Diabetes Mellitus and Glucose Metabolism

CLINICAL STUDIES IN OBESITY, DIABETES RISK, AND CARDIOVASCULAR OUTCOMES

Dietary Reduction of Branched-Chain Amino Acids

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Background: One of the primary risk factors for the development of diabetes is obesity. Although moderate weight loss can lead to improvements in metabolic health, reduced-calorie diets are difficult to sustain. A number of groups have shown that low protein diets are associated with metabolic health in both rodents and humans. In particular, the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine are associated with insulin resistance and diabetes in humans. Blood levels of the BCAAs decrease in humans fed a low protein diet, and we recently showed that reducing either dietary BCAAs or protein rapidly restored normal body composition and insulin sensitivity to diet-induced obese mice without reducing calorie intake. We are determining the effect of a low BCAA diet in humans with prediabetes and overweight/obesity.

Objectives: The primary outcome is the reduction of dietary BCAA intake by at least 50% in subjects in the low BCAA group while maintaining overall baseline calories. Secondary outcomes are compliance and tolerability of the low BCAA protein powder.

Method: This is a randomized, controlled, single-blind pilot study. The intervention arm uses a low BCAA protein powder to replace two meals per day for 60 days. The control arm uses a control protein powder with standard amounts of amino acids to replace two meals per day for 60 days. We are enrolling 16 males with the following criteria: ages 35 to 65, BMI 28 to 35, and hemoglobin A1c 5.7%-6.4% or fasting glucose 101-125 mg/dL. A registered dietitian reviews a 4-day food diary prior to diet initiation and creates an individualized meal plan based on those values in order to maintain baseline calories during the study diet. Baseline measurements prior to diet initiation include waist circumference, body mass index, fasting insulin and glucose, an oral glucose tolerance test, resting metabolic rate, body composition testing using dual energy x-ray absorptiometry, jumping mechanography to assess muscle function, and a stool sample to assess the microbiome. These tests are repeated after 60 days on the diet. Safety labs are performed while on the diet and 2-3 weeks after the end of the diet. Weekly safety telephone calls occur while on the diet. The food diaries are repeated after 30 and 60 days on the diet.

Results/Conclusion: Ten of sixteen subjects have completed the trial to date. One out of four subjects in the low BCAA group dropped out; the remainder successfully completed the study. BCAA intake was successfully reduced by 50%. Missed beverages were uncommon. No significant safety concerns or side effects have been noted. In conclusion, our early results suggest that replacement of two meals a day with a protein powder lacking BCAA for up to two months is a safe and feasible intervention. Ongoing analysis will determine if this intervention impacts metabolic health.

Bone and Mineral Metabolism

OSTEOPOROSIS AND VITAMIN D

Comparison of Vitamin D Metabolism in Deficient and Sufficient States

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Objective: to study the differences in calcium-phosphorus and vitamin D metabolism in healthy individuals with deficient and sufficient baseline state of vitamin D. Materials and methods: The study included 16 young conditionally healthy individuals, divided into two equal groups: with levels of 25(OH)D below and above 30 ng/ml determined by the immunochemiluminescent method (Group A and Group B respectively; DEQAS certified). All participants were evaluated for the biochemical parameters of blood and urine, characterizing calcium-phosphorus metabolism, PTH by commercial methods, and vitamin D metabolites (25(OH)D3, 25(OH)D2, 3-epi-25(OH)D3 and 24,25(OH)2D3) by HPLC/MS-MS before oral intake of 150 000 IU of an aqueous solution of cholecalciferol and 7 days after administration. Results: At baseline, the level of vitamin D metabolite 25(OH)D2 in Group B was lower with no significant differences in other studied parameters. In group A, strong positive correlations were observed between levels 25(OH)D3 and 3-epi-25(OH)D3, 24,25(OH)2D3, while in group B there were no such associations. After taking a loading dose of cholecalciferol, the groups showed generally similar changes in the studied vitamin D metabolites: a statistically significant increase in 25(OH)D3, 3-epi-25(OH)D3, a decrease in 25(OH)D2, and a ratio of 24,25(OH)2D3 to 25(OH)D3. However, the level of 24,25(OH)2D3 did not change in group B, with a significant increase in group A. The medians of the studied biochemical parameters in blood/urine, as well as PTH, remained unchanged in both groups. Conclusion: In patients with inadequate baseline levels of 25(OH)D, after a loading dose of cholecalciferol, there is a tendency to formation of more inactive forms of vitamin D. These deviations in the metabolism of vitamin D need to be clarified, since they can potentially affect the effectiveness of cholecalciferol therapy.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Analysis of Adverse Events in Adult Patients with Acromegaly Receiving Oral Octreotide Capsules: Results from the Phase 3, Randomized, Double-Blind, Placebo-Controlled CHIASMA OPTIMAL Study

