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Exercise for Weight Loss: Further Evaluating Energy Compensation with Exercise

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ABSTRACT

FLACK, K. D., H. M. HAYS, J. MORELAND, and D. E. LONG. Exercise for Weight Loss: Further Evaluating Energy Compensation with Exercise. *Med. Sci. Sports Exerc.*, Vol. 52, No. 11, pp. 2466–2475, 2020. **Purpose:** This study assessed how individuals compensate for energy expended during a 12-wk aerobic exercise intervention, elucidating potential mechanisms and the role exercise dose plays in the compensatory response. **Participants and Design:** Three-arm, randomized controlled trial among sedentary adults age 18 to 40 yr, body mass index of 25 to 35. Groups included six exercise sessions per week, two sessions per week, and sedentary control. **Methods:** Rate of exercise energy expenditure was calculated from a graded exercise test averaged across five heart rate zones. Energy compensation was calculated as the difference between expected weight loss (based on exercise energy expenditure) and changes in fat and fat-free mass (DXA). Resting energy expenditure was assessed via indirect calorimetry and concentrations of acylated ghrelin, leptin, insulin, and Glucagon-like peptide 1 (GLP-1) were assessed fasting and postprandial (six timepoints over 2 h). **Results:** The 6-d·wk^{-1} group expended more energy (2753.5 kcal) and exercised longer (320.5 min) per week than the 2-d·wk^{-1} group (1490.7 kcal, 1888.8 min, $P < 0.05$), resulting in greater fat loss compared with the 2-d or control groups ($P < 0.05$). Exercise groups did not differ in the % or total kcal compensated. Greater decreases in area under the curve (AUC) for acylated ghrelin predicted greater fat loss, regardless of group, energy expended per week, exercise duration, or exercise intensity. Changes in leptin AUC was the only independent predictor for energy compensation, with a greater decrease in leptin AUC predicting less energy compensation. Exercise frequency, energy expended, duration, or intensity did not influence energy compensation. **Conclusions:** Leptin is an important factor in successful weight loss through exercise, with greater postprandial decreases promoting less compensation. Greater amounts of exercise do not influence the compensatory response to an exercise-induced energy deficit. **Key Words:** ENERGY COMPENSATION, EXERCISE, WEIGHT LOSS, LEPTIN, GHRELIN

Individuals classified as overweight or obese represent over 70% of US adults, putting these individuals at risk for a multitude of comorbidities including cardiovascular disease, diabetes, heart disease, and certain cancers (1). Obesity treatment has therefore emerged as a prime focus of health care and a top concern among the general public. Recent reports indicate that 41.5% of individuals are currently trying to lose weight, with exercise being the most common strategy at a prevalence rate of 65% (2). Unfortunately, weight loss from an exercise program is often less than expected (3,4). The lack of weight loss success with exercise is due to compensatory responses counteracting the negative energy balance created by exercise to maintain homeostasis, thereby alleviating the energy deficit required for weight loss (5). Maintaining energy balance can be viewed as an evolutionarily conserved mechanism in place to retain bodily energy stores and reproductive function, a useful survival strategy in times of famine (6). However, this response is not as advantageous in our current obesogenic environment, detracting from the desired additional body weight loss and weight loss maintenance. Some have speculated that the primary compensatory response resisting weight loss with exercise is an increased energy intake based on the fact that the rate of energy intake far exceeds the rate of energy expenditure (3–5). To this end, research has evaluated how hormonal mediators of hunger may function as mechanisms to influence energy intake when faced with an energy deficit (7). Specifically, increases in acylated ghrelin and decreases in peptide YY, insulin, and leptin (either postprandially or fasting levels) have been observed with exercise and weight loss, potentially promoting feeding behaviors (7–9). Others have championed for metabolic adaptations, or mass-independent reductions in energy expenditure, as a major player in energy compensation (10–12).

