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FREQUENT INTENTIONAL WEIGHT LOSS IS ASSOCIATED WITH HIGHER GHRELIN AND LOWER GLUCOSE AND ANDROGEN LEVELS IN POSTMENOPAUSAL WOMEN

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Abstract

Population-based studies suggest that repetitive cycling of weight loss and regain may be associated with future weight gain. Therefore, to better define the relationship between weight cycling, energy homeostasis, and future weight gain, we examined associations between frequent intentional weight loss and hormonal profiles in postmenopausal women. This cross-sectional study evaluated the relationship between a history of frequent weight loss and biomarkers, including serum glucose, insulin, leptin, and ghrelin, as well as sex steroid hormones. We hypothesized that frequent intentional weight loss would be associated with changes in normal appetite and body-weight-regulatory hormones, favoring increased appetite and weight gain. 159 healthy, weight stable, sedentary, overweight, postmenopausal women who had been recruited for an exercise intervention participated in this study. History of intentional weight loss (frequency and magnitude) was assessed by questionnaire. Hormonal assays were performed by radioimmunoassay (insulin, leptin, ghrelin, estrogens, androgens, and DHEA), chemiluminescence immunoassay (IGF-1), and immunometric assay (SHBG). ANOVA and regression analyses were used to investigate the relationship between weight-loss history and metabolic hormones. A higher degree of weight cycling, characterized by the frequency of intentionally losing > 10 pounds, was associated with an appetite-stimulating hormonal profile, including higher concentrations of ghrelin (p-trend=0.04), lower glucose (p-trend=0.047), and, to some extent, lower insulin (p-trend=0.08). Frequent weight loss was also associated with lower androgen concentrations, including androstenedione (p-trend=0.02), testosterone (p-trend=0.04), and free testosterone (p-trend=0.01). No independent associations between the concentrations of leptin or estrogens and weight cycling were observed. This study suggests that frequent intentional weight loss may affect hormones involved in energy regulation.

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COMPETING INTERESTS
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Keywords

weight cycling; dieting; ghrelin; leptin; energy balance; women

1. Introduction

Although the population prevalence of obesity is increasing, the desire to be thin is pervasive [1,2]. Dieting for weight loss is widespread and national surveys find up to 50% of women in Western countries are currently or have recently attempted to lose weight [3–5]. Individuals who attempt to lose weight rarely succeed in the long term [5–7]; instead, they regain the weight and attempt again. This “yo-yo” dieting pattern, termed “weight cycling,” refers to a repetitive pattern of weight loss and regain [2,8–11].

Although weight cycling is a relatively common phenomenon, no standard definition has been developed; thus its prevalence is ill-defined [10]. A study in Finland found 11% of men and 19% of women to be mild weight cyclers, and 7% of men and 10% of women to be severe cyclers [10]. They defined weight cycling as intentional weight loss of ≥ 5 kg 1–2 times (mild) or 3 times (severe), followed by regain over 10 years. In the Nurses’ Health Study II, 18.9% of women were characterized as mild weight cyclers and 1.4% were severe cyclers [2]. Weight cycling was defined as intentionally losing ≥ 10 pounds (4.5 kg) (mild) or ≥ 20 pounds (9.1 kg) (severe) at least 3 times over 4 years. A study in healthy German adults found weight cycling, defined as unintentional weight gain and intentional weight loss of > 5 kg over 2 years, in approximately 4% of men and women [9].

Initial studies report associations between weight cycling and negative health outcomes, including immune system dysfunction [12], bone density loss [13], insulin resistance [14], hypertension [15], cardiovascular disease [16], mortality [16], binge eating behaviors [17], abdominal adiposity [14,18,19], body mass index (BMI) and percent body fat [18,20]. A number of population-based studies suggest that weight cycling may be associated with future weight gain [2,9,21–25]. The mechanism responsible for this association is unclear. It was hypothesized that weight cycling caused a decrease in resting metabolic rate (RMR), making subsequent weight loss more difficult [11]. However, investigation of this hypothesis demonstrated that RMR remains decreased during periods of energy restriction but not thereafter [11].

