Energy Balance in Hypothalamic Obesity in Response to Treatment with a Once-Weekly GLP-1 Receptor Agonist

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Abstract

Background/Objectives: Hypothalamic obesity (HO) frequently occurs following suprasellar tumors from a combination of decreased energy expenditure and increased energy intake. Glucagon-like peptide-1 receptor agonist (GLP1RA) therapy is associated with increased satiety and energy expenditure. We hypothesized GLP1RA therapy in patients with HO would cause both lower energy intake and increased energy expenditure.

Subjects/Methods: Forty-two patients aged 10–26 years (median 16 years) with HO with suprasellar tumors were randomized to GLP1RA (exenatide extended release once-weekly, ExQW, n=23) or placebo (n=19). Thirty seven (81%) patients completed the 36-week double-blind placebo-controlled trial. Total energy expenditure (TEE) was measured with doubly labeled water, physical activity was assessed with actigraphy, and intake was estimated with ad libitum buffet meal. Results are presented as adjusted mean between-group difference.
Results: As compared with treatment with placebo, treatment with ExQW was associated with decreased energy intake during a buffet meal (−1 800 kJ (−430 kcal), 95% CI −3 184 to −418 kJ, p= 0.02). There were no significant differences in physical activity between groups. ExQW (vs. placebo) treatment was associated with a decrease in TEE (−695 kJ/day (−166 kcal/day), 95% CI −1 130 to −264 kJ/day, p< 0.01, adjusted for baseline TEE). The treatment effect was still significant after further adjustment for change in body composition (−372 kJ/day (−89 kcal/day), 95% CI −699 to −42 kJ/day, p= 0.04) or change in leptin (−695 kJ/day (−166 kcal/day), 95% CI −1 130 to −264 kJ/day, p< 0.01). This decrease in TEE occurred despite an increase in lean mass and fat mass (1.7 vs. 1.3 kg lean mass, p= 0.88 and 1.5 vs. 4.6 kg fat mass, p= 0.04, ExQW vs. placebo).

Conclusions: Treatment with a GLP1RA was associated with a decrease in food intake but also a decrease in TEE that was disproportionate to change in body composition.

INTRODUCTION

Hypothalamic obesity (HO) is characterized by fatigue, decreased physical activity, hyperphagia, decreased satiety, and severe obesity (1–4). The most common cause of HO is craniopharyngioma (CP), but other causes include other suprasellar tumors, inflammation, and genetic syndromes (5). HO is a refractory form of obesity and effective treatment options are lacking. Evidence based therapies are urgently needed as patients with HO have increased cardiovascular morbidity and mortality (6).

Although some patients with HO have significant hyperphagia, it is not a consistent finding (1, 2, 7, 8). Instead, the energy imbalance in HO is most likely due to reduced energy expenditure without a compensatory decrease in energy intake (1, 7). However, information on energy balance in HO derives mostly from food intake studies and physical activity assessments. We previously measured resting energy expenditure (REE) by indirect calorimetry in a small cohort of 9 HO patients and did not find evidence of low energy expenditure (7). Indirect calorimetry while resting under a ventilated hood is commonly used to assess REE, since REE represents approximately 2/3 of daily energy expenditures, but REE does not reflect energy expenditures due to physical activity, non-exercise activity thermogenesis or thermic effect of food. Doubly labeled water (DLW) is preferred for accurate assessment of free living energy expenditure, including physical activity-related energy expenditure (9).

