and the BioBreeding (BB) rat have identified a peripheral inflammatory state associated with diabetes susceptibility that is consistent with microbial antigen exposure and pattern recognition receptor ligation. *Lactobacillus plantarum* 299v (Lp299v), a probiotic strain, is reported to increase plasma and stool levels of anti-inflammatory short chain fatty acids (SCFA) and promote IL-10 signaling in colonic derived macrophages and T-cells. Here we investigated the effect of Lp299v supplement on T1D progression and inflammatory phenotypes in diabetes prone BB DR*lyp/lyp* rats. Rats were weaned at 21 days onto a normal cereal diet (ND) or a gluten-free hydrolyzed casein diet (HCD), with and without daily Lp299v supplementation. All DR*lyp/lyp* ND rats developed T1D by day 83 (mean time to onset of 62.8+/-7.9 days). DR*lyp/lyp* ND+Lp299v rats exhibited an insignificant delay in T1D onset (62.6+/-6.5 days), however 8% remained diabetes-free to day 130. Providing DR*lyp/lyp* rats HCD prevented T1D in 17% of rats (to age 130 days) and significantly delayed onset (mean time to onset 72.8+/-7.3 days, $p<0.001$). Providing DR*lyp/lyp* rats HCD+Lp299v prevented T1D in 25% of rats and more robustly delayed onset (mean time to onset 84.9 +/-14.3 days, $p<0.001$). While multiplex ELISA failed to detect significantly altered plasma cytokine/chemokine levels at 40 days of life, plasma induced transcription revealed the greatest normalization of systemic inflammation in the HCD+Lp299v group. Plasma SCFA levels (propionate and butyrate, $p<0.01$) were elevated in the HCD+Lp299v group compared to the ND group. Global gene expression analysis of pancreatic islets was conducted at 40 days, prior to insulitis. Endoplasmic reticulum (ER) stress has been implicated in the formation of islet neoantigens that may underlie the initial loss of immune tolerance in T1D. Under one or both diets, Lp299v favorably modulated islet expression levels of pathways and transcripts related to inflammation and innate immunity (*Cxcl9, Cxcl10*), oxidative stress (*Gsta1, Gsta4, Gstp1, Gstk1*), as well as ER stress and unfolded protein response (*Cirbp, Edem1, Hspa1a, Atf4*). These ongoing studies add to a growing understanding that inherited susceptibility can be modulated by diet and microbiota.

Pediatric Endocrinology

DIABETES, INSULIN, AND LIPIDS IN PEDIATRIC ENDOCRINOLOGY

Sphingosine 1- Phosphate Lyase Insufficiency Syndrome (SPLIS); A Role in Multiple Endocrinopathies

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Sphingosine 1-phosphate lyase insufficiency syndrome (SPLIS) was described in 2017 as a novel condition affecting sphingolipid metabolism. There is a multisystemic phenotype including nephrotic syndrome and primary adrenal insufficiency (PAI) and to a lesser extent ichthyosis, neurological disease and lymphopenia. A proportion of patients also presented with hypothyroidism and hypogonadism. To interrogate the endocrine aspect of the syndrome we reviewed clinical data within our patient cohort with SPLIS and those within the wider literature. To date there have been 45 patients identified with SPLIS with significant associated mortality (n=23/45, 51%; 4 of these *in utero*). There is no clear genotype-phenotype correlation. Whilst nephrotic syndrome is most prevalent (n=34/45; 76%), a significant proportion of patients (n=27/45, 60%) also presented with glucocorticoid deficiency, some with additional mineralocorticoid deficiency (n=7/27). Five further patients were noted to have adrenal calcifications though biochemistry was not undertaken. Most patients presented with PAI in the first 2 years of life (n=21/27), with the oldest presentation being 11 years of age. Adrenal calcifications are a common finding in those who had documented imaging (n=13/15, 87%). Primary gonadal failure has been reported in 8 male cases, all with concomitant PAI. Presenting features included microphallus (n=7/8) and cryptorchidism (n=8/8), indicating reduced *in utero* androgen exposure. All who had biochemical evaluation demonstrated raised basal LH and FSH/ exaggerated response to LHRH stimulation, a lack of testosterone response to HCG stimulation and low antimullerian hormone (AMH) levels. To date there are no reports of pubertal delay in female patients, and those of age within our cohort have normal ovarian reserve as evidenced by AMH levels (n=2). Primary hypothyroidism, with mildly raised TSH and low Free T4 is reported in 12 patients. Most did not have goiters and had concomitant PAI and nephrotic syndrome (n=11/12). SPLIS is unique amongst sphingolipid disorders in presenting with significant endocrinopathy. This may be the consequence of the particular sphingolipid signature of the disease and the pathogenic mechanisms need to be explored further. It is clear that endocrine dysfunction needs to be considered at diagnosis and surveillance undertaken to detect evolving disease which could have a significant impact on morbidity and mortality.