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Distinguishing non-specific signs and symptoms of acromegaly from treatment emergent adverse events (TEAEs) in patients treated with somatostatin receptor ligands has proven difficult given limited data from placebo-controlled studies. The phase 3 Octreotide capsules versus Placebo Treatment In MultinationAL centers (OPTIMAL) study provides a novel data set to evaluate the incidence of adverse events from patients randomized to octreotide capsules or placebo. A multinational, randomized, placebo-controlled study was conducted in 56 adult patients with active acromegaly. Eligible patients were ≥18 years of age, had active disease (IGF-I ≥1.3 x ULN after last pituitary surgery), and an average IGF-I ≤1.0 x ULN in response to a stable dose of somatostatin receptor ligand injection. Patients were randomized to octreotide capsule or placebo (28 per group) for 36 weeks, followed by an optional open-label extension for up to 1 year. Safety and tolerability were evaluated based on incidence of AEs, including incidence of new or worsening adverse events of special interest (AESIs). In this study, the safety profile of octreotide capsules was consistent with the known safety profile of injectable octreotide (Melmed et al 2015). No new or unexpected safety signals were detected. Nearly all patients (55/56) experienced a TEAE (28 patients [100.0%] in the octreotide capsule group and 27 patients [96.4%] in the placebo group). Thirty-three patients (58.9%) experienced a TEAE considered to be related to study drug by the blinded PI (64.3% of the octreotide capsule group [18 patients, 40 events] and 53.8% of the placebo group [15 patients, 41 events]). TEAEs with an incidence ≥5% that were more common in the octreotide capsule group vs placebo group included GI disorders, increased blood glucose, sinusitis, osteoarthritis, and cholelithiasis. TEAEs with an incidence ≥5% that were more common in the placebo group vs octreotide capsule group included arthralgia, headache, fatigue, hyperhidrosis, and peripheral swelling. GI disorders were the most common TEAE, reported in 64% of all patients (36/56) and at similar rates between octreotide capsule (68%) and placebo groups (61%). AESIs (defined as new or worsening signs of acromegaly) were observed in 15 patients (53.6%, 34 events total) in the octreotide capsule group and more frequently in 26 patients (92.9%, 82 events total) in the placebo group. In this study, the safety profile of octreotide capsules was consistent with the known safety profile of injectable octreotide. Most patients receiving octreotide capsules or placebo demonstrated TEAEs, although the profile of most common TEAEs varied between groups. TEAEs observed in the placebo group may be indicative of underlying disease activity. Further analysis may elucidate the difference between treatment related AEs and signs/symptoms of active disease in acromegaly.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Knockout of Membrane Androgen Receptor ZIP9 Results in Reduced Female Fecundity and Abnormal Egg Activation in Zebrafish

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Recently, our research group cloned and characterized a putative membrane androgen receptor from teleost ovarian tissue that was found to be homologous with the zinc transporter protein ZIP9 (Slc39a9). To date, ZIP9 is the only zinc transporter that is known to be ligand activated or possess steroid receptor activity. Since the discovery of its androgen receptor activity, ZIP9 has been found to mediate androgen actions in a variety of tissues including teleost ovarian follicle cells, human cancer cell lines, and murine Sertoli cells. However, ZIP9 has not been examined in an *in vivo* model so the precise physiological functions of this receptor remain unclear. A ZIP9-mutant strain of zebrafish was developed using a CRISPR-Cas9 system in order to examine the role of the protein in teleost reproduction. While ZIP9-mutant males had similar breeding occurrence and fertilization rates to wild-type fish, mutant females exhibited severe reductions in fecundity compared to wild-type fish. ZIP9-mutant females spawn significantly fewer eggs of which a high proportion failed to undergo chorion elevation, a characteristic of normal egg activation. Eggs that showed this failed chorion elevation phenotype had significantly lower fertilization rates and produced larvae that exhibit a high incidence of pericardial/yolk sac edema and reduced growth compared to larvae hatched from wild-type eggs. However, no differences were observed in the proportions of oocytes at later stages of development between ZIP9-mutant and wild-type fish, suggesting the observed phenotypes are not related to abnormal oogenesis. We observed that mature wild-type eggs have numerous cortically located vesicles that are autofluorescent under ultraviolet light and decrease in number when the eggs undergo activation, suggesting they undergo exocytosis during the cortical reaction. While zinc is known to be stored in vesicles that undergo exocytosis in mammalian eggs, the role of zinc in teleost egg activation is currently unknown. In eggs from wild-type fish, we observed an increase in extracellular zinc levels upon egg activation and treatment with a zinc ionophore (zinc pyrithione) significantly reduced the number of eggs that undergo normal chorion elevation when activated. This suggests a role for zinc in zebrafish egg activation similar to that observed in mammals. Of interest, ZIP9-mutant eggs that did not undergo chorion elevation had significantly smaller vesicles than those found in wild-type fish eggs. This abnormal vesicle morphology and failure to undergo chorion elevation suggest a role of ZIP9 in egg activation. Additional insight into the role of zinc in zebrafish egg activation and the mechanism by which ZIP9 disruption leads to abnormal cortical vesicles and egg activation will help determine if ZIP9 plays a role in zinc transport and flux in zebrafish eggs during activation.