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Human Plasma Ghrelin Levels Increase during a One-Year Exercise Program

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Weight loss resulting from decreased caloric intake raises levels of the orexigenic hormone, ghrelin. Because ingested nutrients suppress ghrelin, increased ghrelin levels in hypophagic weight loss may result from decreased inhibitory input by ingested food, rather than from lost weight. We assessed whether ghrelin levels increase in response to exercise-induced weight loss without decreased caloric intake. We randomized 173 sedentary, overweight, postmenopausal women to an aerobic exercise intervention or stretching control group. At baseline, 3 months, and 12 months, we measured body weight and composition, food intake, cardiopulmonary fitness (maximal oxygen consumption), leptin, insulin, and ghrelin. Complete data were available for 168 women (97%) at 12 months. Exercisers lost 1.4 ± 0.4 kg ($P < 0.05$ compared with baseline; $P = 0.01$ compared with stretchers) and manifested a significant, progressive increase in ghrelin levels, whereas neither measure changed among stretchers. Ghrelin increased 18% in exercisers who lost more than 3 kg ($P < 0.001$). There was no change in caloric intake in either group and no effect on ghrelin of exercise *per se* independent of its impact on body weight. In summary, ghrelin levels increase with weight loss achieved without reduced food intake, consistent with a role for ghrelin in the adaptive response constraining weight loss and, thus, in long-term body weight regulation. (*J Clin Endocrinol Metab* 90: 820–825, 2005)

GHRELIN IS AN orexigenic (appetite-stimulating) peptide hormone secreted into the circulation primarily by the stomach and small intestine (1–4). Although it is an endogenous ligand for the GH secretagogue receptor, ghrelin is implicated in the regulation of food intake and body weight through GH-independent mechanisms (5). Ghrelin is the only known circulating orexigen and one of only a few substances of any kind shown to increase appetite and food intake when injected into humans (6). Preprandial increases and postprandial suppression of circulating ghrelin levels associated with every meal have been demonstrated in multiple species, including humans (7–10). These and other observations are consistent with a role for ghrelin in premeal hunger and meal initiation. Unlike most other gut-derived, meal-patterning peptides, however, ghrelin is also implicated in long-term body weight regulation. Continuous or repeated ghrelin administration in animals durably increases food intake and decreases energy expenditure, leading to weight gain (2, 3, 11, 12). Acute blockade of endogenous ghrelin signaling by several methods has been reported to decrease food intake and body weight (3, 13–16). Mutations in the human pre-pro-ghrelin gene are reported to be associated with protection against fat accumulation and related metabolic sequelae (17). These findings suggest that ghrelin could participate in a negative feedback loop regulating body weight. This hypothesis predicts that weight loss should trigger an increase in circulating ghrelin levels as part of the known adaptive response to energy deficit. Indeed, plasma ghrelin levels have been shown to increase in response to weight loss resulting from hypocaloric diets, cancer cachexia, anorexia nervosa, and chronic failure of the heart, kidneys, or liver (18–28).

All of the examples of negative energy balance previously reported to be associated with increased ghrelin levels are characterized by low food intake. Because ingested nutrients suppress ghrelin, elevated levels in these conditions could, theoretically, result from hypophagia, rather than from weight loss *per se*. The hypothesized role of ghrelin in the adaptive response to weight loss would be better supported if ghrelin levels were found to increase in the setting of weight loss that is not associated with decreased food intake, such as that resulting from chronic aerobic exercise. The goal of this study was to assess the effect on circulating ghrelin levels of weight loss achieved by chronic exercise in the absence of a reduction in food intake.

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; VO_2max, maximal oxygen consumption.

Subjects and Methods

This study was a randomized, controlled, intervention trial comparing the effect of a 12-month, moderate intensity aerobic exercise intervention *vs.* a stretching control program on body weight, measures of

adiposity, and circulating hormone levels in postmenopausal women. These parameters were measured at baseline (prerandomization) and 3 and 12 months after randomization. Details of the aims, experimental design, and measurement protocols of the Physical Activity for Total Health Trial have been reported previously (29). All study procedures, including written informed consent, were reviewed and approved by the Fred Hutchinson Cancer Research Center institutional review board.