In the present study, we utilized a robust cohort of adolescents and young adults enrolled in the randomized, multicenter, double-blind placebo-controlled clinical trial “Energy Balance & Weight Loss in Craniopharyngioma-related or Other Hypothalamic Tumors in Hypothalamic Obesity” (ECHO) to assess energy balance in HO using the gold standard methods of DLW and ad libitum buffet feeding, before and after a pharmacologic intervention with a glucagon-like peptide-1 receptor agonist (GLP1RA). We hypothesized GLP1RA therapy in patients with HO would cause both lower energy intake and increased energy expenditure that could account for the improved adiposity we previously reported in people with HO treated with GLP1RA versus placebo (10).
METHODS

Participants

Participants 10 – 25 years at the time of enrollment with HO were recruited via outpatient clinics and online advertisements from three clinical sites (Children’s Minnesota, St. Paul, Minnesota, USA; Seattle Children’s Hospital, Seattle, Washington, USA; and Vanderbilt University Medical Center, Nashville, Tennessee, USA). The clinical trial was approved by the Institutional Review Board at each clinical site and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Informed consent and age-appropriate assent were obtained from all participants prior to enrollment and the study is registered at clinicaltrials.gov (NCT02664441).

A detailed description of the clinical trial was previously published (10). Briefly, all participants had a clinical diagnosis of HO due to a suprasellar tumor and were ≥6 months post-surgical or radiation treatment. Hypothalamic injury was confirmed by review of a brain MRI by a single neuroradiologist.

Experimental Procedures

After screening and a 2-week placebo run-in to evaluate medication compliance, participants were randomized 1:1 to a 36-week treatment with a GLP1RA (exenatide extended release 2mg subcutaneously once weekly, ExQW) or placebo. Participants and study staff were blinded to treatment assignment.

Assessments of body composition, energy intake and energy expenditure were performed at 0 and 36 weeks. Participants were asked to maintain their usual diet and abstain from caffeine and strenuous exercise in the 3 days prior to testing. Patients arrived to the clinical site after a minimum of 8 hours of fasting.

Participant height was calculated as the average of three repeated measures using a calibrated stadiometer. Weight was calculated in light clothing as the average of three repeated measures on a calibrated electronic scale. Dual energy x-ray absorptiometry (DXA) was performed (GE Lunar Prodigy Advance; GE Lunar iDXA; and Hologic Discovery and Hologic Horizon) to estimate fat and fat-free mass.

Total energy expenditure (TEE) in the free-living environment was measured using DLW by the Energy Balance Laboratory at Vanderbilt. In brief, through periodic urine collection, DLW estimates carbon dioxide production by measuring the elimination of the tracers deuterium (2H) and oxygen-18 (18O) from the body (9, 11). Participants were asked to void followed by ingestion of DLW (0.1 g/kg body weight of 2H2O 99.98 atom % 2H and 0.16 g/kg body weight of 100% 18O). The DLW drinking container was then rinsed twice with the participant also consuming the rinse water. Urine samples were collected at baseline, 2 to 4 hours (in clinic) and once in the morning at 7 and 14 days (at home) for isotope analysis (deuterium and 18O). Analysis was performed using a LaserAssisted Cavity RingDown Spectrometer with intra-assay CV <2% (Metabolic Solutions, Inc., Nashua, New Hampshire, USA). The elimination doses of O and H were used to determine the average daily rate of carbon dioxide production (rCO2 in mol/day) over the measurement period. The rCO2 was
then converted to the average daily volume of CO2 production (VCO2, L/day) and TEE was calculated using an equation of Weir and an assumed food quotient (0.85) (12, 13).

Physical activity was assessed using recordings from the Actigraph GT9X accelerometer (ActiGraph, Pensacola, Florida, USA), worn on the non-dominant wrist for 2 weeks. Raw accelerometry data were integrated into the 15-second epochs for assessing wear/nonwear and time spent in bedrest (sleep) and various physical activity intensities, respectively (14, 15). Non-wear was defined as at least 60-minute intervals of “zero” activity counts with 2-minute incidental wear intervals (16). Total daily wear time was calculated by subtracting non-wear time from 24 hours. Accelerometry data were collected at baseline, 18 weeks, and 36 weeks. To be included in the data analyses, recordings must have met valid wear-time criteria of a minimum of 7 valid days (5 weekdays and 2 weekend days) with at least 10 hours of a wake time recorded between 5:00 am and 11:59 pm. Previously validated vector magnitude cut points were used to determine sedentary, low, moderate and vigorous intensity physical activity (15).

