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Alterations in energy balance following exenatide administration

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Abstract

Objective—The study aim was to measure change in total energy expenditure (TEE) and body composition during exenatide administration and by deduction the relative contributions of energy expenditure and energy intake to exenatide-induced weight loss.

Research Design and Methods—Forty-five obese (BMI 30–40 kg/m²) subjects were identified. After exclusion criteria application, 28 subjects entered into and 18 subjects completed the study which consisted of 6 visits over 14 weeks. Respiratory gas analysis and doubly-labeled water measurements were performed before initiation of exenatide and near the end of approximately 3 months of exenatide administration.

Results—Eighteen adult obese nondiabetic subjects (12 female, 6 male) completed the study injecting exenatide for an average of 84 ± 5 days. The average weight loss from the beginning of injection period to the end of the study in completed subjects was 2.0 ± 2.8 kg ($P=0.01$). Fat mass declined by 1.3 ± 1.8 kg ($P=0.01$) while the weak trend to decrease in fat-free mass was not significant (0.8 ± 2.2 kg, $P=0.14$). There was no change in weight-adjusted TEE ($P=0.20$), resting metabolic rate ($P=0.51$), or physical activity energy expenditure ($P=0.38$) and no change in the unadjusted thermic effect of a meal ($P=0.37$). The significant weight loss due to exenatide administration was thus the result of decreasing energy intake over the study period

Conclusion—In obese nondiabetic subjects, exenatide administration did not increase TEE and by deduction the significant weight loss and loss of fat mass was due to decreased energy intake.

Keywords

Doubly-labeled water; Energy Expenditure; Exenatide; Weight Loss

The incidence of type 2 diabetes mellitus (DM) and obesity have increased recently both in the United States and globally (1). Exenatide is a glucagon-like peptide-1 (GLP-1) analog used in the treatment of type 2 DM, effective not only in reducing average and postprandial blood glucose values but also inducing weight loss that is progressive and sustained (2–8).

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Although approved only as a hypoglycemic agent, exenatide may be a useful agent in the treatment of the rising numbers of patients with type 2 DM and obesity.

Body weight is maintained by a balance between energy intake and total energy expenditure (TEE). Long-term weight loss that occurs with exenatide administration indicates negative energy balance, but studies of the relative roles of energy intake and energy expenditure in this weight loss, however, have not been performed. Instead, the majority of studies to date examining the mechanisms of exenatide or GLP-1 administration have been short-term. Nearly all of these studies report the anorectic effects of exenatide or GLP-1 (9–11). Possible mechanisms for the observed reduction in energy intake include exenatide-induced nausea, delayed gastric emptying, and increased satiety (9–11). Several studies, however, also report that exenatide increases energy expenditure (10, 12–14). Thus, the relative roles of energy intake and energy expenditure in exenatide associated weight loss are not clear.

Although we hypothesize that the anorectic effects of exenatide are likely the key to the mechanism in exenatide associated weight loss, current methods for the measurement of energy intake are not accurate enough to test that hypothesis. Short of placing subjects in a metabolic ward for periods of several months, energy intake must be assessed using self-reported energy intake from either diaries or food-frequency questionnaires. These self-report instruments, however, are inaccurate, especially in subjects who are overweight or obese and the systematic bias often changes during interventions (15,16).

Although energy intake cannot be measured accurately in outpatient studies, it may be assessed by measuring outpatient energy expenditure and change in body composition and then calculating energy intake using the principle of energy balance (17). TEE is comprised of the resting metabolic rate (RMR), the thermic effect of meals (TEM), and physical activity energy expenditure (PAEE). TEE can be estimated by measuring each of the 3 components using a combination of respiratory gas analysis and physical activity monitors, but a more accurate approach is to use doubly labeled water (DLW). The DLW technique allows accurate measurement of all three components of energy expenditure over a period of 2 weeks in free-living individuals in a single accurate measure (17). Through periodic urine collection, DLW estimates carbon dioxide production by measuring the elimination of the tracers deuterium (^2H) and oxygen-18 (^{18}O) from the body. Carbon dioxide production data can then be used to calculate TEE using standard indirect calorimetry equations. In combination with measurements of RMR and estimates of TEM via indirect calorimetry, it allows measurement of PAEE.

