Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Weight Loss With a Novel Peptide YY Analogue for Obesity: A Randomised, Placebo-Controlled Phase I Trial

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Background: Obesity and its co-morbidities remain a prime driver of global morbidity and mortality. Current therapies for obesity are limited in efficacy and durability, have serious adverse effects or are not scalable to the numbers required to treat this widespread disease. Gut hormones such as peptide YY (PYY) have emerged as candidate therapies for obesity which activate natural satiety pathways, reduce food intake and therefore body weight. We report the results from a Phase I trial of a PYY analogue, Y14, in overweight volunteers. **Methods:** In a first time in human Phase I randomized placebo-controlled trial, an extended-release formulation of Y14 with zinc chloride for subcutaneous injection, utilizing various Zn:peptide molar ratios, was tested. Part A of the trial was a partially blinded single ascending dose study. Part B was double-blinded and tested multiple ascending doses given at 7–14 day intervals over the course of 28 days with up to 5 doses given per subject. The primary outcome was the safety and tolerability of extended-release Y14; the secondary outcome was to assess its pharmacokinetics. Exploratory outcomes included the assessment of food consumption, body weight and glucose tolerance in response to 75g oral glucose load after multiple doses of Y14. [ClinicalTrials.gov NCT03673111]. **Findings:** Between Apr 11, 2017, and Dec 24, 2018 44 participants were enrolled into Part A of the trial and 24 into Part B and were included in the full analysis and safety datasets. The multiple doses of Y14 given in Part B led to significant mean placebo-subtracted reductions in body weight of 2.76 to 3.59 kg at 31 days after the first dose, in association with profound reductions in food intake and no evidence of tachyphylaxis. No significant changes in glucose tolerance were detected. The most common adverse events were nausea, vomiting and injection site reactions. No serious adverse events occurred. The pharmacokinetic characteristics of extended-release Y14 were compatible with administration every 7–14 days. **Interpretation:** Our results support the continued development of Y14 as a novel treatment for obesity. **Funding:** UK Medical Research Council Developmental Pathway Funding Scheme.

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NOVEL INSIGHTS FROM THE CLINIC INTO THE DEVELOPMENT OF METABOLIC DISEASE: CASE REPORTS

A Novel Variant of the SH2B1 Gene in an Obese Child With Type 2 Diabetes

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Obesity in children and adolescents is at epidemic levels in the United States and creates high risk for comorbidities later in life. Childhood obesity is thought to be the result of behavioral and nutritional problems. Although genetic factors may play a role in the etiology of obesity, monogenic forms of obesity are rare. We present a child with obesity, behavioral problems, leptin resistance, and type 2 diabetes who also carries a mutation of Sarcoma Homologous 2B adapter protein 1 (SH2B1). The subject was evaluated at 13 $^{7}/_{12}$ years old. He had polyphagia, learning disability, aggressive behavior and marked obesity. At ages 9,11, and 13 years respectively, his BMI was 9%, 16%, and 52% above the 95th percentile. At 13 $^{7}/_{12}$ years old, his height was at the 80th percentile and BMI was 66% above the 95th percentile. He had marked acanthosis nigricans and he was prepubertal. Fasting blood glucose and insulin levels were 116 mg/dl and 592 mIU/L, respectively. Hemoglobin A1c was 6.5% and metformin therapy was initiated for type 2 diabetes. Fasting leptin level (41.5 ng/mL) was markedly elevated indicating leptin resistance. DNA methylation study excluded Prader-Willi syndrome. DNA sequencing indicated a novel heterozygous c.1555G>T variant of SH2B1 gene, which is predicted to result in the amino acid substitution p. Asp519Tyr. The analysis by PolyPhen-2 and MutationTaster predicts that the variant is a pathogenic mutation affecting protein functions. SH2B1 interacts with JAK2 and may play a role in insulin signaling. Pathogenic heterozygous variants in SH2B1 have been associated with obesity, insulin resistance and maladaptive behavior phenotypes (Pearce et al, 2014). *Sh2b1-null* mice develop severe leptin resistance, obesity, and type 2 diabetes. Our report underscores the importance of investigating monogenic causes of obesity in subjects who present severe obesity, diabetes, and behavioral problems. Additional studies are needed to determine the association between this novel mutation and the clinical features of this patient.