To assess energy compensation, patients were provided a high calorie preload of macaroni and cheese that provided 20% of estimated daily caloric requirements. Ninety minutes later, participants were served a pre-weighed ad libitum buffet meal consisting of a wide variety of food items that provided more than the estimated daily energy requirement of participants (5,000 kcal). Participants had access to the buffet for 30 minutes. Calorie and macronutrient intake were determined upon weighing all buffet meal items with food intake data entered in Nutrition Data System for Research software (NDSR, University of Minnesota, Minneapolis, MN). Hunger and fullness were assessed every 30 minutes using visual analog scales (VAS). Minute 0 was before the start of a 75g oral glucose tolerance test, minute 120 was the time the standardized preload was consumed, and minute 210 was the start of the buffet meal. Self-reported daily energy intake was assessed by Automated Self-Administered 24-Hour Dietary Recall (ASA24-Kids, http://appliedresearch.cancer.gov/tools/instruments/asa24/). ASA24-Kids is a web-based diet assessment tool that allows 24-hour diet recall using branded food items. Eating behaviors were reported by caregivers using the Child Eating Behavior Questionnaire (CEBQ) (17) and the Hyperphagia Questionnaire (HQ) (18). The CEBQ is a 35-item questionnaire with each item rated on a five-point Likert scale ranging from never to always. It comprises 8 scales: food responsiveness, emotional overeating, enjoyment of food, desire to drink, satiety responsiveness, slowness in eating, emotional under-eating and food fussiness. The HQ is an 11-item questionnaire with each item rated on a five-point scale with “1” equal to not a problem and “5” equal to a severe and/or frequent problem. It is made up of 3 scales: hyperphagic behavior, hyperphagic drive and hyperphagic severity.

Leptin was measured at a single site, Northwest Lipid Metabolism and Diabetes Research Laboratory at the University of Washington, using a commercially available radioimmunoassay (HL-81K; MilliporeSigma, Burlington, Massachusetts, USA) utilizing a polyclonal antibody raised in rabbits against recombinant human leptin (inter- and intra-assay CVs 5.2% and 3.5% respectively).
Data Collection and Statistical Analysis

The randomization schedule for ExQW versus placebo was generated and maintained by an unblinded study statistician. We used permuted-block randomization with varying block sizes, stratified by study site, age (10–14, 15–25 years old), and sex. Data were recorded in REDCap hosted at the Institute of Translational Health Sciences (partner of Seattle Children’s Hospital).

Baseline data are presented as median, interquartile range. Separate multivariable linear regression model were fit for each outcome of interest to estimate the association of treatment group with change in outcome. Each model included an indicator variable for treatment and controlled for the baseline value of the outcome in order to improve the precision. Treatment effects are summarized using the adjusted mean difference between treatment and placebo groups with corresponding 95% confidence intervals. Multivariable linear regression was also used to estimate the association between TEE change and treatment accounting for changes in body composition (fat free mass and fat mass) or leptin. Two models were estimate in which we controlled for baseline TEE and either change in body composition or change in leptin. Analysis was conducted with R version 3.6.3.

RESULTS

Enrollment

A total of 42 patients enrolled in the study; 23 patients were randomized to ExQW and 19 patients to placebo. One patient in the placebo group withdrew before receiving the first dose of study medication and is not included in this analysis. At the 36-week assessment there were 37 patients remaining; 22 in the ExQW group and 15 in the placebo group. Not all patients completed each study procedure, for example there were 4 patients in each group that did not have adequate actigraphy data for analysis. The detailed subject numbers for each measure are included in Tables 1 and 2.

Demographics and baseline clinical characteristics (Table 1) were similar between groups as previously published (10). Patients ranged from 10 to 26 years old (median 16 years) and were 61% female. Among the 41 analyzed patients, HO was due to craniopharyngioma (n= 38), mixed germ cell tumor (n= 1), suprasellar ganglioglioma (n= 1) and suprasellar germinoma (n=1). All patients had obesity with a median BMI 37.8 kg/m^2. The majority of patients (83%) had hypopituitarism and one patient had type 2 diabetes treated with metformin (A1c 7% at baseline).

