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Exenatide has a Pronounced Effect on Energy Intake but not Energy Expenditure in Non-Diabetic Subjects with Obesity: a Randomized, Double-blind, Placebo-Controlled Trial

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Abstract

Aims—Exenatide is a glucagon-like peptide 1 (GLP-1) mimetic which induces weight loss predominantly, it is presumed, via decreased food intake. However, circulating GLP-1 is also a determinant of energy expenditure. We sought to quantify the effect of exenatide on energy expenditure (EE) and energy intake.

Materials and Methods—In this single-center, randomized double-blind placebo controlled trial, we randomized 80 healthy, non-diabetic volunteers with obesity (46 women, age: 34.4±8.7 y, body fat by DXA: 44.2±7.8%) to subcutaneous exenatide 10 μg twice daily or placebo. Subjects were admitted to our clinical research unit for measurement of 24h-EE in a whole-room indirect calorimeter and *ad libitum* food intake using an automated vending machine paradigm before and after randomization. Furthermore, energy expenditure and *ad libitum* food intake measures were repeated at 24-week after readmission for 7-day inpatient stay. Body weight was obtained weekly for up to 5 weeks and was recorded at each monthly follow up visit up to 24 weeks.

Results—Prior to randomization, participants over ate during the 3-day vending machine period in the whole study group (114.6±35.2 %), expressed as percentage of weight maintaining energy needs (WMEN) with those who were eventually randomized to exenatide overeating more (121.6±37.7 %) compared to placebo group (107.6±31.5 %). In the exenatide group, *ad libitum* absolute energy intake decreased by 1016.1±724.5 kcal/day (95% CI: −1250.9 to −781.2) versus a 245.1±710.5 kcal/day (95% CI: −475.4 to −14.7) decrease in placebo (Δ= −624.8 Kcal/day, $p < .0001$) whereas the reduction in ad libitum caloric intake relative to WMEN was a more modest

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366.8±752.1 kcal/day (95% CI: −614.0 to −119.6) decrease compared to 8.0±860.1 kcal/day (95% CI: −286.8 to 270.8) reduction in placebo ($\Delta = -382.3$ Kcal/day, $p = 0.03$). The decrease was uniform across all macronutrients groups.

No differences in 24hEE or substrate oxidation rates were found. In the exenatide group, body weight decreased more over the 5 weeks ($\beta = -0.039$ kg/week, $p = 0.02$) and was lower compared to placebo at the end of fifth week (−1.48±0.77 kg; 95% CI: −3.02 to 0.05, $p = 0.06$). At the 24-week follow up, there was no difference in energy intake between exenatide group and placebo group and the treatment group decreased 24-h EE more compared to placebo ($\beta = -160.6$ Kcal/day, 95% CI: −307.6 to 13.6, $p = 0.03$) compared to their pre-randomization measurement. However, this reduction was not present after adjustment for changes in FM and FFM ($\beta = -87$ kcal/day, $p = 0.14$). No difference was observed in body weight ($\Delta = -1.72$ kg, 95% CI: −5.77 to 2.30, $p = 0.39$) in exenatide versus placebo over 24 weeks.

Conclusion—Compared with placebo, exenatide decreased early ad libitum energy intake but did not change 24h-EE. However, the reduction was more modest in relative versus absolute terms (i.e. below that needed for WMEN). Thus, although rate of weight change was greater in the exenatide treated subjects at 5 weeks, the absolute difference in weight was not significant. These findings indicate that although exenatide reduces food intake, it may be more beneficial in blunting overeating and thus may serve to more prevent weight regain following initial weight loss.

Clinical Trial Registration Numbers—NCT00856609; clinicaltrials.gov

Keywords

GLP-1 receptor agonists; energy expenditure; energy intake; weight loss

1. Introduction

Analogs of the incretin hormone glucagon-like peptide 1 (GLP-1) induce weight loss [1] and one such analog, liraglutide, has been FDA approved for weight loss. Exenatide is the first short acting GLP-1 agonist approved for treatment of type 2 diabetes mellitus (DM) and has also been shown to induce weight loss in patients with obesity with [2-4] and without diabetes [5, 6] with a large variability (ranging by −0.2 to −7.2 kg).

GLP-1 is an incretin hormone released from the L cells of the intestinal mucosa in response to a meal [2]. In addition to its insulinotropic action, infusion of GLP-1 suppresses short-term food intake in humans [7]. Endogenous circulating GLP-1 is positively correlated with resting energy expenditure (REE) [8], and acute infusion caused an insulin-dependent increase in EE [9]. In humans without obesity, intravenous GLP-1 infusion increases EE during hyperglycemic clamp but, after infusion of somatostatin, the insulin secretion was inhibited and, in turn, the GLP-1 effect was abolished [9]. During GLP-1 infusion increase in EE may have been caused by GLP-1-induced hyperinsulinemia due to sympathetic activation and/or glucose utilization due to activation of thermic response [10, 11]. Hwa et al [12] have shown that both central and peripheral GLP-1 administration increased oxygen consumption, an index of EE, in rats.

GLP-1 levels have also been negatively associated with respiratory quotient (RQ), a proxy for the ratio of carbohydrate to lipid oxidation, indicating that GLP-1 may be involved in shifting cell preference from carbohydrates to lipids [13, 14]. The quantification of the effect of a GLP-1 analog on energy expenditure, substrate oxidation and energy intake has not been completely elucidated. In people with DM, exenatide results in a large variability in achieved weight loss [15]. Whether inter-individual differences in energy expenditure (EE) and energy intake (EI) responses to exenatide account for this variability is unknown. The aim of this randomized, double-blinded, placebo-controlled study was to fully enumerate the effects of exenatide on 24-hour EE and EI as primary outcomes. Further, we sought to determine the association of any exenatide-induced changes with weight loss after 5-weeks of treatment. In a subset of subjects who continued on study medication for 24 weeks, we also investigated whether any changes in EE or EI were apparent with longer duration of treatment compared to placebo.

2. Methods and study design

2.1 Study design and participants

From June 2009 to December 2015, 145 adults age <55 with BMI>30 kg/m^2 interested in weight loss but weight stable (variation < 2.3 kg within past 6 months) were recruited from the greater Phoenix area. Of these, 84 met initial inclusion criteria (Fig. 1) and were admitted to our clinical research unit (CRU) for at least 4 days (full inclusion/exclusion criteria, Supplementary Appendix) to perform initial tests such as oral glucose tolerance test (OGTT) after 3 days of weight maintaining diet to assess glucose regulation. Four subjects, due to personal reasons, withdrew from the study. Based on medical history, physical examination and standard laboratory tests, individuals had no evidence of medical diagnoses other than obesity and/or impaired glucose tolerance. Upon admission, subjects were initially given a weight maintaining diet (macronutrient content 20%, 30% and 50% protein, fat, and carbohydrate, respectively) with caloric content determined using unit specific equations and adjusted daily to maintain body weight at ±1% during the baseline assessments [16]. Body composition was determined by total-body dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, enCORE 2003 software version 7.53.002, GE Lunar, Madison, WI, USA). Glucose regulation was assessed by 75 g oral glucose tolerance test (OGTT) on day 4 to exclude diabetes per American Diabetes Association criteria [17]. The initial 4 days of the inpatient stay included routine laboratory testing, physical examination, medical history and 75 g oral glucose tolerance test. Subjects stayed to complete an additional 11 inpatient days for assessment of energy expenditure, substrate oxidation and *ad libitum* food intake (described in detail below) before and after randomization (in a double blind fashion) to placebo or exenatide (Fig. 2).

