

scored more than 1 SD and 2 SDs outside the normal range on any of the major assessment scales was 33% and 6%, respectively (vs 15.8% and 2.2% in the general population for any individual scale).

Conclusion:

Children with PSIH are predominantly male and most are born at term. While the majority of infants presented with hypoglycemia in the first day of life, diagnosis occurred most often 12

days later, with definitive treatment achieved after two weeks of life. Patients with PSIH are at high risk of neurodevelopmental deficits, and are more likely to perform below average on developmental testing.

Diabetes Mellitus and Glucose Metabolism

TYPE 2 DIABETES MELLITUS

MODY-14: A Rare Cause of Inherited Diabetes

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Case: A 29-year-old physically active, lean man presented with a three-year history of poorly controlled diabetes diagnosed during a flu-like illness and no history diabetic ketoacidosis. Despite treatment with various oral hypoglycemic medications his glycated hemoglobin was consistently above target (never falling below 9.3%) and correlated with home blood glucose readings. His mother had gestational diabetes with all three of her pregnancies. His maternal grandmother was also known to have diabetes. Pancreatic islet antibodies were negative. C-peptide levels were low. Monogenic diabetes (MODY) was suspected. Discussion: Genetic testing revealed a mutation in the Adaptor Protein, Phosphotyrosine Interaction, PH domain, and leucine zipper containing 1 (APPL1) gene. APPL1 is involved in insulin secretion and insulin signaling via the Akt pathway [1,2,3]. Other mutations of APPL1 causing MODY-14 have been previously described [4]. In our case, the substitution of glutamate for aspartate at the 265 position occurs within the unique fourth alpha helix of the BAR domain of APPL1 [5]. Generally, BAR domains contribute to APPL1 dimerization and plasma membrane association [5]. Substitution of glutamate could disrupt protein folding, impairing dimerization and phosphorylation of Akt, thereby decreased insulin secretion as seen in other mutations of the BAR domain of APPL1 [4]. Although this remains a hypothesis, loss-of-function of APPL1 would explain the lack of insulin secretion without evidence of pancreatic autoimmunity. If the hypothesis is correct, it would be a novel mutation attributable to this MODY subtype. 1. Cheng KKY, Lam KSL, Wu D, et al. APPL1 potentiates insulin secretion in pancreatic β cells by enhancing protein kinase Akt-dependent expression of SNARE proteins in mice. *Proc Natl Acad Sci U S A*. 2012;109(23):8919–8924. doi:10.1073/pnas.1202435109 2. Ryu J, Galan AK, Xin X, et al. APPL1 potentiates insulin sensitivity by facilitating the binding of IRS1/2 to the insulin receptor. *Cell Rep*. 2014;7(4):1227–1238. doi:10.1016/j.celrep.2014.04.006 3. Saito T, Jones CC, Huang S, Czech MP, Pilch PF. The interaction of Akt with

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Healthcare Delivery and Education EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

Structure, Process and Outcomes of Transitional Care in Endocrinology: Pilot Results from the Intersect Study (International Study of Endocrine Care During Transition to Adult-Oriented Care)

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BACKGROUND: Structured transitional care (TC) is the planned, purposeful transfer from pediatric to adult care that aims to maintain high quality, developmentally appropriate continuous care. Relatively little is known about how endocrine TC is structured internationally, the process of TC and what outcomes are a priority for endocrine TC. This pilot study aimed to better understand endocrine TC and identify key elements for successful implementation internationally. **METHODS:** The Donabedian framework (structure-process-outcome) guided the international web-based survey examining TC programs for adolescents and young adults (AYAs) 16–25 years-old. The survey examined: 1) best practices i.e. six core elements of TC (Center for Health Care Transition Improvement ‘Got Transition’); 2) nursing involvement; 3) perceived importance of the ‘10 priority outcomes’ identified by an international multidisciplinary Delphi process (Fair et al. *JAMA Pediatrics*, 2016); and 4) promoters/barriers to implementation. Descriptive analysis was conducted for close-ended questions and thematic analysis for open-ended questions. Rankings by endocrine clinics were compared to the ‘10 priority outcomes’. **RESULTS:** Invitations were sent to authors of publications/posters on endocrine TC from the past 10 years. Eight responses were recorded from academic medical centers across seven countries with structured (n=3), semi-structured (n=2) and unstructured TC (n=3). Only 2/8 received institutional funding. Two practices involved nurses in assessing transition readiness and cited direct clinical care, therapeutic education and emotional support for AYAs/families as important contributions. Groups lacking nursing involvement expressed desire for a nursing role if financed. The most commonly used ‘Got Transition’ core elements were: providing supporting materials, confirming adult visit and consulting with adult providers. Only one group formally collected TC outcome data. “Self-management” was rated the most important TC

outcome. “Understanding the condition/complications” and “attending medical appointments” were seen as having relatively higher priority for endocrine TC. Barriers related to lack of financial support and low institutional priority. Involving key stakeholders facilitated implementation. Having a dedicated nurse was noted as an opportunity for improving TC. **CONCLUSIONS:** Implementation of structured TC has been piecemeal and most practices do not fully utilize recommended best practices (‘Got Transition’). Few practices formally collect outcome data. The major perceived barrier to implementing TC is financial. Practices incorporating nurses value discipline-specific contributions. These pilot data point to a role for nursing in providing comprehensive, high quality, comprehensive care for AYAs with chronic endocrine conditions.