Body Composition

While there was not a significant difference in change of body weight between the ExQW and placebo groups (−3.6 kg, 95% CI −7.6 to 0.5, p= 0.09), fat mass did not increase as rapidly in the ExQW group (−3.1 kg, 95% CI −5.9 to −0.2, p= 0.04). The change in lean mass was similar between groups (0.2 kg, −2.0 to 2.4, p= 0.88).
Food Intake

At baseline, patients consumed 55% of their TEE during the buffet meal. There were no significant differences between treatment groups at baseline (Table 1). Treatment with ExQW (compared with placebo) was associated with decreased energy intake during the buffet meal compared with baseline (mean difference −1800 kJ (−430 kcal), 95% CI −3184 to −418 kJ, p= 0.02). This decrease was seen across macronutrients including total fat (−20 g, 95% CI −38 to −3, p= 0.03), total carbohydrates (−51 g, 95% CI −102 to 0, p= 0.06) and total protein (−14 g, 95% CI −24 to −4, p= 0.03); the distribution of nutrients (% energy consumed) did not change significantly. Reported fullness increased in the ExQW group but there was no statistically significant treatment effect (Figure 1). Self-reported 24-hour diet recall (Table 1) was not different at baseline and had more missing data than other assessments at the end of the study (Table 2). ExQW treatment was associated with a nonsignificant decrease in energy intake compared with baseline in the treatment group (−607 kJ/day; −145 kcal/day, IQ range −2 732 to 1 519 kJ/day, p=0.6). Although all patients had stable or increasing weight upon study enrollment, when we compared the diet recall estimate of energy intake to the measured TEE, it appeared underestimated: 82% of patients underreported their baseline estimated required intake by an average of 26% (−2 870 kJ/day; −686 kcal/day, IQ range −4 573 to −1 393 kJ/day, n=34).

Parent-reported questionnaires are reported at baseline (Table 1) and the change in outcomes at 36 weeks (Table 2). Hyperphagia symptoms were highly variable at baseline (mean HQ total score 26, Inter-Quartile range 21 to 33, score range 12–54, n=33) and HQ total score did not change significantly with ExQW treatment compared with placebo (mean difference 3.3, 95% CI −1.7 to 8.4, p= 0.21). This degree of hyperphagia is comparable to non-syndromic pediatric patients (10 years, IQ range 7–12.3) in the Vanderbilt Childhood Obesity Registry (HQ total score 23, IQ range 17 to 30, n=95) (unpublished data). On the parent reported CEBQ, the highest baseline scores were seen in enjoyment of food (4.8, IQ range 4.1 to 5, n= 36). The only significant change with treatment was an increase in the CEBQ score for slowness in eating in the ExQW vs. placebo group (mean difference 0.4, 95% CI 0.1 to 0.7, p= 0.02).

Energy Expenditure

TEE was similar between groups at baseline (Table 1). Change in outcomes at 36-weeks is presented in Table 2. At the end of treatment period, ExQW (vs. placebo) was associated with a decrease in TEE (mean difference −695 kJ/day (−166 kcal/day), 95% CI −1 130 to −264 kJ/day, p< 0.01, adjusted for baseline TEE). Further analysis showed that the treatment effect was still significant after adjustment for change in body composition (mean difference −372 kJ/day (−89 kcal/day), 95% CI −699 to −42 kJ/day, p= 0.04), driven by change in fat mass (Figure 2) or change in leptin (mean difference −695 kJ/day (−166 kcal/day), 95% CI −1 130 to −264 kJ/day, p< 0.01, Figure 3). While treatment with ExQW was associated with a significant decrease in fat mass vs. placebo (mean difference −3.1 kg, 95% CI −5.9 to −0.2, p= 0.04), there was not a significant change in lean mass between groups (mean difference 0.2 kg, 95% CI −2.0 to 2.4, p= 0.88).
Overall compliance with Actigraph wear was high. One patient did not return the monitor at baseline and two patients had insufficient data quality at the 36-week visit. The remaining 31 patients wore the Actigraph 96% of daytime minutes (6 pm-10 am) at both time points. Patients spent most of their awake time in sedentary and low-intensity activity. Since the amount of time spent in vigorous activity was minimal, moderate and vigorous physical activity categories were combined for analysis. At baseline, patients spent 24 minutes per day in moderate or vigorous physical activity (IQ range 15 to 35). Low intensity activity, typified by housekeeping activities or walking at <3 mph, accounted for 23% (214 min) of awake time. There was no association between treatment group and change in physical activity during the study.

