in vivo 2) to further test established models of cholesterol metabolic regulation on LDLr and PCSK9 turnover after feeding mice a cholesterol enriched diet. We hypothesize that a cholesterol enriched diet will decrease both LDLr and PCSK9 synthesis rates. In order to test this, mice were fed a cholesterol enrich diet for 1 week and metabolically labeled with heavy water (^2H_2O) up to 36 hours. LDLr and PCSK9 were immunoprecipitated from liver and deuterium incorporation into LDLr and PCSK9 were measured via mass spectrometry. Our results revealed high cholesterol feeding down-regulated cholesterol synthesis and LDLr fractional synthesis rate decreased from 10.0% to 6% per hour. PCSK9 concentration also decreased from 1 to 0.2 (ng/ml / total mg protein), but the synthesis rate increased from 9.0%/day in control mice to 19.5%/day in high cholesterol diet. These results suggest high cholesterol feeding increases PCSK9 synthesis that potentially depletes the intracellular pool to target LDLr to the lysosome thus decreasing LDLr turnover. This research provides a flux-based approach to measure the kinetics of LDLr and PCSK9 for a molecular based kinetic insight of their functions in physiology, disease and therapy.

Diabetes Mellitus and Glucose Metabolism

IMPACTS OF METABOLISM ON CLINICAL CHALLENGES

Efficacy and Safety of Higher Dulaglutide Doses (3.0 MG and 4.5 MG) When Added to Metformin in Patients With Type 2 Diabetes: A Phase 3, Randomized, Double-Blind, Parallel ARM Study (Award-11)

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OR26-08

Dulaglutide (DU) approved at doses of 0.75 and 1.5 mg once-weekly is an effective glucose lowering agent for treatment of type 2 diabetes (T2D). We hypothesized that higher investigational DU doses may provide further improvements in glucose control and body weight (BW) with an acceptable safety profile. The primary objective was to demonstrate superiority of once-weekly DU 3 mg and/or 4.5 mg to DU 1.5 mg for A1C change from baseline (BL) at 36 weeks (wks) in patients (pts) with inadequately controlled T2D on metformin therapy. Secondary objectives (controlled for multiplicity) included change in BW and % of pts achieving A1C <7% at 36 wks. Patients were randomized (1:1:1) to once-weekly DU 1.5 mg (n=612), DU 3 mg (n=616), and DU 4.5 mg (n=614). All pts initiated once-weekly DU 0.75 mg for 4 wks, followed by step-wise dose escalation every 4 wks to the randomized dose of 1.5 mg, 3 mg, or 4.5 mg. Two estimands were defined for efficacy analyses: an efficacy estimand (data on-treatment without rescue medication) and a treatment-regimen estimand (all data regardless of adherence or initiation of rescue). At BL, patients had a mean of: age 57.1 yrs, T2D duration 7.6 yrs, and A1C 8.6%, BW 95.7 kg, and BMI 34.2 kg/m^2. Using the efficacy estimand, the DU 3 mg and 4.5 mg doses were superior to the DU 1.5 mg dose for A1C change from BL (1.5 mg, 1.53%; 3 mg, 1.71% [p=0.003]; 4.5 mg, 1.87% [p<0.001]), % of patients achieving HbA1c <7% (1.5 mg, 57%; 3.0 mg, 65% [p=0.006]; 4.5 mg, 71% [p<0.001]) and BW change from BL (1.5 mg, 3.1 kg; 3 mg, 4.0 kg [p=0.001]; 4.5 mg, 4.7 kg [p<0.001]). Using the treatment-regimen estimand, DU 4.5 mg was superior to DU 1.5 mg for A1C change, while the DU 3 mg dose did not achieve statistical significance (1.5 mg, 1.54%; 3.0 mg, 1.64% [p=0.096]; 4.5 mg, 1.77% [p<0.001]). Using the treatment-regimen estimand, more patients achieved A1C <7% with higher DU doses (1.5 mg, 50%; 3 mg, 56%; 4.5 mg, 62%) and results for BW change were similar to the efficacy estimand (1.5 mg, 3.0 kg; 3 mg, 3.8 kg; 4.5 mg, 4.6 kg), but the approach for type I error control did not permit formal statistical comparisons of these secondary objectives using this estimand. The safety profile for the higher DU doses was consistent with that known for 1.5 mg. The most commonly reported adverse events were nausea (DU 1.5 mg, 13.4%; DU 3 mg, 15.6%; DU 4.5 mg, 16.4%), vomiting (DU 1.5 mg, 5.6%; DU 3 mg, 8.3%; DU 4.5 mg, 9.3%), and diarrhea (DU 1.5 mg, 7.0%; DU 3 mg, 11.4%; DU 4.5 mg, 10.7%). Treatment discontinuation due to adverse events through 36 wks was low and similar across dose groups (DU 1.5 mg, 4.2%; DU 3 mg, 5.5%; DU 4.5 mg, 5.0%). In pts with T2D and inadequate glycemic control on metformin, escalation from DU 1.5 mg to DU 3 mg or DU 4.5 mg once-weekly provided clinically relevant, dose-related improvements in glycemic control and BW with an acceptable safety profile.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

Development of a Conceptual Model to Present the Impacts of Obesity on Physical Functioning