All subjects were informed of the aims, nature, benefits and risks of the study prior to providing informed consent. The experimental protocol was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The study was reviewed annually be a Data Safety and Monitoring Board for safety parameters and previously determined stopping guidelines. At each review, the DSMB approved the study to continue.

Following the initial 15 days inpatient stay subjects returned for four weekly follow-up visits (up to 5 weeks) for lifestyle counseling and measurement of weight, assessment of side effects and lab tests including amylase and lipase.

The original protocol (until 2012) followed the same initial timeline as outlined above but continued for 24-weeks of study medication. After week 5, subjects returned monthly for follow up visits up to 24-week for the same measures noted above. At week 24, subjects were readmitted for a 7-day inpatient stay while on study medication. During this admission, the OGTT, energy expenditure and *ad libitum* food intake measures were repeated. Given the emerging evidence of the efficacy of GLP-1 agonists for weight loss during the study period, the protocol was amended to concentrate on the mechanism of these weight loss effects. Thus, the initial inpatient admission remained the same throughout the study, but the outpatient portion was shortened to 5 weeks.

2.2 Randomization and blinding

After the baseline measurements, subjects were randomized to either exenatide or placebo using permuted block randomization with sex specific block sizes ranging from 2 to 6. Both the subjects and the study investigators were blinded to study medication allocation. The blinded, coded medication and placebo were provided from pooled supplies (Bristol Myers Squibb) to the pharmacy in identical, numbered containers and were dispensed according to the predetermined randomization scheme. The pharmacy alone had access to the randomization information. To maintain blinding and because exenatide has known side effects, all subjects were informed that they were likely to experience nausea given the results of prior studies[18] where subjects treated with either placebo or exenatide experienced nausea.

2.3 Treatment

At randomization, subjects received either exenatide 10 μg twice daily or placebo. Subjects were trained to self-administer the subcutaneously injected preparations, and performed their own injections (monitored by study staff) during their inpatient stay. Subjects were trained to use a glucometer and about sign, symptoms and treatment of hypoglycemia. Glucose measurements and side effects were reviewed by a study physician at each follow up visit. Study compliance was evaluated at outpatient visits by measuring the remaining volume of product in the cartridge. Lifestyle counseling was done by separate trained research staff who remained blinded to the individual's side effect profile. The lifestyle counseling was standardized and based on the principles of the diabetes prevention program [19] and which encourage increased physical activity and healthy eating habits.

2.4 Assessment of 24h Energy Expenditure and Macronutrient Oxidation

Twenty-four-hour energy expenditure (EE) was measured using whole-room indirect calorimetry as previously described [20] prior to and 2 days after starting study medication (n=70) and at the 6-month follow-up admission (n=24). Meals were provided at 0700, 1100, 1600, and 1900 at approximately 80% of weight maintaining diet (WMD) calories [16]. The calories provided for the first (baseline) and second chamber (post-randomization) were the same. Air temperature was maintained at approximately 23.9°±1.4° C. Spontaneous physical activity (SPA) was measured by a radar system [21]. The CO_2 and O_2 concentrations of the outflowing air were measured as previously described [21] and calculations of oxygen consumption and carbon dioxide production were used to calculate 24-h respiratory quotient (RQ) and EE [21]. From the 24-h RQ, carbohydrate and fat oxidation were calculated, after accounting for protein oxidation, measured from a 24-h urinary nitrogen calculation. SMR was also calculated and defined as the average energy expenditure between 2330 and 0500 while spontaneous physical activity was <1.5% [22]. Each subject remained in the chamber for 23.25 hours but all measures were extrapolated to 24 hours. AFT was calculated as the difference between EE in the inactive state and SMR[23].

2.5 *Ad libitum* food intake assessment using a vending machine paradigm

Ad libitum food intake (Vend) was measured over three days using an automated vending machine paradigm [24]. First, food preferences were assessed by the food selection questionnaire (FSQ)[25].The vending machines were then stocked with 40 different foods that the subject gave an intermediate hedonic rating on the FSQ (i.e. 4 to 8). Subjects then self-selected all meals and snacks from the vending machine during the 3-day time period and food choices were tracked. Unfinished items were returned to the vending machine and subsequently weighed, so the absolute exact calorie intake over the 72-hour period was calculated (The Food Processor software, ESHA Research, Salem, Oregon) and expressed as both average kilocalories consumed per day and the percentage of the weight maintenance energy needs (%WMEN) calculated as the daily average intake from the vending machine divided by the weight maintaining calories times 100. Furthermore, the caloric intake after randomization was also calculated as the change relative to WMEN, either expressed in kcal/day. Specifically, we calculated this as the difference between the daily average intake from the vending machine and the weight maintaining diet, or expressed in percentage, as the change in caloric intake relative to WMEN divided by the weight maintaining calories times 100.

Kilocalories consumed by each subject were also categorized by macronutrient content. This measure of ad libitum food intake has been found to be highly reproducible [26]. However, although this paradigm is valuable and useful during an inpatient study such as this, it likely does not reflect energy balance in a different environment.

3. Statistical analysis

Power calculations determined that 80 individuals (41 exenatide, 39 placebo) had greater than 90% power with an alpha of 0.01 to detect a clinically significant difference of 200±250 kcal/day in 24h EE and a 500±680 kcal difference in ad libitum energy intake on the vending machine between exenatide and placebo groups. All statistical analyses were performed using the procedures of SAS, version 9.2 (SAS Institute, Cary, NC). Data that were normally distributed are presented as mean±standard deviation; data that deviated from normality are presented as median with interquartile range.

Primary study outcomes were differences in energy intake and EE between placebo versus exenatide-treated subjects. Secondary outcomes included differences in macronutrient oxidation and weight. Alpha was set at 0.01 for primary outcome measures and 0.05 for secondary outcome analyses.