**DISCUSSION**

HO is a refractory form of obesity thought to be due to a combination of decreased energy expenditure and increased food intake (19). We utilized gold standard methods of DLW, *ad libitum* feeding, and actigraphy to objectively measure energy balance at baseline and after a pharmacologic intervention with a glucagon-like peptide-1 receptor agonist (GLP1RA). GLP1RA are well known to suppress appetite via decreased gastric emptying and direct stimulation of satiety centers in the hindbrain and hypothalamus (20). GLP1RA may also increase energy expenditure through increased sympathetic nervous system activity and increased activation of brown adipose tissue (21, 22). We found that the degree of hypothalamic damage correlated with increased response to GLP1RA, possibly due to heightened responsiveness of extra-hypothalamic sites (23). These non-hypothalamic GLP1RA pathways led us to hypothesize that treatment with a GLP1RA would result in a reduction in energy intake with a relative increase in energy expenditure.

Our data support the hypothesis that GLP1RA therapy can decrease food intake in patients with HO. Patients treated with ExQW ate significantly less from an *ad libitum* buffet meal and reported a non-significant increase in fullness on VAS. This was further supported by the parental reports of increased slowness in eating on the CEBQ with positive responses to questions such as “my child takes more than 30 minutes to finish a meal” and “my child eats more and more slowly over the course of a meal” in the ExQW group. Compared to the objective measurements of a standardized meal, interpretation of subjective food recall questionnaires was hindered by underreporting and wide variability. Patients with obesity have repeatedly been shown to underreport food intake by 19–59% compared with measured TEE, consistent with our observed rate of underreporting (24). Patients with HO can also have problems with memory and executive function, making food recall particularly problematic in this population (25).

In contrast to our hypothesis that was based on rodent studies (26–28), we did not see an increase in energy expenditure with GLP1RA therapy in humans. The measured decrease in energy expenditure (~695 kJ/day) was similar to the estimated decrease in energy intake (~607 kJ/day) in the ExQW group, which would explain the lack of observed weight loss. However, the ExQW group did have an improvement in body composition with reduced gain of fat mass and a trend towards increased gain of lean mass compared with the placebo group. The ExQW group had a decrease in TEE that was disproportionate to the changes
in their body composition, since both lean mass and fat mass increased during the study in EXQW-treated participants. Decreased TEE is expected with significant weight loss (29), however, our treatment group gained weight less rapidly than the placebo group rather than losing weight. In particular, the most important component for energy expenditure, fat free mass, was preserved. A slower rate of weight gain should not trigger adaptive decreases in thermogenesis. The reduction in energy expenditure was also not explained by a change in physical activity and did not correlate with the change in serum leptin concentrations. In adults with weight loss, leptin is an important signal that regulates energy expenditure via a threshold model; when fat mass decreases and leptin levels drop below a threshold, energy expenditure decreases (30). Replacement of leptin post weight loss reverses approximately 2/3 of the energy expenditure changes (31), indicating that other mechanisms are involved and perhaps important in patients with HO. This disproportionate decrease in energy expenditure likely contributes to the refractory nature of HO and highlights the need for pharmacologic intervention. The overall low levels of physical activity observed in our study indicate room for further lifestyle modifications in HO. Only one patient met the Centers for Disease Control and Prevention Physical Activity Guidelines for America (2nd edition) pediatric goal of 60 minutes/day of moderate-vigorous activity. Physical activity can mitigate the decrease in energy expenditure caused by weight loss (32, 33).