We now have a clearer understanding of how weight changes stimulate adjustments in energy homeostatic hormones (leptin, ghrelin, and insulin) that activate regulatory mechanisms to restore either lost or gained weight [26]. Following weight loss, serum leptin and insulin levels fall, while ghrelin levels rise. Conversely, after weight gain, leptin and insulin levels rise, while ghrelin levels fall [26]. The role of such mechanisms in weight cycling has been evaluated only in a small number of cross-sectional studies in obese men and women [18,20,25], but thus far, results have been inconsistent. Benini *et al* reported a strong positive correlation between weight-cycling parameters and serum leptin in women [18]. Graci *et al* showed no independent associations between weight-loss frequency and insulin [20], glucose [20], or HOMA [20]. Similarly, Strychar *et al* found no independent associations between weight cycling and leptin, ghrelin, serum glucose, or insulin sensitivity, but did find weight cycling to be associated with higher BMI, body fat mass, and waist circumference [25]. Our research, although also cross-sectional, differs from these studies by investigating a comprehensive set of hormones (including sex hormones). Among 159 postmenopausal, overweight or obese women, we evaluated the relationship between intentional weight loss and hormonal profiles, including metabolic and energy homeostasis variables (fasting glucose, insulin, homeostasis assessment model [HOMA], leptin, ghrelin,

insulin-like growth factor [IGF-1]), estrogens (estrone, estradiol, free estradiol, sex hormone binding globulin [SHBG]), and androgens (androstenedione, testosterone, free testosterone, dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEA-SO_4]). We hypothesized that a history of frequent intentional weight loss would be associated with changes in normal appetite and body-weight-regulatory hormones that would favor increased appetite and weight gain. We also expected sex steroids to display a complementary altered profile in weight cyclers. For example, we expected to observe higher levels of ghrelin, and lower levels of insulin, leptin, androgens, and estrogens in the women with a history of frequent intentional weight loss.

2. Methods and materials

This study was conducted at Fred Hutchinson Cancer Research Center and the University of Washington. Subjects (n=173) participated in a randomized clinical trial examining the effect of a 12-month aerobic exercise intervention [27]. All data presented here were collected at baseline, prior to randomization.

2.1. Study Population

Study participants were sedentary, postmenopausal women aged 50–75 years with a BMI between 25.0 and 45.0 kg/m^2 (or BMI 24.0–25.0 kg/m^2 if percent body fat >33.0%). They were nonsmokers who were not taking hormone therapy during the past 6 months with no history of invasive cancer, diabetes, cardiovascular disease, or asthma. Women were excluded if they were volunteering to lose weight, had a history of weight-loss surgery, or were currently in, or planning to enter, a structured weight-loss program. Participants had been weight stable for at least 3 months.

2.2. Measures of Body Weight and Height

Body weight was measured without shoes and in light clothing to the nearest 0.1 kg using a Detecto (Jericho, NY) balance-beam scale and height was measured to the nearest 0.1 cm using a stadiometer. Measurements were duplicated (coefficients of variation were 0.05% and 0.2%, respectively), and the average was used to calculate BMI (kg/m^2).

2.3. Questionnaires and Definitions

Participants completed a questionnaire including the following: ‘Within the last 20 years, when you were not pregnant or sick, did you ever lose 10 pounds or more on purpose?’ In similar questions, women were asked how often they had lost between 10 and 19 pounds, between 20 and 49 pounds, and 50 pounds or more.

Significant weight-loss history was defined as intentionally losing 10 pounds or more over the past 20 years. We estimated magnitude (≥10, ≥20, ≥50 pounds) and frequency (0, >0 but <5, ≥5 times) of weight loss. No specific data were available on weight regain. However, since participants were overweight or obese, it was assumed that weight regain had occurred over the past 20 years.

Participants completed an adaptation of the Minnesota Physical Activity Questionnaire [28], reporting the type, duration, and frequency of physical activity they engaged in. Activity estimated to be >3 METs (metabolic equivalents, kcal/kg/h) was recorded, and the average MET minutes/week were calculated for each participant.

2.4. Metabolic Measures

Participants provided a 12-h fasting 50-mL sample of blood, which was processed within 1 hour of collection. Serum was aliquoted into 1.8-mL tubes and stored at −70° C. For all

assays, laboratory personnel were blinded to the sample identity. Detailed descriptions on assay methods are given in previous publications [29–33].

