Adipose Tissue, Appetite, and Obesity
INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

A Metabolomic Analysis to Assess How Time-Restricted Eating Improves Cardiometabolic Health

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Time-Restricted Eating (TRE) is a consistent 6-12-hour daily eating window without any overt caloric reduction. TRE has been shown in pre-clinical and clinical studies to have widespread benefits including improved cardiometabolic health. Most clinical trials have studied healthy or overweight participants, but the effect of TRE on patients undergoing medical treatment for cardiometabolic disease is unclear. In this single-arm paired-sample pilot study, 19 participants with metabolic syndrome and who had an eating window of 14 hours or more at baseline were put on a 10-hour TRE intervention for 3 months. Despite most participants already taking antihypertensives and statins at baseline, there were significant decreases in blood pressure and LDL cholesterol. There were also significant decreases in HbA1c, waist circumference, and body weight. To better understand the mechanism behind these improvements, here we report the changes in plasma metabolite changes following the 3-month TRE intervention. These findings are important to understand the physiological effects of TRE, especially for individuals to use as a co-treatment.

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A Phase 3 Trial in Participants With Obesity Due to Bardet-Biedl Syndrome or Alström Syndrome: Efficacy and Safety of the Melanocortin 4 Receptor Agonist Setmelanotide

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Introduction: This randomized Phase 3 trial evaluated the effect of setmelanotide, a melanocortin 4 receptor agonist, on weight loss, hunger reduction, and safety outcomes in individuals (aged ≥6 years) with obesity and a genetically confirmed diagnosis of Bardet-Biedl syndrome (BBS) or Alström syndrome (AS), conditions believed to disrupt hypothalamic leptin-melanocortin signaling. **Methods:** For inclusion, obesity was defined as body mass index ≥30 kg/m^2 (in those aged ≥16 years) or weight >97th percentile (in those aged 6–15 years). Individuals were randomized and received setmelanotide or placebo for 14 weeks, followed by open-label setmelanotide so that all participants received at least 1 year of drug. Body weight, height, hunger scores, and treatment-emergent adverse events (AEs) were assessed. The primary endpoint was the proportion of participants (≥12 years) who achieved ≥10% reduction in body weight from baseline after 52 weeks of treatment. For statistical analysis, the primary endpoint had binomial proportions calculated for each of the 100 multiple imputed data sets, which were combined using Rubin's Rule to compare against the null hypothesis with 95% confidence intervals (CIs) and *P* values. Efficacy analyses (including change in body weight, body mass index Z score, and hunger) were conducted in participants ≥12 years old at baseline. Safety analyses were conducted in all participants. **Results:** A total of 38 individuals with BBS (n=32) or AS (n=6) were enrolled. Five participants <12 years and 2 participants ≥12 years who discontinued before receiving active therapy were not included in the primary analysis. The prespecified significance cut points for the primary and key secondary endpoints were met. After ~52 weeks of setmelanotide, 34.5% (95% CI, 17.5%-51.6%; *P*=0.0024) of participants achieved ≥10% reduction in body weight from baseline. All observed responders had BBS. Mean ± SD percent change in body weight from baseline was −6.2% ± 8.6% (*P*<0.0001). In participants with BBS aged ≤17 years (n=14), mean ± SD percent change in body mass index Z score from baseline was −24.5% ± 22.3%. Mean ± SD percent Job #11307-1 1/27/2021Haws BBS AS Phase 3 ENDO 2021 EncorePage 2 change in maximal daily hunger score (based on participant responses to scoring their "most" hunger during the day) from baseline was −30.8% ± 25.0% (*P*<0.0001); 60.2% (95% CI, 35.3%-85.1%; *P*<0.0001) of participants achieved ≥25% reduction in weekly average daily hunger score from baseline. Common AEs included skin hyperpigmentation (57.9%), injection site erythema (44.7%), and nausea (34.2%). There was 1 serious treatment-related AE of anaphylactic reaction that occurred in a participant receiving placebo. **Conclusions:** In this Phase 3 trial in patients with BBS and AS, setmelanotide was associated with significant body weight and hunger reduction, with responses being greater in individuals with BBS.

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Abnormal Non Esterified Fatty Acid Suppression After a Mixed Meal Test in Patients With Partial Lipodystrophy

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