Differences in baseline measures between the exenatide and the placebo groups were evaluated using Student's unpaired t-test. Changes in energy intake (in absolute term and relative to WMEN), EE, and substrate oxidation between the two groups were evaluated by analysis of covariance (ANCOVA) accounting for baseline values. For EE and substrate oxidation measures, models included adjustment for baseline FFM, FM, chamber temperature, age, race and sex. Predicted values for 24-h EE at follow-up visits were calculated based on regression equations including age, sex, race, chamber temperature, FM and FFM at baseline. Predicted versus observed values were compared by Student's unpaired t-test.

Weight change at 5 weeks and 24 weeks was calculated in the two groups and compared by Student's t-test. Repeated-measures mixed models including all follow-up data were performed to compare the weight trajectories of the two groups over 5 and 24 weeks using a first-order autoregressive covariance structure. Associations of the changes in EE and EI in the exenatide group with body weight change were quantified by the Pearson's correlation coefficients. Differences in safety, tolerability and adherence between the groups were compared with Chi-squared tests.

4. Results

4.1 Participants

Screening, eligibility, and available data are reported in the CONSORT diagram (Fig. 1). Baseline characteristics of study participants are described in Table 1.

4.2 *Ad libitum* Food Intake

Prior to randomization, participants over ate during *ad libitum* food intake period (114.6±35.2 %, expressed as percentage of weight maintaining energy need for whole study group). By chance this was greater in the exenatide group (121.6±37.7 %) compared to placebo group (107.6±31.5 %).

At the baseline admission and following randomization, the absolute decrease in the mean 3-day *ad libitum* energy intake was greater in the exenatide versus the placebo group, whether expressed as mean difference in kcal/day (Δ = −624.8 Kcal/day, 95% CI: −901.8 to −347.8, exenatide: −1016.1 ± 724.5 kcal/day, placebo: −245.1 ± 710.5 kcal/day, $p < 0.0001$, Fig. 3A) or %WMEN (Δ= −17.6%, CI 95% −27.3 to −7.9, p = 0.0005, figure 3B). When analyzed in terms of the reduction compared to WMEN, the difference was less pronounced but still significant whether expressed as mean difference in Kcal/day (Δ= −382.3 Kcal/day, 95% CI: −725.9 to −8.4, exenatide: −366.8±752.1 kcal/day, placebo: −8.0±860.1 kcal/day, p = 0.03, figure 3C) or %WMEN (Δ= −12.8%, CI 95% −25.1 to −0.45, p = 0.04, figure 3D). The reduction in calories occurred evenly across macronutrient groups (Supplemental Figure S1, panel A). The absolute decreased energy intake in the exenatide compared to placebo group (kcal/day) was observed from day one of the ad libitum vending machine period and did not exhibit tachyphylaxis (Supplemental Figure S1, panel B). There were no differences in caloric intake from soda between the 2 groups (Δ = −35.8 kcal/day, 95% CI: −80.9 to 9.3, p = 0.1). Analyzed by sex, the reduction in food intake was greater in males (Δ = −1310.9 kcal/day, 95% CI: −1703.7 to −918.1) compared to females (Δ = −788.2 Kcal/day, 95% CI: −1061.6 to −514.8, p = 0.02) in the exenatide group. No difference was observed between men (Δ= −379.6 Kcal/day, 95% CI: −2399.0 to −664.7) and women (Δ= −1310.9 Kcal/day, 95% CI: −2399.0 to −664.7) in the placebo group (p = 0.3). Similar results were obtained when the reduction in food intake, analyzed by sex, was adjusted for FFM in the exenatide group (p = 0.01) and in the placebo group (p = 0.7).

At the 24-week follow up, there was no difference in EI between exenatide-treated individuals (n=12) and placebo treated individuals (n=18) (β = −379.2 Kcal/day, 95% CI: −1175.6 to 417.2, p = 0.3), nor in the overall decrease in EI in the exenatide group compared to baseline (β = −449.9 Kcal/day, 95% CI: −957.3 to 57.5, p = 0.08). Food intake reduction did not differ by sex (p = 0.9).

4.3 Energy expenditure

At the baseline admission, there was no change in 24h-EE (β = −24.1 kcal/day, 95% CI: −89.7 to 41.4, p = 0.4) (Fig.4A), RQ (β = −0.0016, 95% CI: −0.017 to 0.014, p = 0.8) (Fig. 4B), AFT (β = −63.0 Kcal/day, 95% CI: −127.7 to 1.8, p = 0.06) (Fig.4C) or SMR (β = 26.7 Kcal/day, 95% CI: −23.6 to 77.1, p = 0.3) (Fig.4D) in exenatide versus placebo treated subjects. This remained so even after adjustment for FFM, FM, age, sex and race (data not shown). There was also no change in SPA (β = −6.3 kcal/day, 95% CI: −21.7 to 9.1, p = 0.4) in the exenatide treated group compared to placebo or in LIPOX and CARBOX either before or after adjustment for covariates (all p>0.7). Furthermore, no differences were found between groups when analyzed by sex (all p > 0.5).

Compared to placebo group, subjects treated with exenatide had similar EE as assessed inside the metabolic chamber every minute over the course of 24 hrs (Δ = −0.02 kcal/min, p = 0.25) (Fig.5).

At 24 weeks, 24-h EE decreased more in exenatide treated (n=8) versus placebo treated participants (n=16) (β = −160.6 Kcal/day, 95% CI: −307.6 to 13.6, p = 0.03) compared to their pre-randomization measurement. This greater decrease in 24h EE in exenatide-treated participants was still present after accounting for weight change at 24 weeks (Δ = −124.8 Kcal/day, 95% CI: −245.4 to −4.2, p = 0.04) but not after adjustment for changes in FM and FFM (β = −87 kcal/day, p = 0.14) (Fig. 6D). Furthermore, there was no difference between groups (p = 0.70) in 24-h EE residuals, i.e., observed minus predicted based on the regression equation calculated from the baseline measurements (data not shown).

There were no changes in RQ (β = 0.0032, 95% CI: −0.027 to 0.033, p = 0.8), SMR (β = −111.1 Kcal/day, 95% CI: −270.4 to 48.1, p= 0.16), AFT (β = −38.2 Kcal/day, 95% CI: −162.5 to 86, p = 0.52) or SPA (β = −7.3 Kcal/day, 95% CI: −31.6 to 16.9, p = 0.53) at the 24-week follow up. Changes did not differ by sex (all p > 0.6).

During the baseline inpatient portion of the study, differences in *ad libitum* food intake prior to and following initiation of exenatide or placebo did not correlate with the changes in 24h-EE or related measures such as RQ, SMR, AFT and SPA (all $p > 0.3$) in either group.