Fasting glucose was quantified on a clinical chemistry autoanalyzer, measuring the combined catalytic activities of hexokinase and glucose-6-phosphate dehydrogenase [30]. Spectroscopy was used to detect the solution's absorbance measured at 340/380 nm. Intra- and interassay coefficients of variation (CVs) were 0.9% and 2.0% respectively.

Insulin was quantified by a 48-hour, polyethylene glycol-accelerated, double-antibody radioimmunoassay [30]. Insulin was quantified by a 48-hour, polyethylene glycol-accelerated, double-antibody radioimmunoassay using primarily guinea pig anti-human insulin and secondarily goat anti-guinea pig immunoglobins. Intra- and interassay CVs were 6.5% and 9.3% respectively.

HOMA is a surrogate measure of whole body insulin sensitivity used as an index of insulin resistance [34]. (Calculated as fasting glucose (mM) × fasting insulin (μU/mL) / 22.5).

Leptin assays were performed using a commercially available radioimmunoassay (Linco Research, St. Charles, MO) [30]. Intra- and interassay CVs were 8.7% and 11.2% respectively.

Ghrelin was measured using a modification of a commercial radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA) [32]. Intra- and interassay CVs were 3.5% and 4.9% respectively.

IGF-1 was quantified via a two-site chemiluminescence immunoassay using the Nichols Advantage Specialty System (Nichols Diagnostic Institute, San Juan Capistrano, CA) [33]. Intra- and interassay CVs were 7.8% and 13.2% respectively.

Estrone, estradiol, testosterone, androstenedione, DHEA, and DHEA-SO_4 were quantified by radioimmunoassay after organic solvent extraction and Celite column partition chromatography [29,31]. Chromatographic separation of the steroids was achieved by the use of different concentrations of toluene in isooctane and ethyl acetate in isooctane. Intraassay and interassay CVs were: estrone (12.4%, 17.6%); estradiol (12.4%, 15.8%); testosterone (8.4%, 12.2%); androstenedione (7.4%, 9.8%); DHEA (6.1%, 11.6%); and DHEA-SO_4 (9.5%, 10.9%).

SHBG was quantified via an immunometric assay using the Immulite Analyzer [31]. Intra- and interassay CVs were 6.75 and 10.0% respectively.

Free estradiol and free testosterone were calculated using the measured values for estradiol, testosterone, and SHBG and a constant for albumin [29,31].

2.5. Statistical Analyses

ANOVA and linear regression analyses were performed to investigate associations between the metabolic and weight-loss history variables. All analyses were performed using SAS version 9.1 (2002–2003; SAS Institute, Carey, NC).

Weight-loss history variables included intentional weight loss (ever lost ≥10, ≥20, and ≥50 pounds) and weight-loss frequency (number of times lost ≥10 pounds intentionally), each over the past 20 years. The continuous exposure variable (weight-loss frequency) was categorized into approximate tertiles, using indicator variables to test for differences between groups. This is a more flexible approach than using a single categorical variable

because the relationship between the exposure categories and outcomes is not *a priori* assumed to be linear.

Biomarker endpoints included energy homeostasis variables (glucose, insulin, HOMA, leptin, ghrelin, IGF), estrogens (estrone, estradiol, free estradiol, SHBG), and androgens (androstenedione, testosterone, free testosterone, DHEA, DHEA-SO_4). Because of non-normally distributed data, all endpoint variables were log-transformed.

To address potential confounding, adjusted models included the covariates of age, BMI, and MET minutes per week. Adjustment by percent total fat mass, VO_2 max, caloric intake, fiber intake, total fat intake, alcohol consumption, and smoking history did not alter parameter estimates for exposure variables (>10%). Participants were excluded if weight-loss history questions had not been answered (n=1) and from specific analyses because of missing data (n=3 for glucose and HOMA; n=6 for DHEA-SO_4). Also, 13 participants were excluded from all analyses because of missing data for MET minutes/week, an essential covariate, yielding a final sample size of n=159. With a type I error of 0.05, we had 80% power to detect an effect size of 0.49 (defined as (mean of group 1 –mean of group 2)/SD) for having ever lost ≥10lb intentionally, and 0.46 for having ever lost ≥ 20 lb intentionally, using two-sided two-sample t-tests. For example, this translates into an approximate absolute difference of 4 mg/dL change in glucose and 1pg/mL of free testosterone.

