mouse and human ß-cell survival against cytokine-induced cell death. Future studies will determine the physiological role of LGR4 and the therapeutic potential of LGR4-ECD on the beta cell *in vivo* in basal conditions and in the setting of diabetes.

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Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Medicsen Smartpatch: A New Approach to Diabetes Management

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Introduction: Diabetes is a metabolic disorder characterized by a dysregulation of the glucose levels. With insulin being the main drug to be administrated for glucose levels modulation, it needs to be injected subcutaneously with daily injections, which can lead to poor patient compliance, apart from several side-effects. Although other administration methodologies have been investigated (oral or inhaled insulin), they show enough drawbacks to not to be consider as feasible alternatives for diabetes therapy. That´s why Medicsen has developed a Smartpatch that integrates a wide range of technologies, with the purpose of ensuring the correct insulin delivery from the skin´s surface to the bloodstream using a non-invasive and painless drug delivery method through a phenomenon induced by sonophoresis. **Materials and Methods:** Several *in vitro* and *in vivo* tests have been performed to prove the efficacy and safety of the technology, allowing us to collect experimental evidence through different methodologies that demonstrate the therapeutic potential of the device. Among these methodologies, permeability studies using Franz diffusion Cell and swine models (that prove efficacy of the technology) as well as safety studies, for both the insulin and the skin are highlighted. **Results:** In voltage experiments, the mean time for the disappearance of the membrane potential between the compartments separated by skin was: 334.7 (SD+/-103.6) seconds. Regarding the slope of the voltage line, as an approximation to the transfer speed, an arithmetic mean of (μ)= 0.0164 Mvolts/sec (+/- SD(σ): 0.006) was obtained. No significant differences were found between the circular dichroism spectra of samples (minimum peak at 219nm (sd+/-8.31) and that of the standard, which suggests that the molecular structure of insulin maintains stability. In the same way, HPLC studies shows no variability between the standard and all groups tested. Regardin skin safety, SEM images shows no significant damage to the skin, and ELISA test for TNF α and IL-2, as well as other biochemical tests, show no differences between control and samples. On In vivo experiments with our technology, glucose changes are comparable to those evoked through direct drug injection using conventional syringes. Lastly, the technology proved to be effective in the delivery of insulin through the skin in a non-invasive way, as observed in a Franz Diffusion Cell system and in the in vivo model of blood glucose reduction. **Conclusions:** Results observed during in vitro and in vivo studies indicate that the technology developed by Medicsen is effective and safe for the patient and the insulin. Following steps, including human trials, will be critical to fully demonstrate its potential in the treatment of diabetes.

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BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Pre-Conception Weight Loss Improves Reproductive, Metabolic and Kidney Health in Obese Mice and Their Offspring

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Background and Aims: An alarming 40% of women of reproductive age have obesity and during pregnancy obesity adversely impacts metabolic health in mothers and offspring. Maternal complications include diabetes, pre-eclampsia and chronic kidney disease (CKD). Our previous work showed that offspring have increased risks of obesity, diabetes, and CKD. While pre-pregnancy weight optimisation is advocated, evidence of benefits for mother and offspring are lacking. We aimed to determine if weight loss prior to pregnancy, either with diet modification or liraglutide, improves maternal and offspring metabolic outcomes, and reduces kidney complications in obese mothers and the offspring.
Methods: C57BL/6 female mice were fed a high-fat-diet (HFD) for 8 weeks and compared to lean chow-fed controls. HFD-fed dams were administered liraglutide (0.3mg/kg, s.c., for 4weeks) or switched to chow, to induce pre-conception weight loss. Pregnancy rates were observed after mating. Maternal anthropometry and glucose tolerance were measured before and after intervention, and at late gestation. Pregnant dams were either culled at gestational day 18–20 with blood and kidney harvested, or allowed to deliver their offspring. Offspring anthropometry, and glucose tolerance were assessed at postnatal week 12 after either HFD or chow feeding. Immunohistochemistry (IHC), western blotting and RT-PCR were used to measure kidney metabolic (FAS, SREBP) and inflammatory markers (CD-68,TGF-b).
Results: HFD-fed dams had reduced glucose tolerance compared to chow-fed dams ($p<0.0001$), and higher expression of renal metabolic and inflammatory markers in late gestation (eg FAS <0.05, TGFb <0.05). Intervention with liraglutide or diet lowered body weight, improving glucose tolerance (both $p<0.001$), and fecundity. Markers of kidney damage, namely albuminuria and fibronectin (by RT-PCR and IHC) were reduced (both $p<0.05$). Liraglutide treated mice exhibited greater gestational weight gain than mice switched to chow ($P<0.001$). Markers of inflammation and oxidative stress were significantly lower in obese mice with preconception weight loss via diet compared to liraglutide

(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