Participants

Participants were postmenopausal women, aged 50–75 yr, who were sedentary at baseline, as defined by less than 60 min/wk of moderate or vigorous intensity physical activity and a maximal oxygen consumption (VO_2max) of less than 25.0 ml/kg·min. They were required to have a body mass index (BMI) of more than 25.0 kg/m^2 (or a BMI between 24.0–25.0 kg/m^2 if percent body fat measured by bioelectrical impedance was >33.0%). Major exclusion criteria included tobacco use, a clinical diagnosis of diabetes or a fasting blood glucose level of 140 mg/dl or more, a history of any cachectic state such as malignancy (except nonmelanoma skin cancer) within 10 yr, or liver or kidney disease. Details of the recruitment procedures have been reported previously (30). We obtained written informed consent from participants before enrollment. Eligible women were then randomly assigned to an exercise intervention (exercisers, n = 87) or a control group (stretchers, n = 86), stratified by BMI (<27.5 *vs.* ≥27.5 kg/m^2) to ensure a balance of heavier and lighter women in both study arms.

Exercise intervention

A minimum of 45 min of moderate intensity aerobic exercise, 5 d/wk for 12 months, was required of the participants assigned to the exercise intervention. Exercisers were required to attend three supervised sessions per week at one of the training facilities during months 1–3 and to exercise on 2 additional days per week at home. For the remainder of the study, exercisers were required to attend at least one session per week at the training facility and to exercise on their own for a total of 5 d/wk, either at home or at the facility. The training program started at 40% of the maximal heart rate for 16 min/session and gradually increased to 60–75% of the maximal heart rate for 45 min/session by wk 8, where it was maintained for the duration of the study. Treadmill walking and stationary bicycling were the primary facility activities. Walking, bicycling, and aerobics were encouraged for exercise at home. Several techniques for promoting adherence to the exercise program were used and were described previously (31). Exercisers kept daily activity logs of all sports or recreational activities they performed, which were reviewed weekly by exercise trainers. Adherence to the exercise regimen was assessed using these activity logs as well as measurements of change in cardiopulmonary fitness (VO_2max). Women randomized to the control group attended once weekly, 45-min stretching sessions for the year and were asked not to change other exercise habits during the study. Exercisers and stretchers were strictly instructed to maintain their usual diet.

Baseline and follow-up measures

Medical histories, demographic information, and a food frequency questionnaire were obtained at baseline and at the 3- and 12-month visits. We measured VO_2max at baseline and 12 months using a standard protocol (32). Baseline, 3-month, and 12-month weight and height (to the nearest 0.1 kg and 0.1 cm, respectively) were obtained using a balance beam scale and stadiometer. Waist and hip circumferences were measured to the nearest 0.1 cm using an anthropometric fiberglass tape measure. All measurements were made in duplicate and averaged. We quantified total body fat and lean mass using a dual energy x-ray absorptiometry whole body scanner (QDR 1500, Hologic, Inc., Waltham, MA). We measured intraabdominal and sc fat at baseline and 12 months by computed tomography, using a single 8-mm scan at the lumbar disc 4–5 interspace (model CT 9800 scanner, General Electric, Waukesha, WI) as previously described (31). All measurements were made by technicians blinded to the participant's randomization assignment.

We collected morning blood samples before breakfast after a 12-h, overnight fast at the baseline, 3-month, and 12-month visits. We have previously shown that a single morning fasting sample correlates very well with 24-h profiles for plasma ghrelin (7). Blood was processed within 1 h of collection, and plasma was aliquoted and stored at −70 C. Storage time for plasma samples ranged from 3 months to 3 yr, an interval that in our experience does not affect measurements of total ghrelin levels. The total plasma immunoreactive ghrelin concentration was measured in duplicate with samples that had never been previously thawed, using our modification of a commercial RIA that employs a polyclonal antibody raised against full-length acylated human ghrelin and ^{125}I-labeled ghrelin as a tracer (Phoenix Pharmaceuticals, Belmont, CA). This assay detects both acylated and des-acyl ghrelin. Although only acylated ghrelin is bioactive, levels of total ghrelin appear to be a reasonable surrogate for those of the acylated form because the ratio of these measures remains constant under a wide variety of conditions that affect ghrelin (14, 33, 34). In our study the lower and upper limits of detection for this assay were 80 and 2500 pg/ml, respectively. All assays included 12 plasma control samples from common stocks obtained before the study. In addition, we created a serum pool from women ineligible for the study, and two specimens of this pooled sample were run in each assay. Based on these controls, the intraassay coefficient of variation (CV) was 3.5%, and the interassay CV was 4.9%. Plasma insulin levels were measured using a 48-h, polyethylene glycol-accelerated, double-antibody RIA, with lower and upper detection limits of 2.2 and 280 μU/ml, respectively. The intraassay CV was 6.5%, and the interassay CV was 9.3%. Plasma leptin was measured using a commercial RIA, with lower and upper detection limits of 0.5 and 100 ng/ml, respectively (Linco Research, Inc., St. Charles, MO). The intraassay CV was 8.7%, and the interassay CV was 11.2%. In each of the hormone assays all samples from a participant were run in the same batch. Samples were placed into batches such that within each batch, the numbers of exercise and control participants were approximately equal, the randomization dates of participants were similar, and the sample order was random.