2.6. Statement of Ethics

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All patients provided informed consent and all study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

3. RESULTS

3.1. Participant Characteristics and Distributions

Table 1 shows participant characteristics for demographics, weight-loss history variables, and metabolic variables. A history of intentional weight loss over the past 20 years was common, with 69% reporting losing ≥10 pounds at least once and 44% reporting losing ≥20 pounds at least once.

Weight-loss history was associated with BMI, but within each category of BMI intentional weight-loss characteristics were variable. For example, among women with a BMI ≤28 kg/m^2 (lowest tertile), 25% reported weight loss of ≥10 pounds, whereas, among those with BMI > 31 kg/m^2 (highest tertile), 44% noted weight loss of ≥10 pounds. 45% had intentionally lost 10 lb 1–4 times, and an additional 25% had intentionally lost 10 lb at least 5 times.

3.2. Energy Homeostasis Variables

In ANOVA analyses adjusted for age, BMI, and MET minutes per week (Table 2), ghrelin concentrations were 11% higher in participants who had intentionally lost ≥10 lb (p=0.37), 22% higher in participants who had intentionally lost ≥20 pounds (p=0.05), and 44% higher for those who had lost ≥50 pounds (p=0.03)). Additionally, higher ghrelin levels were observed in participants who had lost weight more frequently (p-trend=0.04). More frequent weight loss was also associated with trends toward lower glucose levels (p=0.047) and a modest trend toward lower insulin levels, which was not statistically significant. Fasting glucose was lower in participants who had lost ≥10 pounds (p=0.004) compared to those

who did not report intentional weight loss, but did not differ for those who had lost higher amounts of weight.

IGF-1 was 14% higher in participants who had lost ≥20 pounds in the past 20 years ($p=0.03$), but revealed no consistent patterns overall. In the unadjusted model, leptin correlated positively with frequency and quantity of weight loss (data not shown). However, no statistically significant differences were observed in the adjusted model.

3.3. Estrogens

There were no statistically significant differences observed in estrogens or SHBG between participants with a history of weight loss and those without (data not shown), nor were there statistically significant trends associated with weight loss frequency. Though not statistically significant, SHBG was consistently higher and free estradiol was consistently lower in women with more frequent and larger weight-loss episodes.

3.4. Androgens

There were no statistically significant differences observed between estrogens or SHBG to weight-loss history (data not shown). Androstenedione, testosterone, and free testosterone were each consistently lower in participants who had intentionally lost ≥10 pounds (see Table 3). We observed significant trends toward reduced androgen concentrations with more frequent weight loss ($p=0.02$, $p=0.04$, and $p=0.01$, for androstenedione, testosterone, and free testosterone respectively).

4. DISCUSSION

We predicted that weight cyclers would have a more appetite-stimulating, energy-conserving hormone profile which promoted weight gain with increased ghrelin, decreased insulin, and decreased leptin, and corresponding decreases in both androgens and estrogens. However, our results revealed only slightly altered appetite-stimulating profiles in weight cyclers with higher ghrelin, to some extent lower insulin, and lower androgens, and no differences in leptin or estrogens. Although the biologic implications underlying such associations between lower androgen levels and more frequent weight loss are currently not well defined, it has been demonstrated that androgens correlate positively with body weight [29]. Our observation of lower androgen levels and greater frequency of weight loss could therefore be compatible with an energy-reduced hormonal profile.

Elevated serum androgens are associated with insulin resistance, and insulin resistance typically occurs in the setting of obesity [35]. Obesity, difficulty losing weight, insulin resistance and elevated androgens (testosterone, androstenedione, DHEA, and DHEA-S), are hallmarks of polycystic ovarian syndrome (PCOS) [36,37]. Several studies have found lower ghrelin levels in this population as compared to BMI- and age-matched controls [38–42]. The hormonal levels we observed in women with a history of intentional weight loss trended in the opposite direction from those generally observed in women with PCOS. If women with no history of weight loss had initial hormonal profiles similar to women with PCOS, this may have resulted in less success with weight loss attempts. Because this is a cross-sectional study, it is possible that the differences in hormonal profiles we observed occurred prior to weight-loss behavior.