We are unaware of published studies that provide information regarding changes in TEE or energy intake following exenatide administration. The aim of this study was to measure the change in energy expenditure, body mass, and composition during exenatide treatment. More importantly, because energy is conserved, combining the measured TEE with measured change in body composition allows assessment of change in metabolizable energy or caloric intake.

RESEARCH DESIGN AND METHODS

Subjects

Prior to initiation, this study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. All subjects gave written informed consent.

Forty-five participants responding to advertisements passed phone screening using the following inclusion criteria: 18–65 years of age, body mass index (BMI) between 30 and 40 kg/m², women with a negative pregnancy test at baseline, are sterile or using contraceptives,

and absence of weight change greater than 3 kg in the previous 6 months. The exclusion criteria included: pregnant or lactating women, enrollment in a commercial or self-prescribed weight loss or exercise program within the last 6 months, use of weight loss medication, history of metabolic disease that would impact outcome of study, presence of medical conditions that are known to affect energy expenditure (i.e., hyperthyroidism, rheumatoid arthritis, HIV, etc.), history of hypoglycemia, abnormal electrocardiogram, previous history of gastroparesis or gastrointestinal motility disorder, history of organ transplantation, use of a carbonic anhydrase inhibitor, plan to move from study area within the year, presence of impaired fasting glucose or DM, presence of a condition increasing the risk of pancreatitis. After screening, 17 subjects were excluded (12 with evidence of impaired fasting glucose [fasting glucose 100 mg/dL and 126 mg/dL], 2 with evidence of hypertriglyceridemia [250 mg/dL], one due to recent use of weight loss medication, and 2 due to impending plans to move from the study area).

Table 1 shows the baseline characteristics of both completing subjects and drop-outs. There were no statistically significant differences in terms of starting weight, age, or baseline creatinine, fasting glucose, hemoglobin A1c (HgbA1c), or thyroid stimulating hormone (TSH).

Protocol

Subject screenings and assessments were conducted at the Clinical and Translational Research Center of The University of Wisconsin Hospital and Clinics. At the initial screening visit, subjects underwent baseline evaluation including hospital-gowned weight, barefoot height, vital sign measurements, complete history and physical including review of medications, and laboratory testing including serum TSH, fasting glucose, HgbA1c, CBC, pancreatic amylase and lipase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and pregnancy test for women. They underwent an electrocardiogram and completed physical activity and well-being questionnaires to screen out concurrent medical conditions and to later investigate treatment-related malaise.

All follow-up visits included vital signs, weight and height assessments, focused physical examination, and completion of a visual analog nausea scale rating severity of symptoms on a scale of 1 to 10, with 10 being the most severe.

At visit 2 (T-2 wks), subjects fasted overnight, and a baseline urine sample for detection of background ^2H and ^{18}O was obtained followed by administration of the first dose of DLW. Additional urine samples were obtained at 1 (discarded), 3, and 4 hours after the dose of DLW. Using a respiratory gas exchange metabolic cart with ventilated hood (Deltatrac, Datex-Ohmeda, Inc.), RMR was assessed over a period of 40 min. This was followed by ingestion of 2 protein Ensure® Plus shakes (total 700 kcal composed of 26 gm protein, 98 gm carbohydrates, 22 gm fat) and measurement of TEM using the above metabolic cart over the next 4 hours.

The subjects returned approximately 14 days later (T-0 wks). Two urine samples, 1 hour apart, were collected for DLW testing. Subjects started self-injecting exenatide 5 µg twice daily for 14 days. Body composition was then measured using a dual x-ray absorptiometer (DPX-IQ densitometer [GE Healthcare Lunar] DXA and software version 4.6b).

Fourteen days later (T+2 wks), the principal investigator called the subject to assess adverse events. If the subject was tolerating exenatide, he/she began injecting 10 µg twice daily for 10 weeks.

Subjects returned for visit 4 (T+6 wks) 1 month following initiation of exenatide 10 µg twice daily. If tolerating treatment, they continued on exenatide for 1 month longer at which time they returned for visit 5 (T+10 wks). At visit 5, respiratory gas analyses for RMR and TEM were repeated, along with DLW as described for visit 2.

Two weeks later (T+12 wks), the subject returned for a final visit 6. Two urine samples, 1 hour apart, were again obtained. Body composition was reassessed on the same DXA machine.