4.4 Body weight change

There was no difference in body weight at 5 weeks between the two groups ($\beta = -1.48$ kg, 95% CI: −3.00 to 0.05, $p = 0.06$) (Fig.6A); however, in the repeated measures analysis of weekly body weight, the exenatide group had a greater rate of weight change over 5 weeks compared with the placebo group ($\beta = -0.039$ kg/week, $p = 0.02$) (Fig. 6B). The results did not change when the repeated measures analysis was not adjusted for the baseline weight ($\beta = -0.045$ kg/week, $p = 0.02$). Similar results ($\beta = -0.042$ kg/week, $p = 0.01$) were observed when only subjects on treatment ($n = 64$) were evaluated.

At 24 weeks, in a linear model, there was no difference in body weight ($\Delta = -1.72$ kg, 95% CI: −5.77 to 2.30, $p = 0.39$) or in body composition (data not shown) in exenatide (n=13) versus placebo (n=20) treated subjects; nor was there any difference in weight trajectory using mixed models (data not shown). Weight change did not differ by sex at 5 or 24-weeks (all $p > 0.4$). The individual change in mean caloric intake in the exenatide group was not associated with overall weight change at 5 weeks ($p = 0.4$, Fig. 6C) or 24 weeks ($p = 0.8$). Results were similar when weight change was expressed in either absolute terms (kg) or as a percentage of baseline weight.

4.5 Safety and adverse events

Self-reported hypoglycemia and injection site reactions were more common in the exenatide group. We did not find any association between reduction in food intake and presence of nausea, defined as at least one episode, in the exenatide group ($p = 0.3$) or placebo group ($p = 0.3$). Details of the adverse events are reported in the Supplement (Supplement Table 2) and were consistent with prior reports [27]. Based on the quantification of product returned, 81 % of volunteers were assessed as having taken all the medication doses.

5. Discussion

In this double-blind placebo controlled study examining the mechanism of exenatide induced weight loss, we demonstrated that exenatide produces an initial profound, nearly 1000 kcal/day or 30%, decrease in absolute energy intake, but has no effect on EE or substrate oxidation. This effect on energy intake is non-macronutrient selective, but wanes over time as demonstrated by the less pronounced reduction at 6 months. However, when we analyzed the reduction in caloric intake relative to how many calories were calculated to maintain weight (i.e. the weight maintaining needs or WMEN), this effect was less pronounced than the absolute change. This calorie deficit was approximately 370 kcal/day. We did observe an effect of exenatide on weight loss trajectory as early as 5 weeks but absolute weight change was not different between the groups.

Previous studies have demonstrated an effect on GLP-1 agonists on energy intake, but not to the degree found in our study; nor did these studies measure ad libitum energy intake over 3 days, using our highly reproducible vending machine paradigm [26].

Early studies with exendin-4 infusions demonstrated a 19% reduction in calories consumed in participants with obesity [28]. A meta-analysis including lean and overweight subjects [29] estimated an 11.7% decrease in food intake. Using an ad libitum dinner paradigm, exenatide administration decreased food intake compared with sitagliptin in subjects with type 2 diabetes [30]. Pinelli et al [31] also demonstrated decreased food intake in lean subjects following administration of exenatide compared to placebo in a single meal test, as has another similar study [32]. In subjects with diabetes, liraglutide decreased energy intake compared to placebo by 18% [33], and a similar effect on energy intake was demonstrated in healthy individuals with obesity at doses of 1.8 mg or 3 mg[34]. We did confirm that decreased energy intake is likely the primary mechanism for weight loss with GLP-1 agonists. However, the more modest reduction in caloric intake relative to weight maintaining caloric needs indicated that at least for exenatide its effect on early weight loss is less substantial. By using a longer (3 day) ad libitum paradigm, we have been able to more precisely quantify this effect, demonstrating a larger effect on energy intake than had been reported previously and across all macronutrient groups. Furthermore, using the same paradigm, we demonstrated that this effect became less pronounced after 6 months of treatment. This may have been due to the smaller cohort or to a true waning effect of exenatide on energy intake over longer follow-up.

The effect of GLP-1 analogues on energy expenditure has been less clear. GLP-1 infusions reduced resting metabolic rate, diet induced thermogenesis and carbohydrate oxidation in two studies [35, 36], but another study found increased EE via an insulin mediated mechanism [9]. Subjects with obesity did not have an increase in total EE after 14 weeks of exenatide administration. However, our group has previously [14] found a positive association between fasting plasma GLP-1 concentrations and both resting EE and fat oxidation. Using whole room indirect calorimetry, we did not observe any effect of exenatide administration on measures of EE or substrate oxidation. We did find a greater decrease in 24h-EE in the exenatide versus placebo group at 6 months. However, this effect, although independent of weight change, was not independent of body composition change, albeit the overall sample size was small and a significant difference might have been detected in a larger cohort.

Although the point estimate indicated greater weight loss in exenatide treated subjects at 5 weeks, this did not reach statistical significance. However, more sophisticated analysis with mixed models demonstrated a greater weight loss trajectory in the exenatide treated group. A large meta-analysis including studies of participants with and without DM demonstrated that these medications do contribute to weight loss [6]. Madsbad et al [37] showed that all six GLP-1 receptor agonists, including exenatide, induced weight loss.

Per the ileal brake hypothesis, ingested nutrients trigger endogenous GLP-1 release inhibiting gastric motility [38, 39], which is considered the dominant mechanism for the decreased energy intake. However, GLP-1 receptors are also present in the brain [40], in particular in the paraventricular and arcuate nucleus, areas crucial to appetite regulation. Consistent with the effects of GLP-1 on both gastric emptying and satiety, participants not only ate less, but reported decreased hunger (Supplemental, Table 2). In mice, decrease in food intake has been reported after both central and peripheral administration of GLP-1 receptor agonists [41, 42]. In rats, GLP-1 activates brain vagal preganglionic neurons resulting in gastroinhibition[43]. In mice, radiolabeled GLP-1 analogue penetrated the blood brain barrier[44]. In humans, exenatide altered brain responses to the consumption of palatable food in diabetic patients with obesity[45]. Thus, GLP-1 analogues may have both a direct peripheral and central effect on satiety and gastric emptying.

Side effects were as expected with nausea, diarrhea, and gastroesophageal reflux as the most common but these did not differ by group (Supplement Table 2). Hypoglycemia was more common in the exenatide group (25%; vs. 7.7%, p = 0.04). None of these were serious (defined as requiring assistance). This prevalence is higher than in other studies, likely due to the immediate use of the 10 μg dose. In our data, the absence of association between presence of nausea, defined as the presence of at least one episode since randomization, and reduction in food intake suggest that nausea does not play a major role in the reduction of food intake.