Given our understanding of food intake and body weight regulatory mechanisms, additional explanations are plausible for our findings of higher ghrelin, a tendency toward lower insulin, lower fasting glucose levels, and higher androgens in women with a history of intentional weight loss. Weight-cycling women could have recently lost weight or could have been actively engaged in weight loss. However, these scenarios are less likely because

participants reported being weight stable for at least 3 months. They reported that they were not currently trying to lose weight, and controlling for caloric intake in our analyses did not alter parameter estimates for exposure variables. Alternatively, a history of repetitive weight loss or a history of a larger magnitude of weight loss could have given rise to a more robust regulatory system, resulting in an appetite-stimulating profile. This scenario is supported by Schwartz *et al*'s central resistance model, which proposes that, despite the compensatory nature of energy-homeostatic mechanisms, resistance to adiposity-regulating hormones is acquired through lifestyle or genetics which in turn undermines biological protection against weight gain [43]. Clearly, additional research is needed to confirm or disprove our observed associations and to explore biologic relationships.

With an appetite-stimulating or energy-reduced metabolic profile, one would expect leptin concentrations to be relatively low. While ghrelin, insulin, and leptin each respond immediately to body-weight change, ghrelin and insulin are also responsive to nutritional factors independent of body weight [44]. Thus, ghrelin and insulin, perhaps more than leptin, may link both short- and long-term regulation of energy balance. Furthermore, leptin is so closely correlated with adiposity that this relationship may overshadow other associations. In the unadjusted model in our study, leptin was associated with weight-loss history, however no associations were observed once BMI was controlled for (data not shown). Finally, our leptin findings could be due to the fact that hormonal profiles were obtained only once after a 3-month period.

Several previous studies have examined an association between individual hormones and weight loss history. Three studies found an association between weight loss and increases in serum ghrelin level [45–47], and our findings support this data. Three previous studies investigated a panel of hormones involved in energy homeostasis in weight-cycling adults, but thus far, results have been inconsistent. One study reported a strong positive correlation between weight-cycling parameters and serum leptin in women [18]. Another study found no independent associations between weight-loss frequency and insulin [20], glucose [20], or HOMA [20]. Yet another study found no independent associations between weight cycling and leptin, ghrelin, serum glucose, or insulin sensitivity [25]. Our study differed in that we investigated associations between weight cycling and a comprehensive set of hormonal biomarkers. Finding complementary alterations in multiple hormones supports the biologic plausibility of the findings; yet, clearly, further investigations are needed, because some associations were of marginal statistical significance or not linearly related (potentially due to small sample sizes in some groups, e.g., those who lost >50 pounds).

Another limitation of our study was the lack of specific information on each weight-loss episode. However, potential misclassification of self-reported weight loss was likely non-differential (i.e. unlikely to differ by metabolic outcomes), biasing the results toward observing no association. In addition, our study was homogenous, consisting primarily of non-Hispanic white, educated, who were overweight or obese women; thus, it is unclear whether the results can be generalized to other groups. Nevertheless, 66% of women in this age group in the United States are overweight or obese [48], emphasizing relevance to a large proportion of the population. A number of analyses were conducted, which may have produced spurious results. Until validated in other populations, our findings should be interpreted with caution.

However, in our study, participants specified that the weight loss was intentional, which was a strength because other weight-cycling studies have defined intentionality less clearly. Further, our participants were overweight or obese, yet free of any chronic diseases, reducing potential confounding of hormonal biomarkers measured in this study. Finally, as noted above, the complementary pattern of metabolic hormones we measured lends some

support to the biologic plausibility of an underlying physiology to weight cycling *vs.* weight stability.

In summary, this study provides evidence that postmenopausal women with a history of frequent intentional weight loss may have a more appetite-stimulating hormonal profile than their counterparts. Given the environmental factors that promote weight gain in today's modern wealthy societies, and the evidence for a biologic tendency toward weight gain, it is concerning that weight cycling, which appears to be quite prevalent, could play a role in further exacerbating the propensity to gain weight. Our findings underscore the need to further investigate and define prospectively the relationship between weight cycling, altered hormonal profiles, and regulation of energy homeostasis.