In summary, patients with HO had decreased food intake and decreased energy expenditure in response to treatment with a long-acting GLP1RA. The decrease in energy expenditure was disproportionate to weight loss and not explained by a change in physical activity or leptin. This maladaptive response to weight loss highlights the need for effective pharmacologic interventions in HO. While GLP1RA may decrease energy intake, additional pharmacologic agents may be needed to preserve energy expenditure and improve weight loss.

Competing Interests:

Astra Zeneca supported the study by providing the active drug and matching placebo. This study was supported by R01DK104936 (CLR, MJA and AHS) from the National Institute of Diabetes and Digestive and Kidney Diseases and CTSA award No. UL1 TR002243 from the National Center for Advancing Translational Sciences. AHS has consulted for Rhythm Pharmaceuticals, Radius Inc., and Saniona A/S on studies of obesity. JAY reports receiving grant support from the Intramural Research Program of NICHD, NIH, as well as grants from Hikma Pharmaceuticals, Soleno Therapeutics, and Rhythm Pharmaceuticals, for studies of obesity.

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FIGURE 1:
Visual analogue scales (VAS) for hunger (panel A) and fullness (panel B) were performed q30 minutes during the buffet meal protocol. A 75g oral glucose load was given at minute 0 as part of an oral glucose tolerance test. A standardized pre-load meal was eaten at min 120 followed by access to an ad lib buffet meal from min 210–240. Results are presented as mean and 95% confidence interval. There was no treatment effect of exenatide extended release (drug) on hunger or fullness during the 90 minutes between the pre-load meal and the buffet meal (p= 0.3).
FIGURE 2:
Change in total energy expenditure (TEE, kcal/day) versus change in fat mass (kg) with best fit line and corresponding 95% confidence intervals.
FIGURE 3:
Change in total energy expenditure (TEE, kcal/day) versus change in leptin (ng/mL) with best fit line and corresponding 95% confidence intervals.
**TABLE 1:**