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SUN-LB102

Title: Development of a conceptual model to present the impacts of obesity on physical functioning **Background.** Obesity is a chronic disease with a significant negative impact on health-related quality of life (HRQoL) and specifically, physical functioning, including the ability to complete activities of daily living (ADLs). Weight loss based on lifestyle management (e.g. diet, exercise), surgery, and pharmacotherapy can improve physical functioning; however, there is a need for further qualitative research to support the content validity of patient-reported outcome (PRO) measures for use in clinical studies of obesity and thus

inform regulatory decision-making. **Objective.** To explore the impacts of obesity on physical functioning and develop a conceptual model (a visual representation of the concepts of importance and relevance to the experience of living with obesity) to ultimately support the content validity of PRO measures.**Methods.** Qualitative semi-structured interviews were conducted in the United States with individuals who have overweight and obesity (Body Mass Index [BMI] ≥ 27.0 kg/m2) with a history of at least one unsuccessful dietary effort to lose body weight. Recruitment quotas targeted a sample with diverse demographic and clinical characteristics, including participants with and without diabetes. Experienced qualitative interviewers used open-ended questions to elicit spontaneous reports of the impact of obesity on individuals' daily lives, and specific probing questions to explore impacts on physical functioning. Interviews were audio-recorded, transcribed and analyzed using thematic techniques. **Results.** A total of 33 participants were interviewed (mean BMI of 37.6 kg/m2 [27.4 kg/m2 to 56.6 kg/m2]; mean age of 45 years [19 to 81 years]). The sample included a mix of races (Caucasian: n=12, 36%), education completed (high school: n=17, 51%) and split of gender (female: n=16, 48%). During development of the conceptual model, two separate domains were identified to group the reported impacts on physical functioning: 'Mobility/Movement' and 'ADLs'. The most frequently reported impacts related to Mobility/Movement were 'running' (n=31/33, 94%), 'bending' (n=27/33, 82%), 'walking' (n=26/33, 79%), 'difficulty standing for prolonged periods' (n=22/33, 67%), and 'lifting' (n=19/33, 58%). All participants reported effects on some aspect of physical functioning, which were often characterized in terms of their direct impact on ADLs such as 'household chores' (n=21/33, 64%). **Conclusions.** The conceptual model will serve as a basis to identify fit-for-purpose PRO measures with strong content validity to evaluate the impact of anti-obesity therapies on physical functioning in future clinical studies. Obesity has a consistent and significant impact on physical functioning, leading to limitations in various aspects of mobility and affecting an individual's ability to carry out specific daily activities.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS I

Implementation of a Quality Improvement Initiative for Advanced Ketone Management in Children With Recently Diagnosed Type 1 Diabetes

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SAT-LB109

Background: Monitoring of blood glucose, ketones and/or adjustment of the daily insulin dose is usually required with intercurrent illness in children with type 1 diabetes (T1D). International Society for Pediatric and Adolescent Diabetes recommends sick day guidelines, including insulin adjustments, should be taught soon after diagnosis. At our center, caregivers of children with newly diagnosed T1D receive extensive inpatient education, including introduction to sick day management. However, there was no standardized education for calculation of extra insulin doses to treat ketosis, i.e. advanced ketone management. This resulted in increased calls for ketone management and potential readmissions to the hospital.Objectives: Through a quality improvement (QI) initiative, we aimed to (1) provide standardized education on advanced ketone management to 50% of patients with a new diagnosis of T1D, aged 5-18 years, at their initial outpatient visit within four weeks of diagnosis, and (2) decrease the number of telephone calls for management of ketosis without increasing calls for hypoglycemia.Methods: Baseline data for telephone calls pertaining to ketosis or hypoglycemia management, within four weeks of diagnosis, were collected retrospectively by chart review for all children with new onset T1D, aged 5-18 years, from April 2018 to September 2018 (n=23). Through a series of plan-do-study-act (PDSA) cycles, a standardized ketosis management patient education bundle and ketone dose calculation tool were created. A pre-assessment questionnaire was used to determine eligibility at the initial follow up visit, within four weeks of diagnosis. Advanced ketone management education was provided to eligible patients. A post-assessment questionnaire was used to assess retention of knowledge at the next follow-up visit. Results: Forty-two children were diagnosed with new onset diabetes from January 2019 to May 2019. Of these, 30 children (71%) qualified to participate in the QI project and were given pre-assessment questionnaires. Twenty children (67%) were eligible to receive education on advanced ketone management. Of these, 95% children received standardized education at their initial outpatient visit. One child did not receive education due to time constraints and education was provided at the next follow-up visit. 70% eligible children received post-assessment questionnaires and of these, 100% scored ≥70%. Telephone calls for ketosis management decreased (26% to 6%, $p<0.001$), but there was no change in calls for hypoglycemia (52% to 48%).Conclusion: Standardized education on advanced ketone management is feasible to be provided within four weeks of diagnosis of T1D. This can decrease telephone calls for sick day ketosis management without increasing calls for hypoglycemia. This can likely result in reduction of parental anxiety and diabetes related hospital readmissions.

Adrenal

ADRENAL - TUMORS

WNT2B Regulates Adrenocortical Progenitor Cell Fate And Zona Glomerulosa Identity In Vivo

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SAT-LB44

Dysregulation of normal adrenal structure and function contributes to a spectrum of diseases from hypoplasia to cancer. Peripheral adrenocortical progenitor cells in the zona glomerulosa (zG) centripetally migrate and differentiate to