Statistical analyses

As an exploratory analysis, preceding the primary analysis of the exercise intervention, associations between baseline ghrelin levels and baseline measures of weight, body composition, energy intake, fitness, leptin, and insulin were assessed using Pearson correlation coefficients. In addition, associations between the mean change in ghrelin and the mean change in the above measures from baseline to 12 months were examined by linear regression among exercisers only.

The primary analysis assessed the effect of the exercise intervention on circulating ghrelin levels, based on the assigned treatment at the time of randomization, regardless of adherence or compliance status (intent to treat). We used linear models (35) to compute the group-specific mean changes in plasma ghrelin from baseline to 3 and 12 months postrandomization. We conducted a similar analysis for changes in body weight, adjusting for the *a-priori*-specified covariates, age and energy intake. Due to the longitudinal and highly correlated nature of the data, we used generalized estimating equations with an unstructured working correlation matrix (36, 37).

In a secondary analysis we assessed the effect of the exercise intervention on ghrelin levels, grouping by intervention type (exercisers and stretchers) and change in weight over the year (no weight loss, mild weight loss of ≤3.0 kg, or moderate weight loss of >3 kg), using similar regression methods. All analyses were unadjusted, except where otherwise indicated in the text, because adjustment for age and caloric intake did not substantially alter the results. All statistical tests were two-sided. Statistical analyses were performed using StataCorp software (version 8, STATA, College Station, TX).

Results

Complete data for all 173 participants were available at baseline and 3 months, including body weight, BMI, waist circumference, and hormonal data. Three women withdrew from the study after 3 months, and two declined 12-month body composition measures (four exercisers and one stretcher); hence, data for 168 (97%) of the participants were available at 12 months. Complete dual energy x-ray absorptiometry and computed tomography data were available for 167 women at baseline and for 160 women at 12 months.

Baseline demographic data, body composition measures, total energy intake, fitness level, and hormone concentrations were not different in the exercisers and stretchers (Table 1). Participants had a mean age of 61 yr; 86% were non-Hispanic white, 4% were African-American, and 6% were Asian-American. By design, participants were overweight or obese (mean BMI, 30.5 kg/m^2; mean percent body fat, 47.4). The mean reported total caloric intake was 1635 ± 792 kcal/d in exercisers and 1722 ± 672 kcal/d in stretchers ($P = 0.62$). The mean baseline VO_2max was equally low in both groups, reflecting the expected low level of fitness among these sedentary study participants.

At baseline, the distribution of ghrelin levels was approximately bell-shaped, with a median of 560 pg/ml and a 25th to 75th percentile range of 333–806 pg/ml. Before the initiation of exercise intervention, ghrelin levels in all study participants correlated negatively with all measurements of body size and adiposity, with Pearson correlation coefficients ranging from −0.24 to −0.37 ($P = 0.001$ through $P < 0.0001$; Table 2). There was no correlation at baseline between ghrelin levels and age, total energy intake, fitness level, or leptin or insulin levels.

The exercisers progressively lost weight, decreasing an average of 1.4 kg from baseline by 12 months ($P < 0.05$), whereas there was no change in the stretchers ($P = 0.01$ for exercisers *vs.* stretchers; Table 3). Exercise-induced weight loss was associated with a progressive increase in plasma ghrelin levels over baseline, achieving statistical significance at 12 months (+32 ± 16 pg/ml; $P < 0.05$). There was no significant change in plasma ghrelin among the stretchers. Time of day and duration of fasting can affect ghrelin levels, and blood drawn later in the morning might theoretically show higher values because of a longer fast and a greater progression of the prebreakfast ghrelin surge. To determine whether variability in the timing of phlebotomy could have confounded our results, we analyzed the exact time of all blood draws. There were no differences in the timing of blood drawn at 3 or 12 months compared with the baseline phlebotomy time, nor was there any difference in the phlebotomy time of exercisers *vs.* stretchers. Neither group changed their total energy intake during the course of the intervention, as determined by food frequency questionnaires (for exercisers, daily caloric intake was 1635 ± 792 kcal/d at baseline and 1620 ± 679 kcal/d at 12 months; for stretchers, intake was 1722 ± 672 kcal/d at baseline and 1608 ± 669 kcal/d at 12 months; all $P > 0.5$). Furthermore, there was no association between changes in fitness level (as judged by VO_2max) resulting from the exercise intervention and changes in the plasma ghrelin level (see Table 5).