Baseline characteristics

|                      | Placebo          | ExQW             | p-value |
|----------------------|------------------|------------------|---------|
| **n**                | 18               | 23               |         |
| **Height (m)**       | 1.62 (1.55, 1.73)| 1.62 (1.54, 1.70)| 0.86    |
| **Weight (kg)**       | 97 (84, 118)     | 97 (85, 116)     | 0.67    |
| **BMI (kg/m²)**       | 38 (34, 44)      | 38 (32, 39)      | 0.23    |
| **Fat mass (kg)**     | 48 (42, 59)      | 48 (40, 54)      | 0.50    |
| **Lean mass (kg)**    | 48 (43, 57)      | 46 (40, 55)      | 0.67    |
| **BUFFET MEAL**       |                  |                  |         |
| **n**                | 18               | 23               |         |
| **Total intake (kJ)** | 4 941 (4 092, 6 745) | 1 436 (6 8, 8 644) | 0.06    |
| **Protein (g)**       | 37 (31, 49)      | 51 (34, 74)      | 0.13    |
| **Fat (g)**           | 54 (41, 71)      | 64 (39, 95)      | 0.42    |
| **Carbohydrates (g)** | 175 (106, 220)   | 150 (118, 226)   | 0.72    |
| **ENERGY EXPENDITURE**|                  |                  |         |
| **n**                | 18               | 22               |         |
| **TEE (kJ/day)**      | 11 016 (10 196, 12 916) | 10 918 (9 514, 12 723) | 0.75    |
| **PHYSICAL ACTIVITY**|                  |                  |         |
| **Sleep (min/day)**   | 463 (383, 540)   | 500 (418, 542)   | 0.45    |
| **Sedentary activity (min/day)** | 673 (634, 701) | 661 (627, 689) | 0.64 |
| **Light activity (min/day)** | 209 (177, 245) | 219 (146, 245) | 0.96 |
| **Moderate-vigorous activity (min/day)** | 23 (15, 34) | 25 (11, 39) | 0.91 |
| **24 HOUR DIET RECALL**|              |                  |         |
| **n**                | 13               | 22               |         |
| **Total intake (kJ/d)** | 8 678 (6 660, 10 702) | 7 326 (5 163, 8 899) | 0.06 |
| **Protein (g)**       | 89 (64, 97)      | 72 (56, 87)      | 0.18    |
| **Fat (g)**           | 99 (70, 113)     | 65 (50, 87)      | 0.02    |
| **Carbohydrate (g)**  | 230 (176, 304)   | 196 (132, 259)   | 0.17    |
| **HYPERPHAGIA QUESTIONNAIRE** | n=14    | n=19  |         |
| **Total Score**       | 26 (23, 34)      | 25 (20, 31)      | 0.24    |
|                      | Placebo     | ExQW       | p-value |
|----------------------|-------------|------------|---------|
| Hyperphagic Behavior | 10 (10, 13) | 9 (8, 14)  | 0.20    |
|                      | n=16        | n=21       |         |
| Hyperphagic Drive    | 11 (10, 14) | 10 (9, 12) | 0.18    |
|                      | n=17        | n=21       |         |
| Hyperphagic Severity | 5 (3, 6)    | 4 (3, 5)   | 0.19    |
| CHILDHOOD EATING BEHAVIOR QUESTIONNAIRE |   |   |      |
| Food responsiveness  | 4.0 (3.7, 4.6) | 3.5 (2.5, 4.4) | 0.08    |
| Emotional under-eating | 2.5 (2.5, 3.1) | 2.2 (1.8, 3.2) | 0.41 |
|                      | n=16        | n=20       |         |
| Emotional over-eating | 3.0 (1.9, 3.5) | 2.5 (1.9, 3.2) | 0.39    |
| Enjoyment of food    | 4.8 (4.2, 5.0) | 4.8 (4.1, 5) | 0.64    |
| Desire to drink      | 4.3 (3.0, 5.0) | 3.3 (2.6, 4.1) | 0.05    |
| Satiety responsiveness | 2.5 (1.8, 2.8) | 2.0 (1.8, 2.4) | 0.35    |
| Slowness in eating   | 2.0 (1.8, 2.6) | 2.1 (1.8, 2.9) | 0.73    |
| Food fussiness       | 2.2 (1.8, 3.8) | 2.0 (1.7, 2.8) | 0.52    |

Baseline characteristics presented as median (interquartile range). Exenatide once weekly (ExQW), body mass index (BMI), total energy expenditure (TEE).
### TABLE 2:

36-weeks change of outcomes by treatment

|                  | Placebo | ExQW | Adjusted mean difference | p-value |
|------------------|---------|------|--------------------------|---------|
|                  | n=15    | n=22 |                         |         |
| Weight (kg)      | 6.7     | 3.2  | −3.6                     | 0.09    |
|                  |         |      | (−7.6, 0.5)              |         |
| BMI (kg/m²)      | 1.4     | 0.5  | −0.8                     | 0.17    |
|                  |         |      | (−2.0, 0.3)              |         |
| Fat mass (kg)    | 4.6     | 1.5  | −3.1                     | 0.04    |
|                  |         |      | (−5.9, −0.2)             |         |
| Lean mass (kg)   | 1.3     | 1.7  | 0.2                      | 0.88    |
|                  |         |      | (−2.0, 2.4)              |         |
| **BUFFET MEAL**  | n=15    | n=18 |                         |         |
| Total intake (kJ)| 937     | −1 201 | −1 800                     | 0.02    |
|                  |         |      | (−3 184, −418)           |         |
| Protein (g)      | 4       | −14  | −14                      | 0.01    |
|                  |         |      | (−25, −4)                |         |
| Fat (g)          | 15      | −10  | −20                      | 0.03    |
|                  |         |      | (−38, −3)                |         |
| Carbohydrates (g)| 12      | −40  | −51                      | 0.06    |
|                  |         |      | (−102, 0)                |         |
| **ENERGY EXPENDITURE** | n=14 | n=19 |                         |         |
| TEE (kJ/day)     | 610     | −33  | −695                     | 0.004   |
|                  |         |      | (−1 130, −264)           |         |
| **PHYSICAL ACTIVITY** | n=11 | n=20 |                         |         |
| Sleep (min/day)  | 43      | 47   | 2                        | 0.94    |
|                  |         |      | (−56, 60)                |         |
| Sedentary activity (min/day) | −36 | −27  | 1                        | 0.96    |
|                  |         |      | (−52, 55)                |         |
| Light activity (min/day) | −10 | −27  | −12                      | 0.60    |
|                  |         |      | (−57, 33)                |         |
| Moderate-vigorous activity (min/day) | 2  | −5   | −6                       | 0.28    |
|                  |         |      | (−16, 5)                 |         |
| **24 HOUR DIET RECALL** | n=9 | n=14 |                         |         |
| Total intake (kJ) | −879   | −259 | −607                     | 0.58    |
|                  |         |      | (−2 732, 1 519)          |         |
| Protein (g)      | −20     | −3   | −2                       | 0.86    |
|                  |         |      | (−26, 22)                |         |
| Fat (g)          | −3      | 2    | −12                      | 0.34    |
|                  |         |      | (−36, 12)                |         |
| Carbohydrates (g)| −23     | −18  | −12                      | 0.73    |
|                  |         |      | (−81, 56)                |         |
| **HYPERPHAGIA QUESTIONNAIRE** | n=10 | n=15 |                         |         |
| Total Score      | −3.7    | 0.2  | 3.3                      | 0.21    |
|                  |         |      | (−1.7, 8.4)              |         |
| Hyperphagic Behavior | −1.2 | −0.1 | 0.8                      | 0.60    |
|                  |         |      | (−2.0, 3.5)              |         |
|                          | Placebo   | ExQW      | Adjusted mean difference | p-value |
|--------------------------|-----------|-----------|--------------------------|---------|
|                          | n=12      | n=20      |                          |         |
| Hyperphagic Drive        | −1.5      | −0.4      | 0.9 (−1.0, 2.7)          | 0.38    |
| Hyperphagic Severity     | −0.7      | −0.2      | 0.4 (−0.5, 1.3)          | 0.38    |
| **CHILDHOOD EATING BEHAVIOR QUESTIONNAIRE** | n=11      | n=18      |                          |         |
| Food responsiveness      | −0.1      | −0.2      | 0 (−0.4, 0.4)            | 0.91    |
| Emotional under-eating   | 0.1       | −0.1      | −0.2 (−0.6, 0.2)         | 0.37    |
|                          | n=12      | n=19      |                          |         |
| Emotional over-eating    | −0.1      | 0         | 0.1 (−0.4, 0.5)          | 0.80    |
| Enjoyment of food        | −0.2      | −0.4      | 0.1 (−0.4, 0.2)          | 0.45    |
| Desire to drink          | −0.3      | −0.1      | 0 (−0.4, 0.5)            | 0.93    |
| Satiety responsiveness   | 0.1       | 0         | 0 (−0.4, 0.3)            | 0.91    |
| Slowness in eating       | −0.2      | 0.2       | 0.4 (0.1, 0.7)           | 0.02    |
| Food fussiness           | 0.2       | 0         | −0.2 (−0.4, 0.1)         | 0.24    |

36-week change of outcomes by treatment group presented as mean change and mean difference (95% confidence interval), adjusted for baseline values. Exenatide once weekly (ExQW), body mass index (BMI), total energy expenditure (TEE).