The strengths of our study include the directly observed administration of the drug during the inpatient stay. Furthermore, we used objective gold standard techniques for the measurement of 24 hours energy expenditure and food intake. In addition, these measurements were made prior to and following randomization and also, in a subset of subjects, repeated at 24 weeks. Our study has several limitations. This was a small single-center study which focused on the mechanism of exenatide induced weight loss. We did have sufficient power to investigate our primary hypotheses of the effect of exenatide on energy intake and energy expenditure, but our ability to detect a difference in secondary outcomes, including weight change, was limited by our relatively small samples size, especially at the 24-week follow-up. We acknowledge also that, although the automated vending machine paradigm is highly reproducible and useful to assess food intake measurement in inpatient setting, it does not reflect energy intake during free-living conditions. In this artificial setting subjects tend to overeat resulting in a large reduction in food intake in absolute terms but less so when this is assessed by the relative decrease compared to weight maintaining energy needs. Furthermore, although subjects were monitored as inpatients and had no reported differences in nausea, we cannot exclude that milder early nausea which affected energy intake was not captured and might have affected our ad libitum energy intake results. An additional measure of energy intake after several weeks of treatment would have been helpful in this regard. In addition, although the drug administration was administered by study personnel during the inpatient stay, albeit adherence was assessed at their 5-week outpatient visit, we cannot be sure of the same degree of adherence during the outpatient portion. Lastly, although evidence indicates that exenatide 10 mcg twice daily achieves a pharmacologic steady state on day 3 of administration [46] (the same day the EE measurement was made in our study), it is not clear if this means a “metabolic” steady state was achieved in terms of fuel utilization.

6. Conclusion

In conclusion, using gold standard measurements of ad libitum energy intake and energy expenditure, exenatide, as representative of GLP-1 agonists, has an early profound and rapid effect in energy intake in absolute terms, which we were able to quantify (decreased calorie intake of over 1000 kcal/day and over a 600 kcal/day decrease compared to placebo) but no effect on energy expenditure. However, when analyzed relative to the decrease in weight maintaining energy needs, which is the caloric deficit that will truly affect weight loss, this effect is less marked (nearly 370 kcal/day below WMEN versus 1000 kcal/day as an absolute decrease). Thus, we did not observe as strong an effect on early weight loss with exenatide and this effect appeared to wane over longer term follow-up. Thus, rather than a tool for inducing early weight loss, exenatide via its effect on blunting of overeating might be more useful as a medication to prevent weight regain following initial weight loss in addition to ongoing lifestyle efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A.B. and J.B. analyzed and interpreted data and wrote the manuscript. J.K. reviewed the manuscript and assisted with the interpretation of the data. M.T. designed, implemented and conducted the study. All authors critically revised the draft and approved the final manuscript. A.B. and J.B. are the guarantors of this work and A.B. has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Abbreviations

WMEN	weight maintaining energy need
EE	energy expenditure
RQ	respiratory quotient
SMR	sleeping metabolic rate
AFT	awake fed thermogenesis
SPA	spontaneous physical activity

Highlights

- Exenatide has an early and pronounced absolute change in daily energy intake
- Decrease in food intake relative to WMEN was less pronounced than absolute reduction
- Exenatide has no effect on energy expenditure
- Exenatide has a modest effect on weight loss at 5 weeks
- Effect on energy intake appeared to wane over long term follow-up