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Glossary

ANOVA	analysis of variance
BMI	body mass index
RMR	resting metabolic rate
HOMA	homeostasis assessment model
IGF-1	insulin-like growth factor
SHBG	sex hormone binding globulin
DHEA	dehydroepiandrosterone
DHEA-SO_4	dehydroepiandrosterone sulfate
MET	metabolic equivalent
PCOS	polycystic ovarian syndrome

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Table 1

Characteristics of Study Participants

Characteristic	N or mean ± SD	Percentage of total* or sample range (reference range**)
Demographics		
Age (years)	60.4±6.5	51–75
BMI (kg/m^2)	30.4±3.9	24.1–40.9
Age tertile (years)		
51–55	45	28%
56–65	74	47%
66–75	40	25%
BMI tertile (kg/m^2)		
≤28	51	32%
>28, ≤31	49	31%
>31	59	37%
Education level		
High school or less	17	11%
Some college or college graduate	79	50%
Postbaccalaureate or advanced degree	63	40%
Employment status		
Unemployed, homemaker, other	20	13%
Retired	33	21%
Employed	81	51%
Unknown	25	16%
Marital status		
Never married	11	7%
Divorced or separated	44	28%
Widowed	14	9%
Married or living with partner	90	57%
Race		
African American	6	4%
Asian or Pacific Islander	9	6%
Hispanic	2	1%
White	137	86%
Other or unknown	5	3%
Weight-loss history within last 20 years		
Ever lost ≥10 pounds (lb) intentionally		
Yes	110	69%
No	49	31%
Ever lost ≥20 lb intentionally		
Yes	70	44%
No	89	56%

Characteristic	N or mean ± SD	Percentage of total* or sample range (reference range**)
Ever lost ≥50 lb intentionally		
Yes	15	9%
No	144	91%
Number of times lost ≥10 lb intentionally		
0	49	31%
>0, <5	71	45%
≥5	39	25%
Hormonal and Metabolic Variables		
Glucose (mg/dL)[a]	97.8±8.8	81–133 (70–105)
Insulin (μU/mL)	19.8±9.9	3.7–55.2 (3–28)
HOMA[a]	4.9±2.7	0.8–16.0 (<1.0)
Leptin (ng/mL)	28.1±8.3	8.8–50.5 (1.1–27.5)
Ghrelin (pg/mL)	626±349	53–1632 (100–1000)
IGF-1 (ng/mL)	108±36	34–251 (64–238)
Estrone (pg/mL)	46.1±16.5	21–113 (14–103)
Estradiol (pg/mL)	19.0±7.6	10–50 (<30.0)
Free Estradiol (mg/mL)	0.52±0.23	0.17–1.6
SHBG (nmol/L)	39.5±21.2	12.0–193 (14.1–68.9)
Androstenedione (pg/mL)	597±233	186–1684 (470–2680)
Testosterone (pg/mL)	236±102	67–740 (60–820)
Free Testosterone (pg/mL)	5.06±2.17	1.0–16.8 (1.0–21.0)
DHEA (ng/mL)	2.69±1.44	0.31–9.56 (0.60–4.14)
DHEA-SO_4 (μg/dL)[b]	70.9±47.7	10.6–338 (9.4–256)

SD=standard deviation.
BMI=body mass index
HOMA=homeostasis assessment model
IGF-1=insulin-like growth factor
SHBG=sex hormone binding globulin
DHEA=dehydroepiandrosterone
DHEA-SO_4=dehydroepiandrosterone sulfate

*May not equal 100% because of rounding percentages.

**Reference ranges are for postmenopausal women, except androstenodione, free testosterone, glucose, and insulin which are for all women.

[a]3 missing values

[b]6 missing values

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Table 2

Association between history of intentional weight loss and energy homeostasis variables.