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These changes in energy expenditure have been realized as declines in resting energy expenditure (REE) and increases skeletal muscle work efficiency (expending less energy at a given workload) when controlling for fat-free mass (FFM) (13,14). Disagreement also exists around the magnitude of the compensatory response, with evidence that greater energy expenditures evoke a greater compensatory response (15), supported by the observed lack of differences in weight loss between groups exercising at 50%, 100%, or 150% of public health recommendations (16) or when exercising at 14 or 23 kcal·kg^{-1}·wk^{-1} (17). On the other hand, we recently demonstrated no differences in energy compensation between groups expending 3000 or 1500 kcal·wk^{-1}, with both groups compensating for roughly 1000 kcal·wk^{-1} (18). The purpose of the present investigation was to extend this previous study on energy compensation by assessing the compensatory response of inactive individuals with overweight/obesity after a 12-wk aerobic exercise intervention when randomizing participants into different exercise frequency groups (sessions per week). We hypothesized that less frequent exercise (2 d·wk^{-1}) would evoke a reduced compensatory response compared with frequent exercise (6 d·wk^{-1}) as fewer sessions could result in fewer episodes of compensatory eating or fewer insults on the biological mechanisms working to maintain energy homeostasis. Although the 2-d·wk^{-1} group was not likely to produce the same exercise energy expenditure as the 6-d·wk^{-1} group, this hypothesized attenuation of the compensatory response would, if proven true, result in both groups losing similar amounts of body weight. To provide further insight into the mechanisms of energy compensation, changes in REE adjusted for FFM, resting respiratory quotient (RQ), and the hormonal response to a breakfast meal were evaluated.

MATERIALS AND METHODS

Participants

A total of 52 participants age 18 to 49 yr volunteered and were randomized into one of three groups during this longitudinal, randomized, controlled trial. Of these, 44 participants completed the study (32 women), with six (four women) withdrawing for personal reasons and two female participants being excluded for noncompliance. All participants had a body mass index (BMI) ranging from 25 to 35 kg·m^{-2} and were inactive (not engaging in any form of exercise for the previous 6 months). We defined exercise as purposeful, leisure time physical activities performed to improve health and/or weight status. This was determined during screening when participants were asked of their exercise behaviors. Participants were excluded if they reported engaging in any exercise over the previous 6 months. The lack of exercise behaviors of the current sample was validated by accelerometry, as baseline 7-d vigorous physical activity (VPA) values were well below the recommended 75 min·wk^{-1} for every participant (Table 1). Recruitment began in the winter of 2018 and continued until recruitment goals were met (spring of 2019) in and around Lexington, Kentucky. Participants were a sample who responded to recruitment media including printed brochures and flyers and online advertisements placed on University of Kentucky's Center for Clinical and Translational Science (CCTS) website. This study was approved by the University of Kentucky Institutional Review Board and is registered with ClinicalTrials.gov identifier: NCT03413826.

TABLE 1. Demographics, VPA, and metabolic rates of the study participants at baseline (includes all randomized participants).

	6 d·wk^{-1} Group, n = 19	2 d·wk^{-1} Group, n = 20	Control, n = 14
Sex (% female)	68.4	85.0	78.8
Age (yr)	29.32 ± 7.27	28.56 ± 5.85	26.00 ± 7.80
BMI, kg·m^{-2}	29.0 ± 2.87	30.51 ± 3.47	29.36 ± 2.87
VPA[a]	9.08 ± 12.88	8.57 ± 17.45	12.91 ± 19.87
REE/kg FFM[b]	31.52 ± 4.76	33.86 ± 4.75	33.37 ± 4.62
RQ[c]	0.93 ± 0.10	0.90 ± 0.09	0.92 ± 0.06
$\dot{V}O_2$ peak[d]	39.76 ± 4.56	38.45 ± 2.57	39.95 ± 4.84

Data are mean ± SD.
[a]Minutes of weekly VPA assessed objectively assessed via accelerometry using Freedson cut points.
[b]REE per kg FFM, in kcal per 24 h, assessed from indirect calorimetry and calculated via the Weir equation from O_2 consumed and CO_2 produced.
[c]Respiratory quotient, CO_2 produced/O_2 consumed during REE test.
[d]$\dot{V}O_{2Peak}$: Estimated from submaximal exercise test, mL·kg^{-1}·min^{-1}.

Study Design

The study was a randomized, controlled trial that included a 12-wk exercise intervention of either six sessions (days) per week, two sessions per week, or a sedentary control group (no exercise) blocked on sex. The study statistician generated and maintained the concealed allocation sequence. Participants were randomized upon completion of all baseline assessments with no blinding of assignment to interventions as participants and research staff needed to monitor weekly exercise sessions to ensure compliance. Participants were assessed for outcome measures at baseline and immediately after the intervention.