Because increased physical fitness *per se* did not appear to have an independent effect on plasma ghrelin levels, we next analyzed the relationship between the magnitude of change in ghrelin and the change in weight from baseline to 12 months in both exercisers and stretchers. We divided participants into those with no change in weight or else weight gain (no weight loss), mild weight loss (0.5–3 kg), or moderate weight loss (>3 kg). Ghrelin levels increased commensurately with the amount of weight lost (Table 4). Among exercisers, plasma ghrelin levels did not significantly change in the group without weight loss (+0.4%; $P = 0.91$) or in the group that lost only 0.5–3 kg (+7.0%; $P = 0.19$). Ghrelin levels significantly increased by 17.7% in those with more than 3 kg of weight loss ($P < 0.001$ compared with baseline; $P < 0.01$ compared with exercisers without weight loss at 12 months). Although stretchers experienced far less weight loss overall, a small number of women lost weight by mechanisms outside of the protocol, presumably by increasing physical activity and/or decreasing food intake. We undertook the same analyses in the stretchers and the exercisers, dividing them into the same categories of weight loss. No significant changes in ghrelin levels were found in any of these categories of stretchers, although there were few stretchers in the mild (n = 14) and moderate (n = 10) weight loss groups [−0.2% ($P = 0.93$) for the no weight loss group; +7.5% ($P = 0.07$) for the mild weight loss group; +10.7% ($P = 0.37$) for the moderate weight loss group]. Adjusting these analyses

TABLE 1. Baseline characteristics of randomized participants in the Physical Activity for Total Health Study

	Exercisers	Stretchers
n	87	86
Age (yr)	60.7 ± 6.7	60.6 ± 6.8
Ethnicity (% non-Hispanic white)	86	87
Weight (kg)	81.4 ± 14.1	81.7 ± 12.1
BMI (kg/m^2)	30.4 ± 4.1	30.5 ± 3.7
Waist circumference (cm)	92.9 ± 11.3	93.4 ± 10.4
Total body fat (kg)[a]	38.4 ± 9.6	38.4 ± 8.4
Lean body mass (kg)[a]	39.6 ± 5.6	39.9 ± 4.9
Intraabdominal fat (cm^2)[b]	145.9 ± 60.4	147.3 ± 56.2
Subcutaneous fat (cm^2)[b]	385.3 ± 124.4	364.1 ± 107.2
Total energy intake (kcal/d)	1635 ± 792	1722 ± 672
Maximal oxygen consumption (ml/kg·min)	20.0 ± 3.5	20.4 ± 3.0
Leptin (ng/ml)[c]	28.4 ± 7.9	27.6 ± 8.9
Insulin (μU/ml)[d]	19.3 ± 8.5	20.9 ± 11.5
Ghrelin (pg/ml)[e]	599 ± 355	629 ± 331

None of the parameters above differed significantly between exercisers and stretchers. Values are the mean ± SD.

[a] Determined by dual energy x-ray absorptiometry.

[b] Determined by computed tomography.

[c] To convert values for leptin to nanomoles per milliliter, multiply by 0.08.

[d] To convert values for insulin to picomoles per liter, multiply by 6.

[e] To convert values for ghrelin to picomoles per liter, multiply by 0.296.

TABLE 2. Baseline Pearson correlation coefficients of ghrelin levels with age and measurements of body composition, energy intake, maximal oxygen consumption, leptin, and insulin in all study participants

	Correlation	*P* value
Age	−0.11	0.15
Weight (kg)	−0.29	<0.0001
BMI (kg/m^2)	−0.29	<0.0001
Waist circumference (cm)	−0.37	<0.0001
Total body fat (kg)[a]	−0.26	0.0004
Lean body mass (kg)[a]	−0.24	0.001
Intraabdominal fat (cm^2)[b]	−0.34	<0.0001
Subcutaneous fat (cm^2)[b]	−0.30	<0.0001
Total energy intake (kcal/d)	0.01	0.94
VO_2max (ml/kg·min)	−0.02	0.72
Leptin (ng/ml)	−0.14	0.08
Insulin (μU/ml)	0.07	0.33

[a] Determined by dual energy x-ray absorptiometry.