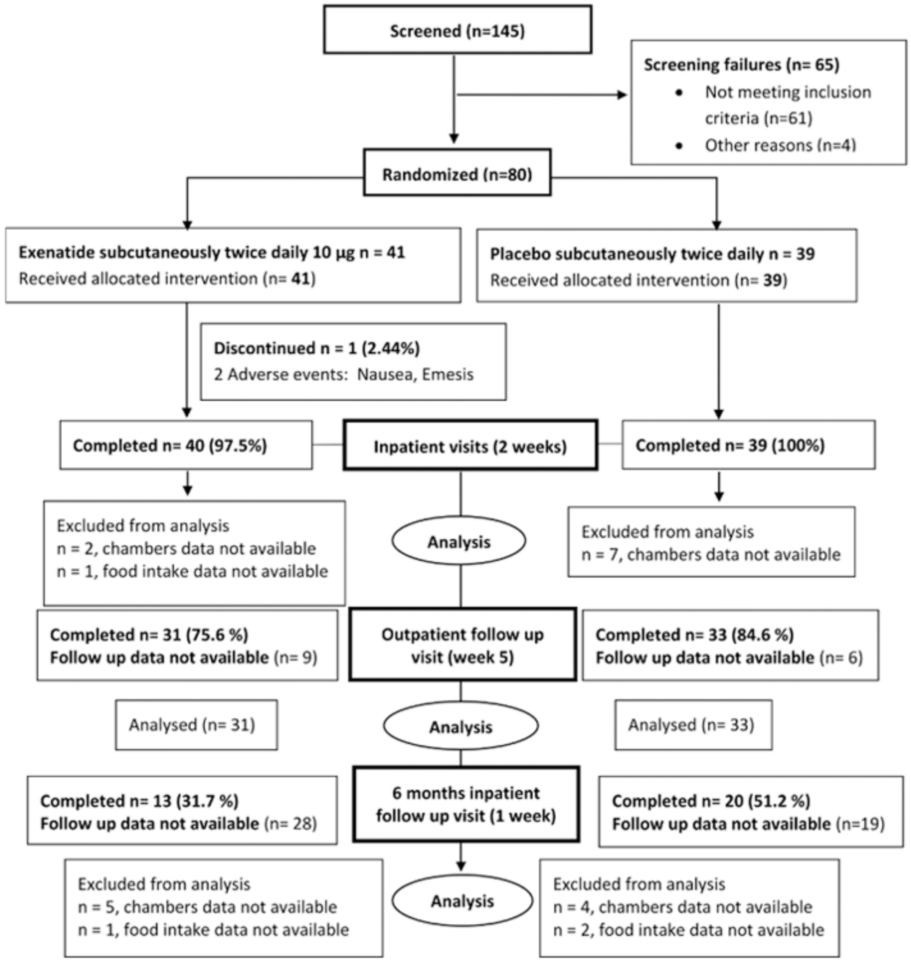

Figure 1. Consort flow diagram

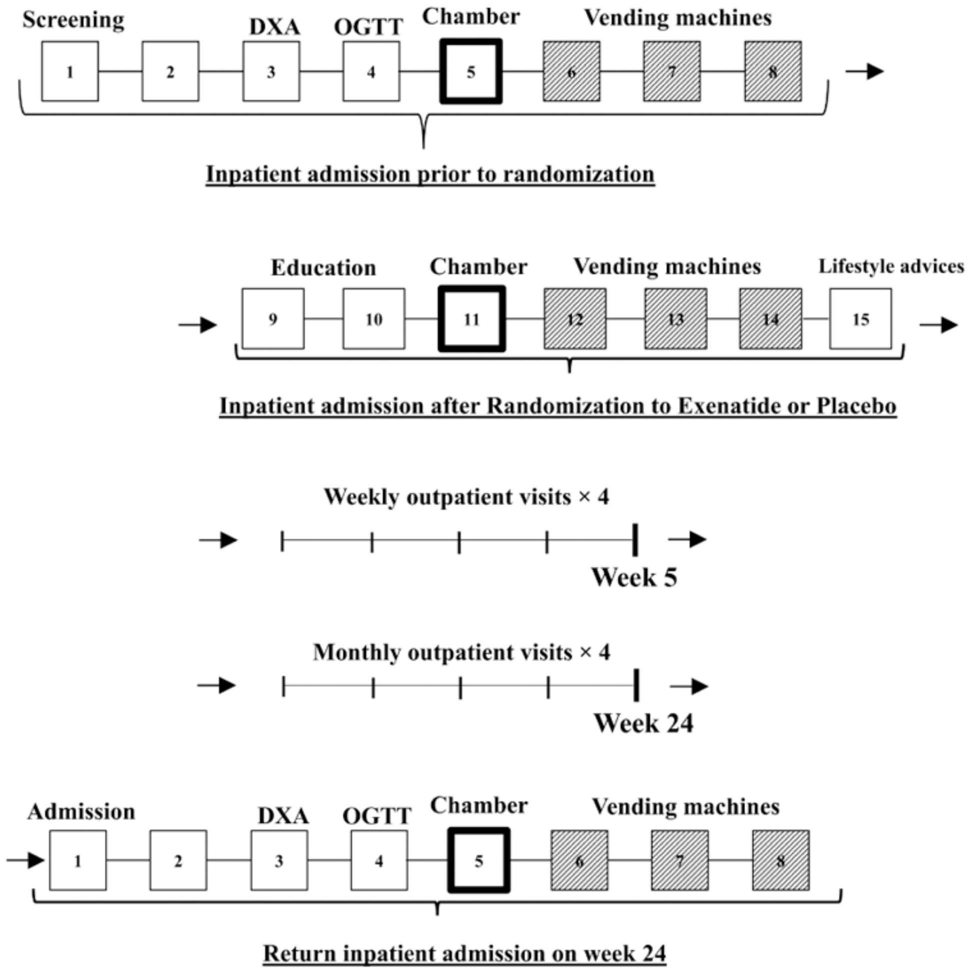

Figure 2. Study diagram of the clinical study

We divided the outline of the study in 2 portions (described in detail below): first inpatient stay (composed by inpatient admission prior to randomization and inpatient admission after randomization) and second (return) inpatient stay at week 24.

Inpatient Admission prior to randomization: Day 1: Screening interview including screening labs and informed consent

Day 3: DXA (dual energy X-ray absorptiometry)

Day 4: OGTT (oral glucose tolerance test)

Day 5: Whole room indirect calorimetry for the assessment of the 24h energy expenditure at baseline

Day 6-7-8: Assessment of ad libitum food intake with vending machine paradigm at baseline

Inpatient Admission after randomization: Day 9-10: Exenatide/Placebo injection education (subcutaneous)

Day 11: Whole room indirect calorimetry for the assessment of the 24h energy expenditure during Exenatide/Placebo

Day 12-13-14: Assessment of ad libitum food intake with vending machine paradigm during intervention period

Day 15: Lifestyle recommendations

After the first 2 weeks of inpatient visit, volunteers returned for weekly follow up visit up to 5 weeks, and then, for monthly follow up visits up to week 24

Return Inpatient Admission on week 24: Day 1: Screening interview including screening labs and informed consent

Day 3: DXA (dual energy X-ray absorptiometry)

Day 4: OGTT (oral glucose tolerance test)

Day 5: Whole room indirect calorimetry for the assessment of the 24h energy expenditure at baseline

Day 6-7-8: Assessment of ad libitum food intake with vending machine paradigm at baseline

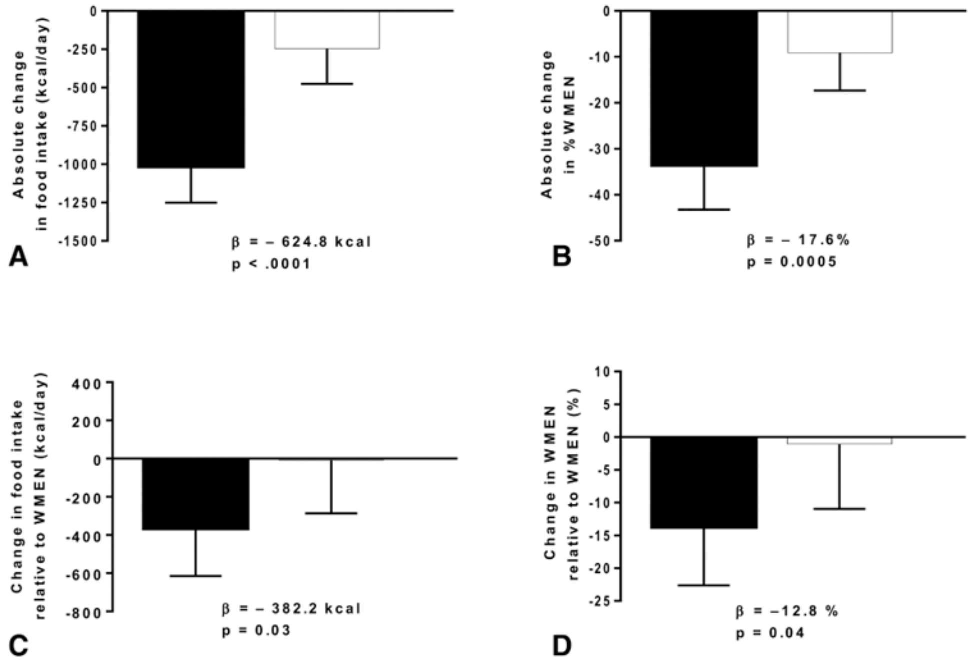

Figure 3. Ad Libitum Food intake changes between pre and post-randomization in exenatide and placebo groups

A. Mean of 3-day food intake absolute change between pre and post-randomization, expressed in Kcal/day; **B**. Mean of 3-day food intake, expressed as the absolute change in percentage of their weight maintaining energy need (WMEN); **C**. Mean of 3-day food intake change relative to the weight maintaining energy need between pre and post-randomization, expressed in Kcal/day **D**. Mean of 3-day food intake, expressed as the change in percentage of their WMEN relative to the weight maintaining calories.

The βs indicate the absolute values of the difference between pre and post-randomization changes in food intake between the exenatide and placebo groups.

Error bars represent the mean with 95% confidence interval. Thirty-nine individuals in each group had complete vending machine data.