Procedures

During the initial screening and consenting visit, participants provided their written informed consent and were screened of eligibility criteria, completing a physical activity readiness questionnaire, health history questionnaire, and screened on their dieting, weight loss history, and physical activity behaviors. Participants were provided an ActiGraph Accelerometer (Pensacola, FL) to wear for the following 7 d to objectively assess physical activity before completing baseline testing. Subsequent visits included assessments for resting metabolic rate, rate of energy expenditure during exercise, body composition, and hormonal response to a standardized breakfast meal (all detailed below).

Assessments

Physical activity. Habitual, free-living physical activity was measured using an ActiGraph accelerometer (GT3X+ model) at baseline to verify participants were not engaging in exercise. Participants were instructed to wear the monitor at the hip using the provided belt during all hours awake except when bathing or swimming. Data were cleaned of nonwear

time, defined as consecutive strings of zeros greater than 20 min. An epoch of 10 s was used for data collection as a shorter epoch is more suitable to reflect bout duration under free-living conditions of sedentary individuals (19). These data were used to determine participants' weekly minutes of VPA using the Crouter et al algorithm, and Freedson cutpoints. Vigorous physical activity was used over the more typical moderate to vigorous physical activity (MVPA) to determine exercise behavior as VPA is a better measure of purposeful exercise opposed to activities like walking across a large college campus (as many participants were obligated to do) which can be counted as MVPA but did not fit our definition of "exercise."

Rate of energy expenditure. A graded exercise treadmill test was used to determine each participant's rate of energy expenditure at five different heart rate (HR) zones. Oxygen consumed and CO_2 produced were analyzed by indirect calorimetry (VMAX Encore Metabolic Cart; Vyaire Medical, Mettawa, IL), which included an integrated 12-lead ECG for monitoring HR and used in conjunction with the Trackmaster TMX428 Metabolic cart interfaced treadmill. Upon completion of a 5-min warm-up walking at 0% grade and 3.0 mph, the treadmill grade increased to 2.5% for 3 min. The treadmill grade was then increased every 3 min to produce an approximately 10-bpm increase in HR from the previous stage with the speed fixed at 3.0 mph. The test continued until an HR of 85% HR reserve (HRR) was attained or the participant felt they could no longer continue. Rate of energy expenditure ($kcal \cdot min^{-1}$) was determined from the amount of oxygen consumed and CO_2 expired using the Weir equation (20). The average rate of energy expenditure during the last 30 s of each stage of the test was regressed against the HR averaged over the last 30 s of the corresponding stage to calculate the rate of energy expenditure at different HR. Heart rate zones were calculated based on the HRR formula as (220 − age) − resting HR × zone % + resting HR. Heart rate zone 1 ranged from 50% to 59% HRR, zone 2 corresponded to 60%–69% HRR, zone 3 was 70% to 79% HRR, zone 4 was 80% to 89% HRR, and zone 5 was 90% or greater. Energy expenditure ($kcal \cdot min^{-1}$) was averaged across each HR zone for determination of energy expenditure per minute for each zone. This test was completed at baseline and again at 6 wk to recalculate energy expenditure to take improvements in cardiorespiratory fitness into account.

Body composition. Body composition was measured using a GE Lunar iDXA machine before the exercise test. The iDXA technique allows the noninvasive assessment of soft tissue composition by region with a precision of 1% to 3% (21). A total body scan was conducted with participants lying supine on the table and arms positioned to the side. Most scans were completed using the thick mode suggested by the software. All scans were analyzed using GE Lunar enCORE Software (13.60.033). Automatic edge detection was used for scan analyses. The machine was calibrated before each scanning session, using the GE Lunar calibration phantom.

Resting Energy Expenditure

Resting Energy Expenditure was measured using indirect calorimetry (Quark RMR; Cosmed USA, Chicago, IL) with a ventilated canopy. Calibrations were performed on the flow meter using a 3.0-L syringe and on the gas analyzers using verified gases of known concentrations before each test. After 30 min of quiet rest in the supine position in a dimly lit, temperature-controlled room between 22°C and 24°C, REE was measured for 30 min. The test was monitored to ensure participants remained awake and between 0.8% and 1.2% $feCO_2$. Criteria for a valid REE was a minimum of 15 min of steady state, determined as a <10% fluctuation in oxygen consumption and <5% fluctuation in respiratory quotient. The Weir equation (20) was used to determine REE from the measured oxygen consumption and CO_2 production. Participants completed the baseline REE assessment before the exercise test and 36 to 72 h after their final exercise session of the intervention. Fat-free mass is the predominate determinant of REE due to its metabolic activity, explaining 53% to 88% of the variance in REE (22,23). For this reason, REE (raw value) was divided by FFM (kg, from DXA) at each timepoint to standardize REE. This is consistent with previous literature and the definition of metabolic compensation, that is, mass-independent reductions in energy expenditure (10–12).