[b] Determined by computed tomography.

TABLE 3. Mean (±SE) change in body weight and change in plasma ghrelin levels in exercisers and stretchers at baseline, 3 months, and 12 months

	Exercisers			Stretchers		
	Baseline	3-Month change	12-Month change	Baseline	3-Month change	12-Month change
n	87	87	83	86	86	85
Weight (kg)[a]	81.7 ± 1.4	−0.5 ± 0.3[b]	−1.4 ± 0.4[b,c]	81.6 ± 1.4	0.0 ± 0.3	0.1 ± 0.4
Ghrelin (pg/ml)[d]	599 ± 38	24 ± 14[e]	32 ± 16[b]	629 ± 36	−4 ± 16	14 ± 15

[a] Adjusted for age and change in total caloric intake between baseline and 3 or 12 months.
[b] $P < 0.05$, significantly different from respective baseline.
[c] $P < 0.05$, significantly different from stretchers.
[d] To convert values for ghrelin to picomoles per liter, multiply by 0.296. The estimated working correlation of the generalized estimating equations ghrelin analysis was 0.94 between baseline and 3-month changes, 0.93 between baseline and 12-month changes, and 0.93 between 3-month and 12-month changes.
[e] $P < 0.10$, compared with respective baseline.

for age and caloric intake did not significantly change the results.

The exercise intervention caused significant changes not only in body weight, but also in other measures of body composition and levels of hormones that are influenced by body composition (31). As a preliminary effort to identify parameters that were associated with the increase in ghrelin levels caused by exercise-induced weight loss, we performed bivariate regression analysis among exercisers for the change in plasma ghrelin levels *vs.* the change in measures of body weight, body composition, energy intake, fitness level, leptin, and insulin (Table 5). The magnitude of increase in plasma ghrelin that occurred with exercise correlated significantly with the magnitude of decreases in body weight, BMI, waist circumference, and total fat mass. The magnitude of change in plasma ghrelin levels did not correlate significantly with the changes in lean body mass, intraabdominal fat, sc fat, energy intake, VO_2max, leptin, or insulin.

There is correlative evidence suggesting that a relationship may exist between circulating ghrelin levels and age (38–40). Although we did not see any relationship between baseline age and plasma ghrelin level in this study (Table 2), we hypothesized that advancing age might modify the response of circulating ghrelin to weight loss, because adaptive physiological responses to weight loss are blunted in the elderly. To explore this possibility, we performed age-stratified regression analyses between change in ghrelin level and change in weight among exercisers and all participants; however, we found no significant effect of age on this relationship (data not shown).

Discussion

In this prospective, randomized study of long-term, moderate intensity aerobic exercise, we show that circulating ghrelin levels increase in the context of weight loss associated with a 1-yr exercise intervention. Although the average weight loss and ghrelin increase in the exercisers as a whole were relatively small, participants who experienced more weight loss had progressively greater increases in their plasma ghrelin levels. Previously reported elevations of ghrelin levels in human models of negative energy balance occurred in the setting of decreased food intake (see introduction). Because ingestion of nutrients suppresses plasma ghrelin, the elevated ghrelin levels in these models could theoretically be explained by decreased caloric intake rather than by decreased body weight.

Weight loss in our study occurred without a detectable change in total caloric intake at any time throughout the study in either group, as assessed by food frequency questionnaires. Exercisers and stretchers were specifically instructed not to alter their normal eating habits. Nevertheless, it is possible that some participants changed their dietary intake despite our monitoring of them during the intervention period and our efforts to prevent this. As this study was a randomized, controlled trial, however, any observed differences in the intervention group (exercisers) should have resulted from the exercise intervention. Although we recognize that food frequency questionnaires are imprecise and typically underestimate food intake compared with more precise measurements of energy expenditure (41–45), we do not suspect differential measurement errors between these previously sedentary exercisers and stretchers or between their assessments at baseline and those during the intervention (46–48). Although underreporting of food intake has been demonstrated among young, elite female athletes (43, 45), studies comparing athletes and nonathletes have shown similar degrees of underreporting in both groups (42, 44). Postmenopausal women have also been shown to underre-

TABLE 4. Plasma ghrelin levels at baseline and change in ghrelin levels (mean ± SE, pg/ml) at 12 months in exercisers and stretchers stratified by amount of weight loss