	N	Glucose (mg/dL)[a]		Insulin (μU/dL)		HOMA[a]		Leptin (ng/Ml)		Ghrelin (pg/mL)		IGF-1 (ng/mL)	
		Geo-metric LS Mean (± SE)	p-value	Geo-metric LS Mean (± SE)	p-value	Geo-metric LS Mean (± SE)	p-value	Geo-metric LS Mean (± SE)	p-value	Geo-metric LS Mean (± SE)	p-value	Geo-metric LS Mean (± SE)	p-value
Ever lost ≥10 lb intentionally													
No	49	101±1.2	Ref.	19.2±1.2	ref.	4.78±0.33	ref.	27.1±1.1	ref.	495±44	ref.	94.9±4.9	ref.
Yes	110	96.2±0.8	**0.004**	17.0±0.7	0.12	4.08±0.18	**0.06**	26.8±0.7	0.78	547±31	0.35	105±3.5	0.12
Ever lost ≥20 lb intentionally													
No	89	98.0±0.9	Ref.	18.1±0.9	ref.	4.41±0.23	ref.	26.8±0.8	ref.	486±31	ref.	95.9±3.6	ref.
Yes	70	96.8±1.0	0.39	17.1±0.9	0.44	4.13±0.24	0.42	26.9±0.9	0.95	592±44	**0.05**	109±4.7	**0.03**
Ever lost ≥50 lb intentionally													
No	144	97.7±0.7	Ref.	17.8±0.6	ref.	4.34±0.17	ref.	26.9±0.6	ref.	512±25	ref.	102±3.0	ref.
Yes	15	95.5±2.2	0.35	16.4±1.9	0.51	3.86±0.49	0.38	26.8±1.9	0.97	738±117	**0.03**	100±9.5	0.87
Number of times lost≥10lb intentionally													
0	49	100±1.2	Ref.	19.3±1.2	ref.	4.79±0.33	ref.	27.2±1.1	ref.	488±42	ref.	95.0±4.9	ref.
>0, <5	71	95.8±1.0	**0.004**	17.5±0.9	0.22	4.16±0.23	0.11	27.0±0.9	0.93	496±35	0.89	106±4.4	0.10
≥5	39	96.9±1.4	**0.07**	16.2±1.2	**0.08**	3.93±0.31	**0.07**	26.2±1.2	0.57	664±66	**0.03**	102±6.0	0.36
		p-trend = **0.047**		p-trend = **0.08**		p-trend = **0.06**		p-trend = 0.59		p-trend = **0.04**		p-trend = 0.30	

ANOVA (analysis of variance) model, testing for differences between exposure (weight loss group) and reference group (ref.), adjusting for age, BMI (body mass index), and moderate to vigorous physical activity MET (metabolic equivalent) minutes per week.

Three missing values

LS=least squared

SE=standard error

HOMA=homeostasis assessment model

Table 3

Association between history of intentional weight loss and serum androgens.

	N	Androstenedione (pg/mL)		Testosterone (pg/mL)		Free Testosterone (pg/mL)	
		Geometric LS Mean (± SE)	**p-value**	**Geometric LS Mean (± SE)**	**p-value**	**Geometric LS Mean (± SE)**	**p-value**
Ever lost ≥ 10 lb intentionally							
No	49	615±34	ref.	239±14	ref.	5.23±0.30	ref.
Yes	110	534±19	**0.04**	208±8.1	**0.06**	4.43±0.16	**0.02**
Ever lost ≥ 20 lb intentionally							
No	89	565±23	ref.	221±9.8	ref.	4.81±0.20	ref.
Yes	70	548±26	0.63	213±11	0.59	4.48±0.22	0.29
Ever lost ≥ 50 lb intentionally							
No	144	563±18	ref.	219±7.4	ref.	4.71±0.15	ref.
Yes	15	509±51	0.35	206±23	0.62	4.30±0.45	0.42
Number of times lost ≥ 10 lb intentionally							
0	49	617±34	ref.	240±14	ref.	5.25±0.30	ref.
>0, <5	71	546±24	**0.08**	213±10	0.12	4.55±0.21	**0.05**
≥5	39	510±32	**0.03**	199±13	**0.049**	4.21±0.27	**0.01**
		p-trend = **0.02**		p-trend = **0.04**		p-trend = **0.01**	

ANOVA (analysis of variance) model, testing for differences between exposure (weight loss group) and reference group (ref.), adjusting for age, BMI (body mass index), and moderate to vigorous physical activity MET (metabolic equivalent) minutes per week.

LS=least squared

SE=standard error