilateral large cystic adnexae possibly ovarian cysts versus septated collections of dialysate fluid. Hormone measurements showed pubertal levels of LH 0.4mIU/mL and FSH 5.4mIU/mL, with a relatively low Estradiol 5.3pg/mL. Brain MRI showed impressive pituitary enlargement measuring 1.3cm craniocaudally. Additional laboratory testing was notable for a low normal free T4 fT4 0.9ng/dL and markedly elevated TSH>1000uIU/mL and Prolactin 835ng/mL. Thyroid US showed thyroid enlargement, and echogenic and hyper vascular gland. Anti-thyroid antibodies titers were normal, AM cortisol and IGF1 were also normal for age. We speculate that this case of profound hypothyroidism was due to dialysis, as thyroid function improved after the child underwent renal transplantation. Levothyroxine was discontinued 5 months after renal transplantation. Elevated TSH may induce a form of pseudopuberty as the TSH alpha subunit is similar to that of LH and binds to the LH receptor to stimulate the ovaries with cyst formation.
Conclusion: In VWGS, primary hypothyroidism with elevated TSH induces central precocious puberty. This child's bloody diasylate was likely the result of transient central precocious puberty associated with uncontrolled primary hypothyroidism with elevated TSH and prolactin. Although the literature on dialysis suggests minimal thyroid hormone losses, this case shows the importance of monitoring thyroid hormones in dialysis patients. Early recognition of VWGS and initiation of thyroid hormone replacement can lead to resolution of symptoms.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Natural History and Neurodevelopmental Outcomes in Perinatal Stress Induced Hyperinsulinism

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MON-087

Background:
Hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in neonates, infants and children. Persistent hypoglycemia due to HI in the neonatal period and infancy has detrimental effects on the developing brain, leading to permanent brain damage. As such, neonatal hypoglycemia due to HI may be one of the most readily preventable causes of neurodevelopmental impairment. While monogenic forms of HI are rare with an estimated incidence in the US of 1:50,000 live births, perinatal stress-induced HI (PSIHI) is common and affects up to 50% of at-risk neonates, with an estimated incidence of 1:12,000 live births. There is a paucity of high quality evidence investigating neurodevelopmental outcomes in PSIHI.
Methods:
Subjects with HI and history of perinatal stress diagnosed between 2013 - 2018 and with demonstrated cure by fasting test by 2 years were included. Exclusion criteria included patients born prior to 32 wks gestation, congenital or syndromic HI and other diagnoses known to impact development. Medical records were reviewed and families were interviewed and asked to complete questionnaires for three validated neurodevelopmental assessments: ABAS-3, BRIEF-P, and CBCL (1.5–5).
Results:
Medical records of 98 eligible subjects were reviewed to date (74% males), 37% were born between 32–37 wks (mean gestational age 37.2 wks). Mean birth weight was 2.53kg. Median age of hypoglycemia presentation was 0 days, as 67% of subjects presented on day of life 0. Median age at HI diagnosis was 12 days, and the median length of time from first episode of hypoglycemia to definitive treatment was 14 days. Mean maximum glucose infusion rate was 12 mg/kg/min. 81% of subjects were successfully treated with diazoxide. Median time to demonstrated resolution of disease was 210 days.
Parent interviews were completed for 33 subjects to date. Developmental concerns were reported by 52% of parents, and 41% reported pediatrician concerns. A diagnosis of speech delay was reported by 45% of parents, and 24% reported concerns for a learning disability. Behavioral concerns were reported by 45%, with 21% reporting diagnoses or specific concerns for ADHD and 12% reported diagnoses or strong concerns for autism.
Neurodevelopmental assessments were completed in 15 subjects to date. The proportion of study subjects who