Calculations

RMR and TEM were calculated using the modified Weir equation ($3.9 \times \text{VO}_2 + 1.1 \times \text{VCO}_2$) (18). For ^{18}O analysis, 1 mL of urine was equilibrated with CO_2 at 25°C for 48 hours. The ^2H and ^{18}O enrichments were then measured by using isotope ratio mass spectrometry. A full description has been reported elsewhere (17). Total body water volume (TBW) was calculated by dilution on the assumption that the oxygen dilution space was $1.007 \times \text{TBW}$, TEE was calculated using the modified Weir equation assuming a respiratory exchange ratio of 0.86, and fat-free mass was calculated as TBW divided by 0.73 (18). Change in body energy stores was calculated as change in fat mass from DXA (kg) $\times$ 9500 (kcal/kg) plus change in fat-free mass from DXA (kg) $\times$ 1200 (kcal/kg).

Statistics

Subject characteristics and other descriptive data are presented as means and standard deviations of the means. Analyses of weight, blood pressure, and body composition changes were performed employing a within-person paired t-test. The within-subject change in TEE was tested using a paired t-test. Because energy expenditure is influenced by body weight, the analyses were repeated using an analysis of covariance (ANCOVA) with weight at the time of the TEE as the covariate. Analyses were done utilizing SPSS version 17.0 (SPSS, Inc., Chicago IL). Changes in RMR and PAEE were analyzed using a paired t-test and weight adjusted ANCOVA. Change in TEM was calculated using only the paired t-test because weight is not known to influence TEM (19).

Sample size was projected based on two end-points: 1) Change in energy expenditure after exenatide administration, and 2) Weight change after exenatide administration. Previously published literature showed an average weight loss of 1.8 kg at 12 weeks of exenatide treatment (20). This was converted to theoretical treatment difference in TEE, assuming the weight lost is adipose tissue (20% fat-free mass and 80% fat mass) with an energy value of 7800 kcal/kg, estimating an average imbalance of $2 \text{ kg} \times 7800 \text{ kcal/kg}$ divided by 84 days or 185 kcal/day. We have demonstrated an average reproducibility of the DLW method of 6% or 240 kcal/day. For a 5% probability of finding this difference with a power of 80%, we determined a need for 14 subjects to complete the study. The same study showed a standard deviation for the 2 kg weight loss of $\pm 3 \text{ kg}$. To detect this weight loss with a 5% probability and 80% power, we estimated the need for 18 subjects to complete the study.

RESULTS

Subjects

Forty-five obese nondiabetic subjects with BMI 30–40 kg/m² (14 men and 31 women) were enrolled (Fig. 1). Of the 28 subjects passing screening, 18 (6 men, 12 women) completed all 6 visits. Of the 10 subjects who did not complete, 5 withdrew due to intolerable nausea and 5 withdrew consent before initiation of the study drug (Fig. 1). There were no statistically significant differences between the completed subjects and drop-outs in terms of baseline

weight or baseline laboratory data (Table 1). On average subjects injected exenatide for an average of 84 ± 5 days.

Weight and Body Composition

The average weight loss from time of initiation of exenatide administration until completion was 2.0 ± 2.8 kg ($P = 0.01$) (Table 2). The average change in BMI was 0.7 ± 1.0 kg/m² ($P = 0.01$). Fat mass declined significantly by 1.3 ± 1.8 kg ($P = 0.01$) and fat-free mass tended to decrease by an insignificant 0.8 ± 2.2 kg ($P = 0.14$). The change in body composition corresponds to a calculated change in body energy stores of 13 ± 28 kcal/day for fat-free mass lost plus 153 ± 205 kcal/day for fat mass lost.

Energy Expenditure

TEE declined by 167 ± 173 kcal/day ($P = 0.001$, 95% CI -249 to -85). Since there was a significant correlation between baseline weight and TEE ($r = 0.63$, $P = 0.01$), TEE was adjusted for weight at the time of the TEE. When adjusted for weight the decline became insignificant ($P = 0.20$). RMR trended down during exenatide administration by an insignificant 28 ± 141 kcal/day ($P = 0.80$) which, when adjusted for weight, remained insignificant ($P = 0.51$). TEM declined by an insignificant 8 ± 31 kcal for a 700 kcal breakfast ($P = 0.37$). The significant decline in unadjusted TEE was mainly due to a decrease in PAEE of 176 ± 67 kcal/day ($P = 0.02$) calculated by difference, which when weight-adjusted, also became insignificant ($P = 0.38$) (Fig. 2).