Weight loss	Exercisers			Stretchers		
	n	Baseline ghrelin	Change in ghrelin	n	Baseline ghrelin	Change in ghrelin
No weight loss (<0.5 kg)	41	616 ± 63	3 ± 23	61	620 ± 45	−1 ± 15
Mild weight loss (0.5–3.0 kg)	22	589 ± 56	41 ± 31	14	692 ± 71	52 ± 28[a]
Moderate weight loss (>3.0 kg)	20	560 ± 72	99 ± 30[b,c]	10	582 ± 78	62 ± 69

To convert values for ghrelin to picomoles per liter, multiply by 0.296. Values shown are the mean ± SE, expressed as picograms per milliliter.
[a] $P < 0.10$ from respective baseline and from no weight loss reference group.
[b] $P < 0.001$, significantly different from respective baseline.
[c] $P < 0.01$, significantly different from no weight loss reference group.

TABLE 5. Bivariate regression analysis for change in ghrelin *vs.* change in measurements of body composition, energy intake, maximal oxygen consumption, leptin, and insulin in exercisers from baseline to 12 months

	Regression coefficient	*P* value
Weight (kg)	−11.9	0.004
BMI (kg/m^2)	−32.7	0.003
Waist circumference (cm)	−9.59	0.044
Total body fat (kg)[a]	−14.7	0.0007
Lean body mass (kg)[a]	−27.8	0.06
Intraabdominal fat (cm^2)[b]	−0.43	0.44
Subcutaneous fat (cm^2)[b]	−0.47	0.09
Total energy intake (kcal/d)	−0.02	0.43
VO_2max (ml/kg·min)	5.42	0.37
Leptin (ng/ml)	−5.32	0.10
Insulin (μU/ml)	1.13	0.36

[a] Determined by dual energy x-ray absorptiometry.
[b] Determined by computed tomography.

port food intake; however, those with greater activity levels do not exhibit a greater degree of underreporting (49). Additionally, a strong predictor of underreporting food intake is previous underreporting, suggesting that individuals remain consistent over time in this regard (50).

Our findings suggest that ghrelin can respond in a compensatory manner to loss of body weight, not simply hypophagia. Ravussin *et al.* (51) previously reported that exercise-induced weight loss was not associated with an increase in ghrelin levels among 13 subjects (change from baseline, +58 ± 34 fmol/liter; $P = 0.17$). In that study, participants were subjected to an exercise-induced energy deficit of 53,000 kcal over a 93-d period while food intake was held constant and monitored, resulting in an average weight loss of 5.0 kg. Although the experimental design of this study was excellent, it may not have had the power to detect a significant change in ghrelin, given the small number of subjects and the large variability in ghrelin levels. Complementing several prior reports showing no effect of acute exercise on circulating ghrelin levels (52–55), we also did not find an association of increased physical fitness with plasma ghrelin levels. Taken together, our data indicate that ghrelin increases in response to modest weight loss resulting from an exercise intervention occurring without an average reduction in food intake and without an independent effect of exercise itself. These observations support a role for ghrelin in the adaptive responses that constrain weight loss and therefore in the regulation of body weight. This key attribute distinguishes ghrelin from other gut-derived, meal-patterning hormones.

The mechanisms by which weight loss leads to an increase in circulating ghrelin levels are not understood. It is unclear which components of body composition are detected by systems that regulate ghrelin and what factors communicate changes in these components to ghrelin-producing cells located primarily in the gut. In our study, baseline ghrelin levels correlated negatively with body weight, BMI, waist circumference, total fat mass, lean body mass, intraabdominal fat, and sc fat. We and others have previously reported similar associations in human studies (18, 22–24, 56–58). We found analogous associations between changes in ghrelin levels and changes in various measures of body composition in response to exercise. These measures of body composition covary with one another, and it is not possible from our data to determine which component(s) of body composition influences ghrelin levels. We and other researchers have reported negative correlations between levels of ghrelin and either leptin or insulin (38, 40, 59, 60). We found no association with leptin or insulin, either dynamically or at baseline, possibly due to the small range of BMI in this study.

In summary, we show for the first time that ghrelin levels increase commensurately with loss of body weight achieved without reduced food intake. This observation is consistent with a model in which ghrelin participates in the adaptive response to weight loss (whether brought about by reducing caloric intake or increasing energy expenditure), acting in a negative feedback loop that regulates body weight. Critical loss of function experiments with selective ghrelin receptor antagonists are required to determine whether ghrelin plays a major or only a minor role in energy homeostasis, and therefore, whether it represents a useful target for antiobesity therapy.

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