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Acquired Brain Injury-Induced Hyperphagia and Obesity, Successfully Treated With a GLP-1 Agonist

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Background: Several Glucagon-like peptides 1 (GLP-1s) were approved since 2005 for the treatment of DM & obesity. Their usefulness in other conditions is not well studied. We present two cases of hyperphagia after TBI successfully treated with GLP-1 agonists. **Clinical cases: Case 1:** A 54-year-old female with a history of multiple

traumatic brain injuries (multiple falls and a ski accident) complained of years of insatiable hunger leading to hyperphagia and over 20 pounds weight gain. With tremendous will-power, she avoided additional weight gain by adopting a strict meal-plan and increasing her water intake (10–12 liters a day) to relieve her hunger. She sipped so much water, that her sodium remained 123 - 133 mmol/L (ref: 135–146) with dilute urine. Initial tests revealed: IGF-1 315 ng/ml (52–328), FSH 77.5 mIU/ml (23–116.3), LH 24.3 mIU/ml (14.2–52.3), prolactin 17.1 ng.ml (10–54.7), estradiol 17 (<31), TSH 1.09mIU/ml (0.45–4.5), FT4 1.0 ng/dl(0.8–1.8), all within the normal limit for her age. Semaglutide 0.25mg/week was started and increased to 0.5mg/week. Within the first six months of treatment, she experienced 22 pounds of weight loss, hunger relief, less water sipping behavior, and more enjoyment of food. Her sodium rose to 137 mmol/L. **Case 2:** A 40-year-old female, s/p craniectomy and aneurysm clipping due to intracranial hemorrhage complicated by an ischemic stroke developed sudden, documented, 45-pound weight gain over thirteen months despite aggressive lifestyle modification attempts. Initial labs revealed: TSH 1.33 mIU/ml (0.45–4.5), FT4 1.22 ng/dl (0.8–1.8), midnight salivary cortisol 0.03 mcg/dl (<0.09), ruling out hypothyroidism and Cushing syndrome. Liraglutide 1.8mg/day was started and has resulted to date in 26 pounds (11.8% of maximum weight) by 9 months with an associated decrease in subjective hunger. **Conclusion:** Hyperphagia can be seen in brain injury, in response to some medications, and some genetic conditions, like Prader-Willi. The exact mechanisms are not clear am may be multifactorial. In the case of brain injury, proposed mechanisms include insatiable hunger due to ventromedial hypothalamic or brain stem dysfunction, or disinhibition and poor impulse control due to frontal lobe injury. GLP-1's may act on the causal mechanism for increased hunger, or it may result in clinical improvement through a parallel pathway. More studies are warranted to investigate the application of GLP-1's to hyperphagia.

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NOVEL INSIGHTS FROM THE CLINIC INTO THE DEVELOPMENT OF METABOLIC DISEASE: CASE REPORTS

Association of NOS3 and TNF Genetic Polymorphisms With the Predisposition to Elevated Cholesterol, Retrospective Study

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Background: Endothelial nitric oxide synthetase (eNOS) encoded by NOS3 gene has an important role in modulating vascular endothelial function. TNFα gene is responsible for coding TNFα protein that plays a significant role in regulating body inflammation and lipid metabolism. Many studies reported an association between NOS3 and TNFα genetic polymorphisms and elevated total cholesterol (TC) level, low-density lipoprotein (LDL), triglyceride (TG). In this study, we investigated the association of NOS3 (G>T) rs1799983 and TNFα -308G>A rs1800629 genetic polymorphisms with TC level.

Methods: A random sample of 250 subjects with an elevated TC level (defined by TC level ≥ 200mg/dL) compared with 500 healthy subjects. Sample obtained from Palestinian adults who consented to genetic and biochemical testing. Subjects genotyped for NOS3 SNP (G > T) rs1799983 and TNFα -308G>A rs1800629 using ARMS PCR. TC level was obtained for all subjects. Logistic regression analysis adjusted for age and body mass index (BMI) was performed to test for association between NOS3 and TNFα genetic polymorphisms and TC level.

Results: NOS3 T allele was significantly more frequent in the elevated TC group, (odds ratio = 1.8, 95% CI =1.02–3.18) with likelihood ratio statistically significant (P = 0.004). Homozygous TNFα variant was more frequent in the elevated cholesterol group without a statistically significant association (P = 0.54).

Discussion: Many studies reported an association between NOS3 and TNFα genetic polymorphisms and elevated TC levels. Homozygous NOS3 variant was associated with a 1.8-fold increase in the risk of high TC after adjustment for age and BMI. TNFα polymorphism didn't show a statistically

significant association with having elevated TC levels. With the increasing popularity and availability of genetic testing, NOS3 can serve as a screening tool to identify people with high risk for elevated TC. Further studies are required to understand the exact role of NOS3 genetic polymorphism in cholesterol metabolism.

Conclusion: NOS3 genetic polymorphism had a statistically significant relationship with TC levels. These results support the association between NOS3 polymorphism and elevated TC.

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Effects of Glucagon-Like-Peptide-1 Analogue Treatment in Genetic Obesity

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Introduction: Obesity is highly prevalent, comes with serious health burden and is difficult to treat. In a minority, there is a genetic cause for the obesity. In these patients, therapy-resistant obesity is often observed despite intensive lifestyle treatment. Moreover, it is still unclear whether bariatric surgery is less successful in genetic obesity. Liraglutide is a Glucagon-Like-Peptide-1 (GLP-1) receptor agonist or GLP-1 analogue, showing positive effects on metabolic parameters, satiety and weight loss