Side Effects

Of the 28 subjects who passed screening criteria, 11 (39%) experienced nausea at some point during the exenatide treatment. Five subjects withdrew from the study before completion due to moderate to severe nausea (nausea scale 6 – 10). Of the 18 subjects who completed the study, 6 had mild to moderate nausea (nausea scale 1 – 5), but in all the nausea had resolved by the end of the study period. Of these 6 subjects, there was a mean weight loss of 2.9 ± 1.1 kg versus a loss of 0.6 ± 0.8 kg in those without nausea ($P = 0.12$). There were no reported serious adverse events requiring hospitalization.

CONCLUSIONS

In our study, we found that exenatide induced weight loss was due to a reduction in caloric intake. There was no increase in TEE to explain weight loss during exenatide treatment. Indeed, TEE decreased compared to that measured prior to exenatide administration. Only when adjusted for weight was TEE unchanged in our obese nondiabetic subjects. Likewise, there were no significant changes in weight-adjusted RMR, PAEE, or unadjusted TEM with exenatide administration. Thus the decrease in unadjusted energy expenditure appears not to be a direct effect of exenatide, but rather the expected decrease secondary to weight loss (5,6,20–22).

Our subjects lost an average of 2 kg over approximately 12 weeks. This result is similar to other previously published studies showing a weight loss of 1.6, 2.8, and 1.6 kg over 30 weeks (20–22), and 4.2 and 0.8 kg over a period of 16 weeks (5,6). In body composition analyses, the weight loss was attributable to a significant loss of fat mass without a significant decrease in fat-free mass.

Regarding energy expenditure, there are limited studies to this point. Shalev *et al.* (12) reported that GLP-1 infusion increased RMR. Flint and colleagues (10,13) reported that GLP-1 infusion increased RMR and resulted in decreased TEM in both non-obese and obese patients. Pannaciuoli *et al.* (14) similarly found that GLP-1 increased short term RMR. It is

unclear why these results diverge from our results, but it may relate to the length of treatment time. Most of the previous studies (12,13) involved measurements following the first administration of GLP-1, whereas our measures were made after 12 weeks of treatment. Moreover, we did not use GLP-1, but rather its analog exenatide.

To our knowledge, there are no published studies measuring TEE, RMR, and TEM following exenatide administration. TEE can be evaluated either through use of a metabolic chamber or through use of DLW, which has the advantage over respiratory gas exchange indirect calorimetry in that it allows precise measurements of TEE over a period of 2 weeks in free-living individuals. In combination with measuring RMR, it allows calculation of PAEE. Through periodic urine collection, DLW estimates TEE by measuring the elimination of the stable isotopes ^2H and ^{18}O from the body. Carbon dioxide production rates can then be used to calculate TEE using standard indirect calorimetry equations. The DLW method has been carefully validated against measured energy expenditure in a metabolic chamber and shown to be accurate within 1–2% and have a coefficient of variation of 4–7% (17).

By measuring TEE and body composition and applying the energy balance equation to calculate energy intake, we were able to test their relative contributions to energy imbalance resulting in weight loss. We did not find an increase in weight-adjusted TEE that would explain the weight loss. Based on the change in body composition and assuming a linear change over time, the weight loss corresponded to an average negative energy balance of 166 kcal/d. At the same time, the average unadjusted TEE decreased by 167 kcal/d compared to baseline. If we assume that TEE decreased linearly with time of treatment, then the average decrease was 88 kcal/d. Taking both of these values and using the energy balance equation (energy intake = TEE + change in body energy store), then metabolizable caloric intake is estimated to have decreased by 255 kcal/d during exenatide treatment. This is consistent with prior single meal studies revealing attenuation of oral intake with both GLP-1 and its analog exenatide (9). Possible mechanisms to explain this observed decrease in oral intake include exenatide-induced nausea, decreased gastric emptying rate, and increased satiety, although prior studies have not shown a consistent correlation between the presence or degree of nausea and lowering of body weight (6).

Studies have examined the role of exenatide or GLP-1 in attenuation of oral intake. Edwards *et al.* (11) found that healthy volunteers consumed 19% fewer calories at a free choice buffet lunch following infusion of exendin-4. A meta-analysis of 7 studies on *ad libitum* energy intake following intravenous GLP-1 infusion showed energy intake reduced by 174 kcal or 11.7% (9). This finding in human subjects, however, was challenged by the observation that GLP-1 receptor deficient mice have normal intake and body weight (23). The anorectic effects of GLP-1 are not well understood, with regulation of feeding and energy balance involving both hormonal and neural input.