Pediatric Endocrinology

DIABETES, INSULIN, AND LIPIDS IN PEDIATRIC ENDOCRINOLOGY

The Effect of Cardiorespiratory Fitness and Insulin Resistance on Bone Health in Hispanic Children

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Obesity appears to have a negative impact on pediatric bone health, and insulin resistance may mediate this relationship. It is unclear if cardiorespiratory fitness (CRF) has a protective effect on bone in obese children. We tested the hypothesis that CRF attenuates the negative effect of obesity and insulin resistance on skeletal health in a large cohort of Hispanic youth.
We studied 413 (193 males and 220 females) children and adolescents from the Viva la Familia Study. They were all pubertal; mean age (SD) 13.4 ± 2.3 years; 27% were normal weight (NW), 19% overweight (OW) and 54% obese (OB). They underwent measurement of body composition, total body bone mineral content (BMC) and density (BMD) by DXA scan; VO2peak using the ramp protocol on a treadmill for CRF; fasting glucose and insulin. The homeostasis

model assessment of insulin resistance (HOMA-IR) was calculated. BMC increased from NW to OW to OB (mean 1.35 ± 0.4, 1.41 ± 0.4, and 1.49 ± 0.4 kg, respectively, p=.005). Peak VO2 decreased from NW to OW to OB (41.3 ± 9.7, 35.5 ± 7.7, 28.9. ± 5.5 mL/kg per min, respectively, p <.001). After adjusting for sex, age and lean body mass, BMC was inversely related to fat mass (r = -0.34, p <.001) and HOMA-IR (r = -0.29, p <.001). Similar relationships were found for BMD. In a regression model with BMC as the dependent variable, lean body mass (standardized coefficient (β)=0.95, p <.001) was positively and fat mass (β=-0.18, p <0.001) negatively associated with BMC (model R^2=0.88, p<.001). HOMA-IR (β=-0.07, p =0.001) and VO2peak (β=0.09, p =0.003) had significant and opposite associations with BMC (model p<.001) but fat mass was no longer a significant contributor. With BMD as the dependent variable, lean body mass (β=0.82, p <.001), HOMA-IR (β=-0.06, p =0.04) and peak VO2 (β=0.17, p <.001), but not fat mass, contributed to the variance in BMD (R^2=0.79, p<.001).

In conclusion, lean body mass is the major determinant of BMC and BMD in Hispanic youth. Adiposity associated insulin resistance has a negative effect on BMC and BMD. CRF contributes positively to the variance in BMC and BMD. This suggests that CRF and higher lean mass attenuate the adverse effects of insulin resistance on bone health in children.

Pediatric Endocrinology

DIABETES, INSULIN, AND LIPIDS IN PEDIATRIC ENDOCRINOLOGY

Trends in HbA1c Change Among Youth Referred to a Pediatric Type 2 Diabetes Prevention Clinic

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Background: Pediatric type 2 diabetes (T2D) has increased in prevalence as childhood obesity rates climb. More youth are being referred to pediatric endocrinology due to the concern for developing T2D, yet prediction of which children will progress to overt T2D is challenging. We describe a single center experience with pediatric prediabetes referrals and trends in HbA1c change.