Diabetes Mellitus and Glucose Metabolism

IMPACTS OF METABOLISM ON CLINICAL CHALLENGES

Lower Serum Myostatin Levels Are Associated with Higher Insulin Sensitivity in Adults with Overweight/Obesity

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In preclinical models, inhibition of the myokine myostatin prevents or improves insulin resistance (IR). However, studies investigating the association between serum myostatin levels and IR in humans are discrepant, perhaps in part because myostatin immunoassays lack specificity and sensitivity. New sensitive and specific myostatin LC-MS/MS assays make it possible to determine if higher serum myostatin levels are independently associated with greater IR in adults with overweight/obesity. If true, therapeutic manipulation of myostatin pathways may be a potential therapeutic target to prevent or treat type 2 diabetes (T2DM) in this high-risk population, in which current strategies, e.g. weight loss, are difficult to implement and maintain.

We studied 75 adults (53% women), 20–65 yo, BMI ≥ 25 kg/m² and generally healthy without T2DM. Serum myostatin levels (1^o independent variable) were measured by LC-MS/MS (Brigham Research Assay Core, Boston, MA), with no cross-reactivity with growth differentiation factor 11 (GDF11), activins or transforming growth factor beta (TGF- β), sensitivity of 0.5 ng/mL and intra- and inter-assay coefficient of variation of 10 and 12%. Insulin sensitivity (IS) (1^o dependent variable) was estimated by QUICKI, appendicular lean mass (ALM) by DXA, visceral adipose tissue (VAT) by CT and intrahepatic (IHL) and intramyocellular lipids (IMCL) by MR spectroscopy. Models were run sex- combined and stratified given sex differences in muscle mass.

Mean age was 47.9 \pm 12.2 years and BMI was 33.2 \pm 5.7 kg/m² (mean \pm SD). Compared to men, women had lower mean ALM (20.9 \pm 3.3 vs 29.2 \pm 3.3 kg, p<0.0001) and serum myostatin levels (7.28 \pm 1.87 vs 8.28 \pm 1.89 ng/mL, p=0.02) and similar mean IS (0.16 \pm 0.02 vs 0.15 \pm 0.02, p=0.13). Lower serum myostatin levels were associated with higher IS in the whole group (R=-0.32, p=0.008) and in women (R=-0.41, p=0.02)—both remained significant after controlling for ALM—but not in men (R=-0.16, p=0.36). In a multivariate model including VAT, IHL, IMCL and ALM, lower serum myostatin levels were associated with higher IS in the whole group (B₁= -0.37, p=0.003), in women (B₁= -0.43, p=0.02) and in men (B₁= -0.37, p=0.05). In a stepwise regression model including VAT, IHL, IMCL and ALM, VAT explained 18%, IHL explained 10% and myostatin explained 8% of the variability in IS in the whole group; in women, myostatin explained 18% and IHL explained 12% of the variability; in men, VAT explained 26% of the variability and myostatin was not a significant determinant.

In conclusion, lower serum myostatin levels were associated with greater IS in adults with overweight/obesity, independent of muscle and adipose depots known to be associated with T2DM risk. Future studies should investigate potential sex differences in the association between myostatin and IS. Therapeutic manipulation of myostatin pathways may be a potential therapeutic target to prevent or treat T2DM.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Bioactivity of Long Acting PTH Fusion Molecules Tested in a Novel Non-Surgical Animal Model of Hypoparathyroidism

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Introduction: There is an unmet need for the development of long-acting PTH molecules to treat patients with hypoparathyroidism. We have established a novel non-surgical rodent model of hypoparathyroidism using oral Cinacalcet-HCl to test long acting analogues of PTH. Here we have tested the pharmacodynamics properties of two long acting PTH fusion molecules.

Methods: PTH fusion molecules tested: Fusion-1 is PTH (1–34) linked to GHBP (residues 1–238), and Fusion-2 is a Hybrid PTH-PTHrP (1) linked to GHBP (residues 1–238). For in vivo studies, normal male wistar rats were gavaged with 30 mg/kg Cinacalcet-HCl, immediately followed by a subcutaneous dose of PTH Fusion at 20 nmol/kg. Control animals received PTH (1–34) and vehicle only. Serum samples were taken and analysed for ionised calcium (iCa).

Results: Oral administration of Cinacalcet-HCl caused a reduction in iCa that was significantly different from vehicle controls at 2 to 24hrs post dose (ANOVA $P < 0.0001$). PTH