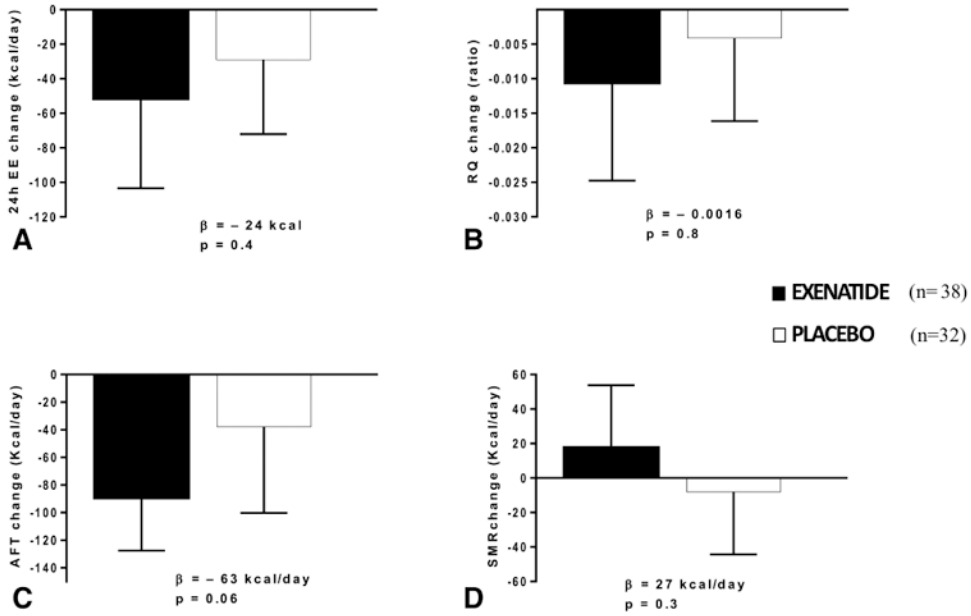

Figure 4. Energy expenditure and RQ changes between pre and post-randomization in exenatide and placebo groups

A Change in 24h-EE expressed as Kcal/day; **B**. Change in RQ; **C**. Change in AFT expressed as Kcal/day. **D**. Change in SMR expressed as Kcal/day.

The β indicate the absolute values of the difference between pre and post randomization measurements between the exenatide and placebo groups.

Error bars represent the mean with 95% confidence interval.

Thirty-eight participants in the exenatide group and 32 in the placebo group had complete EE data.

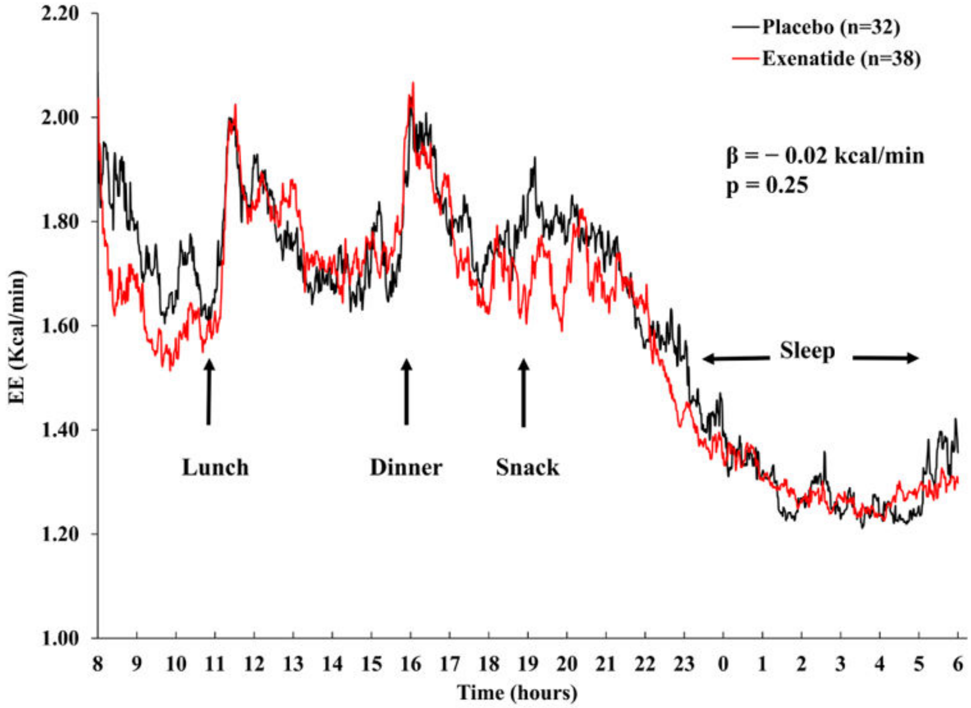

Figure 5. Post-randomization EE measures as assessed in the whole-room indirect calorimeter over 24 hours in exenatide and placebo groups

The graph shows the average EE trajectories measured every minute. The β coefficient indicates the difference between the EE trajectories of exenatide and placebo groups by mixed model analysis adjusting for age, sex, FFM, FM, physical activity and accounting for repeated measures.

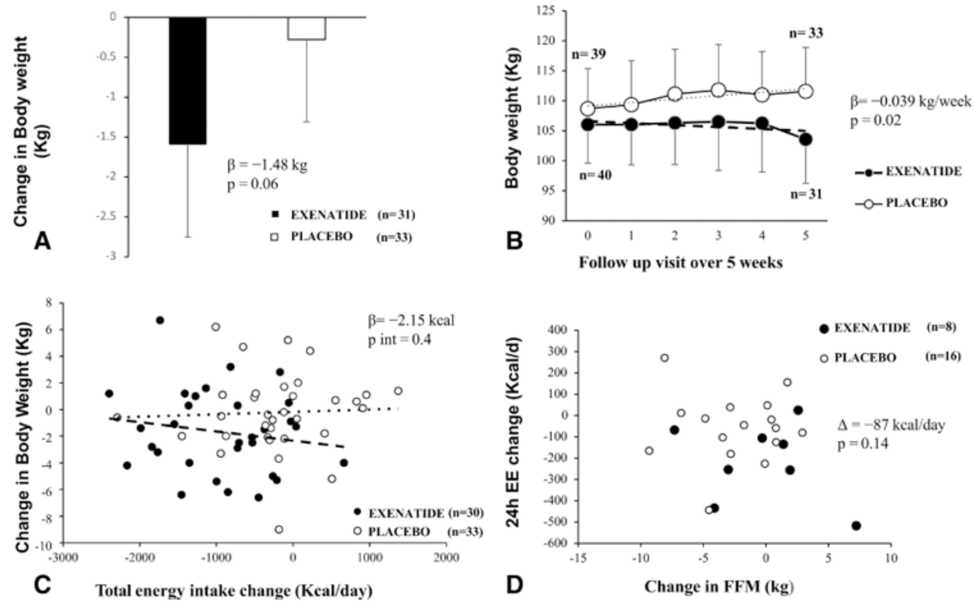

Figure 6.