It is evident that the current body of literature lacks sufficient information to explain the role of GLP-1 agonists and energy metabolism. Our study, however, points to weight loss being due to decreased energy intake and not increased energy expenditure.

Our study was limited by the number of subjects who did not complete the study as a result of nausea. However, baseline characteristics were similar between those who completed and those who dropped out of the study. Of the subjects who passed screening, 39% reported nausea as a side effect, and 18% were unable to complete the study. This may indeed limit exenatide's utility as a weight loss medication in nondiabetics. Subanalysis of the completed subjects revealed that of the 6 subjects experiencing nausea during the study, there was a higher mean weight loss than in those without nausea, although the difference did not reach

statistical significance. This invites the possibility that, contrary to prior studies, the presence of nausea may have an important association with the degree of weight loss. It should be noted, however, that the nausea was short-lived and mild in all subjects that completed the study.

The lack of dietary records in this study may be seen as a limitation regarding the conclusion that metabolizable energy intake was reduced; however, the energy balance equation is based on the law of conservation of energy. Moreover, there are no accurate methods for measuring dietary intake in an outpatient setting. It has been demonstrated that self-reported dietary energy intake is inaccurate, that the degree of inaccuracy increases with obesity, and that degree of inaccuracy changes during interventions (16). In summary, the lack of dietary records does not limit our determination that the weight loss was a result of decreased caloric intake.

In conclusion, in obese nondiabetic subjects, exenatide administration resulted in decreased oral intake with no significant changes in weight-adjusted TEE, RMR, PAEE, or unadjusted TEM. The weight loss associated with exenatide thus appears to result solely from attenuation of oral intake and not a change in energy expenditure.

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Figure 1.
Diagram illustrating patient screening and retention.

Figure 2.
The unadjusted energy expenditure in completed subjects (* = $P < 0.05$).

Table 1

Baseline demographics and clinical characteristics of drop outs and completed subjects.

	Drop Outs (n = 10)	Completed Subjects (n = 18)	P value
Baseline Characteristics			
Sex (m/f), (n)	2/8	6/12	
Age (yr)	44 +/- 9	39 +/- 11	0.25
Weight (kg)	91.5 +/- 10.0	101.7 +/- 12.3	0.07
Baseline Biochemical Data			
Fasting Glucose (mg/dL)	91.0 +/- 6.9	90.3 +/- 7.7	0.90
Creatinine (μ mol/L)	0.8 +/- 0.1	0.9 +/- 0.2	0.12
Thyroid Stimulating Hormone (mIU/L)	1.5 +/- 0.5	1.7 +/- .0.7	0.30
Hemoglobin A1c (%)	5.4 +/- 0.2	5.6 +/- 0.2	0.48
Amylase (U/L)	44.8 +/- 11.5	40.6 +/- 15.2	0.46
Lipase (U/L)	178.5 +/- 44.2	164.8 +/- 42.0	0.42
Triglycerides (mg/dL)	121.4 +/- 65.7	115.3 +/- 41.0	0.76

All units are mean $\pm$ standard deviation of the mean.

All analyses were performed employing a paired t-test.

Table 2

Changes in weight, blood pressure and body composition in the completed subjects (n = 18).

	Pre-Exenatide	Post-Exenatide	Change Pre- and Post-Exenatide	Within person <i>P</i> value
Weight (kg)	102.3 +/- 12.4	100.3 +/- 12.4	-2.0 +/- 2.8	0.01
BMI (kg/m ²)	34.7 +/- 3.1	34.0 +/- 3.2	-0.7 +/- 1.0	0.01
Systolic BP (mmHg)	125 +/- 12	122 +/- 13	-2.4 +/- 8.1	0.23
Diastolic BP (mmHg)	74 +/- 10	74 +/- 8	-0.2 +/- 9.0	0.94
Fat mass (kg)	43.4 ± 7.3	42.3 ± 12.2	-1.3 ± 1.8	0.01
Fat-free mass (kg)	58.9 ± 12.2	56.9 ± 11.0	-0.8 ± 2.2	0.14

BMI=body mass index

BP=blood pressure

All values are mean ± standard deviation of the mean.

Analyses of weight change, change in blood pressure, and change in body composition were performed employing a within-person paired t-test.