Methods: Retrospective review of new patients seen at a Type 2 Diabetes Prevention (T2DP) Clinic July 2015 - December 2019. All children referred to T2DP Clinic have an elevated BMI and findings of insulin resistance/prediabetes/early T2D. They are evaluated by pediatric endocrinology providers and dieticians at each visit.

The outcome of interest was categorical HbA1c change between patients' initial and most recent T2DP Clinic visit. Only HbA1c measurements conducted at the study site were included to address inconsistencies in lab assays. HbA1c at the initial visit was categorized into 3 groups: 1) < 5.7%; 2) 5.7 to <6.5%; 3) 6.5% to <8.5%. Final HbA1c was categorized similarly with the option to progress to a 4th HbA1c group of ≥8.5%. Patients were categorized as progressors, regressors, or stable depending on change in group (e.g., group 1 --> group 2) between initial and most recent HbA1c. Comparisons between groups were made using ANOVA and Fisher's exact tests.

Results: Among 297 patients seen for an initial visit, mean BMI z-score was 2.3 and body fat percentage was 44%. High blood pressure occurred in 47%, high ALT in 24%, low HDL in 14%. Prevalence of initial HbA1c < 5.7%, 5.7 to < 6.5%, and 6.5% to < 8.5% was 46%, 42%, and 12%, respectively. One-third (31%) were prescribed metformin at their initial visit.

Only 63 patients (21%) had 2 or more visits in the T2DP Clinic with study site HbA1c data available. Of those 63 patients, mean age at initial visit was 12.5 years, BMI z-score 2.0, and body fat 46%. Most patients were female (68%) with public insurance (70%). Race/ethnicity was 35% black, 29% white, 30% Hispanic. Mean time between initial and most recent HbA1c was 11.9 months. Assessment of categorical HbA1c change showed 14% of patients with progression (n=9), 65% stable (n=41), and 21% with regression (n=13). Female sex, ALT elevation, HbA1c, fasting glucose were found to be statistically different between the groups at baseline ($p < 0.05$). Age, race/ethnicity, BMI, body fat percentage, elevated blood pressure, lipid profile, 120-minute glucose on OGTT, and metformin use were not different between the groups.

Conclusions. Only 14% of children who presented for follow up in our T2DP clinic demonstrated progression in HbA1c. Risk factors for those who progress include female sex and ALT elevation. Further development of predictive models to identify this high-risk population who will progress is necessary. Retaining consistent follow up in pediatric prediabetes clinics presents a challenge.

Pediatric Endocrinology

DIABETES, INSULIN, AND LIPIDS IN PEDIATRIC ENDOCRINOLOGY

Trends of Diabetes and Prediabetes Prevalence Among Korean Adolescents From 2007 to 2018

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Background: To provide updated prevalence data and to estimate changes in the prevalence of diabetes among Korean adolescents by sex and age between 2007 and 2018.

Methods: We used the data of children and adolescents (8,718 subjects aged 10 to 18 years) from the Korea National Health and Nutrition Examination Survey IV-VII (KNHANES 2007-2018). The recent prevalence of diabetes and pre-diabetes estimated by using the latest KNHANES VII. The linear trends were estimated by comparing 3-year KNHANES cycles according to sex and by using logistic regression. **Results:** The prevalence of diabetes and prediabetes was 0.298% (95% CI, 0.289-0.308) and 7.914% (95%CI, 0.43-0.49). The prevalence of diabetes was a significant increase from 0.189 to 0.430 during KNHANE IV and VII. A positive linear trend is significant for diabetes (p trends=0.006) in only male subjects. The prevalence of prediabetes was a significant increase from 5.86 to 12.08 in both sexes. During KNHANES IV and VII, the prevalence of obesity increased significantly. **Conclusion:** Between