(eg. MnSOD, PGC1α p<0.05). The offspring of obese mothers with pre-conception weight loss had lower body weight (p<0.001) and improved glucose tolerance (p<0.01). Kidney metabolic and inflammatory markers (MCP-1, FAS, SREBP, CD68) were significantly altered in HFD-fed offspring of obese mothers administered liraglutide pre pregnancy (p<0.05). **Conclusions:** Preconception weight loss improves fertility, weight and metabolic outcomes in mothers and the offspring, with benefits on reproduction, metabolic health, and chronic kidney disease risk. Therefore, obese women should be targeted for preconception weight loss to improve intergenerational metabolic health.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Predictors of Normalization of Fasting Glucose in Patients With Prediabetes Using Remote Continuous Care Emphasizing Low Carbohydrate Intake

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Background: Prediabetes phenotypes differ based on whether an individual exhibits impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both. The traditional diabetes prevention approach focused on weight loss via fat/caloric restriction and exercise appears less effective in those with IFG. Given that even transient regression to normal glucose regulation is associated with reduced risk of progression to type 2 diabetes, interventions that elicit normal fasting glucose (NFG) may be beneficial. Here, we explored predictors of normalization of fasting glucose (FG) over one-year treatment with carbohydrate restricted nutrition therapy (Carb-R) delivered via a continuous remote care model.
Methods: Data were obtained from medical records of adults with prediabetes who were treated at least one year at time of analysis. Of 738 patients with an antecedent prediabetes diagnosis, 460 had IFG (100mg/dL to 125mg/dL) at enrollment in the clinic and were included in this analysis. Patients were counseled on Carb-R targeting nutritional ketosis (NK) and reported fasting blood glucose, blood beta-hydroxybutyrate (BHB), and weight via an app facilitating remote monitoring and medical/coaching support. BHB ≥0.5 mM indicated NK. Cox proportional hazard regression was used to model time of first incidence of NFG at 3, 6, 9, and 12 months and to assess if normalization of fasting glucose was associated with baseline factors, weight change, metformin use, and degree or frequency of NK achieved, analyzed separately. Mean±SE is reported.
Results: Patients with IFG were 53.9±0.4 years of age, 64.0% female, HbA1c 5.92±0.02%, and fasting glucose 114.5±0.8 mg/dL at enrollment. During treatment, 199 (43.3%) patients normalized FG at ≥1 time point with mean weight loss of 10.0±0.4 kg (-8.9%) at time of normalization, 192 (41.7%) did not, and 69 (15.0%) were missing glucose data. In an adjusted multivariate model, lower baseline HbA1c (HR 0.60, p=0.03), female sex (HR 1.39, p=0.04), and greater mean BHB value (HR 1.83, p<0.001) or higher proportion of days on which NK was reported (HR 3.23, p<0.001) were associated with reversion to NFG. Age, metformin use, weight change, and baseline fasting glucose, weight, triglycerides, HDL-C, and LDL-C were not associated with reversion to NFG (p>0.05). **Conclusions:** Greater adherence to Carb-R indicated by greater BHB values and a greater proportion of days in NK were strongly associated with normalization of FG in prediabetes patients with IFG. Weight loss, a common goal for diabetes prevention, was not associated with reversion to NFG. Future studies should assess the effects of Carb-R including NK in other prediabetes phenotypes and on progression to type 2 diabetes.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Racial Disparities Among Clinical Trials for Inherited Forms of Lipodystrophy

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Background: There has been renewed interest in understanding how medical research serves minority communities disproportionally affected by disease. A recent study in a predominantly white population identified 12 subjects with partial lipodystrophy by genetics without clinical diagnosis of lipodystrophy (Gonzaga-Jauregui et al., 2020). Partial lipodystrophies are rare monogenic disorders leading to diabetes that can be challenging to diagnosis due to their similarity with common obesity-associated metabolic syndrome. We hypothesize minority populations may be underdiagnosed with lipodystrophy, and thus underrepresented in clinical trials.
Methods: We compared racial demographics of lipodystrophic subjects participating in clinical trials to subjects with predicted loss-of-function (pLOF) mutations in 4 genes associated with lipodystrophy in the GnomAD dataset (>140K exome sequences): *LMNA* & *PPARG* (causing dominantly inherited partial lipodystrophy), and *AGPAT2* & *BSCL2* (causing recessively inherited generalized lipodystrophy, which is more phenotypically apparent, as an internal control for the study design). We also compared rates of synonymous mutations in these 4 genes among races to test if subjects of different ethnicities may be more genetically predisposed to developing inherited forms of lipodystrophy. Comparisons were done using chi-square analysis.
Results: We identified 322 subjects with pLOF mutations in genes associated with lipodystrophy in the GnomAD dataset. The racial composition of GnomAD subjects with pLOF mutations in each gene was different than GnomAD subjects without pLOF mutations (p<0.001). 144 lipodystrophic subjects with known pathogenic variants in these genes participated in clinical trials. The racial