A. Change in body weight (kg) from baseline over 5 weeks. The baseline weight was the weight at the time of the DXA scan. The β is the absolute difference (Kg), between the body weight at the 5-week follow up visit and the baseline weight. **B. Weight trajectory in the exenatide versus placebo groups over 5 weeks**. Data represents the mean body weight at the time of the DXA scan, at the day of discharge and at each weekly follow up visit. The two fitted regression lines represent the weekly rate of weight change in the 2 groups. The β value represents the difference in the rates of body weight change between the 2 groups. Analyses used mixed models for repeated measures of change from baseline adjusted for baseline weight (as baseline comparator). C. **Correlation between body weight change and total energy intake from baseline over 5 weeks.** Correlation between the pre and post-randomization change in *ad libitum* food intake, expressed as mean Kcal/day versus weight change at 5 weeks.

D. **Correlation between FFM change and 24h EE change from baseline over 24 weeks.** This panel shows the association between 24h-EE, expressed in Kcal/day, in the Exenatide-treated individuals (8) compared to placebo (16) over 24 weeks and change in fat free mass, expressed in Kg. The Δ value indicate the difference in reduction in 24h-EE change between the 2 groups.

- In the panel A, the sample size (Exenatide=31, Placebo= 33) indicate the numbers of volunteers who have the weight measure at 5-week follow up visit. In the panel B, some values were not analyzed due to unavailability of some body weight measurements. In the panel C, the sample size (Exenatide =30, Placebo=33) shows participants having 5-week follow up weight and completed data of food intake. In the panel D, the sample size (Exenatide =8, Placebo=16) shows participants having 24-week follow up body composition measurements and completed data of chambers.

- Error bars represent the mean with 95% confidence interval.

Table 1

Anthropometric and metabolic measures of the study groups at baseline

	Whole study group (n=79)	Exenatide (n =40)	Placebo (n = 39)	p	Men (n=33)	Women (n=46)	p
Ethnicity	10 AA, 21 W, 10 H, 36 NA, 2 O	1 AA, 11 W, 4 H, 22 NA, 2 O	9 AA, 10 W, 6 H, 14 NA, 0 O	**<0.0 5**	4 AA, 9 W, 4 H, 16 NA, 0 O	6 AA, 12 W, 6 H, 20 NA, 2 O	0.8
Sex (F/M)	46/33	23/17	23/16	1.0	33	46	
Age (years)	34.4 ± 8.7	35.1 ± 8.4	33.7 ± 9.0	0.5	38.1 ± 7.7	31.7 ± 8.4	**<0.001**
Body weight (kg)	107.1 ± 19.9	105.5 ± 19.2	108.8 ± 20.7	0.5	112.5 ± 20.7	103.7 ± 19.5	0.06
BMI (Kg/m^2)	38.1 ± 6.7	38.0 ± 6.6	38.2 ± 6.8	0.9	36.5 ± 6.4	39.3 ± 6.7	0.07
FFM (Kg)	36.3 ± 12.8	34.6 ± 11.5	37.9 ± 8.7	0.3	43.6 ± 13.5	31.1 ± 9.4	**<0.001**
FM (Kg)	29.4 ± 8.8	27.9 ± 8.8	30.8 ± 8.7	0.1	26.1 ± 7.5	31.7 ± 9.0	**<0.05**
Body fat (%)	44.2 ± 7.8	44.0 ± 6.9	44.4 ± 8.7	0.8	37.0 ± 5.3	49.4 ± 4.3	**<0.001**
Fasting glucose (mg/dl)	97.8 ± 8.6	96.9 ± 8.5	98.8 ± 8.8	0.3	100.7 ± 8.3	95.8 ± 8.4	**<0.05**
2-h glucose (mg/dl)	137.2 ± 25.6	139.4 ± 25.7	135.1 ± 25.6	0.5	137 ± 25.4	137.4 ± 26.0	0.9
WMEN (Kcal/day)	2874.8 ± 248.7	2874.6 ± 241.3	2875.0 ± 259.1	0.9	3008.1 ± 205.6	2743.2 ± 199.6	**<0.001**
Mean energy intake (kcal/day)	3294.5 ± 1096.3	3495.5 ± 1169.6	3093.5 ± 992.3	0.1	4076.1 ± 942.3	2721.3 ± 814.6	**<0.001**
% WMEN	114.6 ± 35.2	121.6 ± 37.7	107.6 ± 31.5	0.08	135.5 ± 33.2	99.2 ± 28.3	**<0.001**
CHO intake (kcal/day)	1689.7 ± 544.0	1785.5 ± 595.0	1593.8 ± 476.1	0.1	2054.6 ± 504.6	1422.1 ± 399.4	**<0.001**
FAT intake (kcal/day)	1218.1 ± 491.2	1305.3 ± 488.4	1130.9 ± 484.6	0.1	1546.6 ± 440.3	977.3 ± 375.6	**<0.001**
PRO intake (kcal/day)	415.6 ± 150.1	434.2 ± 159.5	396.9 ± 139.6	0.1	511.6 ± 141.6	345.1 ± 113.3	**<0.001**
Soda intake (kcal/day)	434.2 ± 159.5	206.5 ± 191.3	183.3 ± 169.1	0.6	236.08 ± 200.6	164.7 ± 158.2	0.08
24h EE (kcal/day)	2325.9 ± 395.3	2319.3 ± 377.0	2333.8 ± 422.0	0.9	2604.9 ± 318.3	2104.1 ± 299.6	**<0.001**
RQ (ratio)	0.86 ± 0.03	0.86 ± 0.03	0.85 ± 0.03	0.35	0.86 ± 0.04	0.85 ± 0.03	0.5
Carbohydrate oxidation (kcal/day)	1097.0 ± 338.3	1121.1 ± 353.5	1068.4 ± 322.5	0.5	1246.4 ± 343.2	978.3 ± 286.6	**<0.001**
Lipid Oxidation (kcal/day)	823.3 ± 353.1	781.0 ± 330.2	873.5 ± 377.6	0.3	894.4 ± 438.9	766.8 ± 258.7	0.16
SMR (kcal/day)	1810.1 ± 279.7	1818.1 ± 277.5	1800.6 ± 286.5	0.8	1998.6 ± 212.5	1660.3 ± 233.3	**<0.001**
AFT (kcal/day)	648.7 ± 203.2	629.9 ± 176.3	671.0 ± 232.0	0.1	754.5 ± 235.4	564.6 ± 121.8	**<0.001**
SPA (kcal/day)	80.0 ± 45.1	80.4 ± 47.1	79.4 ± 43.4	0.8	96.5 ± 48.5	66.8 ± 38.0	**<0.001**

Data are presented as the mean ± SD, unless otherwise indicated. AA, African American; H, Hispanic; NA, Native American; W, white: O, other

* p values are for differences between exenatide vs. placebo groups, and between males and females in the whole group, as determined by Student's *t*-test or Chi-squared test