Hormonal Response to Standardized Breakfast

Participants reported to the outpatient wing of the University of Kentucky's CCTS, located within a research hospital after an overnight fast between 10 and 14 h. Participants provided a blood sample to analyze hormone and peptide concentrations associated with hunger and body weight regulation immediately before a standardized breakfast. The standardized breakfast provided 20% of estimated energy needs for each individual based on their REE and a sedentary activity factor of 1.4. The standardized breakfast consisted of 2% milk and cornflakes (with the option of substituting unsweetened soy milk for those with a lactose sensitivity) and one Nutra-grain™ bar. Participants consumed the breakfast within 15 min with postprandial blood draws completed at minutes 15, 30, 45, and 60. After the first hour blood was taken every 30 min thereafter for 2 h (minutes 90, 120, 150, and 180). Blood samples were collected in EDTA-coated and serum tubes. Serum $PYY_{3–36}$, glucagon-like peptide 1., leptin, and acylated grehlin were measured using ELISA (Millipore, Phoenix Pharmaceuticals, Alpco). Serum insulin was measured with a chemiluminescent immunometric assay (Siemens) and serum glucose was measured by the hexokinase glucose-6-phosphate dehydrogenase reaction (Roche Diagnostics).

Compensation

To calculate compensation for the energy expended during the exercise program, the accumulated energy balance (AEB) was calculated from pre–post changes in fat mass (FM) and

FFM as body composition changes reflect long-term alterations in energy balance (15). Gains of 1 kg FM and 1 kg FFM were assumed to reflect 12,000 kcal and 1780 kcal, respectively (24). Losses of 1 kg FM and 1 kg FFM were assumed to equal 9417 and 884 kcal, respectively (25). Exercise energy expenditure (ExEE) was calculated from the training-induced energy expenditure (TrEE) with the addition of 15% excess postexercise energy expenditure (26). The REE that would have occurred during the exercise sessions (REE × 1.2) was subtracted so not to include it twice. Thus, ExEE = (TrEE × 0.15) + (TrEE − training duration × [REE × 1.2]) (15). Compensation in response to the increase in ExEE was assessed as described by Rosenkilde et al. (15), with the compensation index (CI) calculated as (ExEE + AEB)/ExEE × 100%. When the CI equals zero, AEB equals −1 × ExEE, or changes in the energy equivalent of FM and FFM equal energy expended during exercise. Positive compensation suggests that changes in body composition indicate a negative energy balance that was less than expected based on ExEE, whereas negative compensation indicates a greater than expected negative energy balance. ExEE, AEB, and CI could be calculated only for those participants who completed the study as both a pretreatment and posttreatment data points were needed to calculate these variables.

Exercise Intervention

Participants were provided a Polar A-300 HR monitor (watch and chest strap, Kempele, Finland) for the duration of the 12-wk intervention and instructed to exercise either 2 or 6 d·wk^{-1}. Participants in the control group were instructed to remain sedentary and were offered the exercise intervention after posttesting, 12 wk later. Those in the exercise groups returned to the laboratory weekly to meet a researcher and download their exercise sessions using the PolarFlow™ software, which allowed research staff to monitor and track compliance. If a participant was not 90% compliant (completed 90% of expected exercise sessions per month) they were dropped from the study. The downloaded exercise session reports provided the amount of time spent in each HR zone, which allowed for the calculation of total energy expended during each exercise session based off individual rates of energy expenditure averaged across each HR zone calculated from the graded exercise test with indirect calorimetry performed at baseline and again at week 6. Participants in the 2-d·wk^{-1} group were instructed to perform two long exercise sessions per week between 90 and 120 min at a self-selected intensity provided they were in at least HRR zone 1. Participants in the 6-d·wk^{-1} group were instructed to keep their sessions between 40 and 60 min per session with the same intensity guidelines as the 2-d group. Participants were provided feedback each week on their time and energy expenditure of each session of the prior week. All participants were instructed not to purposely change dietary habits during the intervention.

Analytic Plan

Baseline participant characteristics and exercise training-induced variables (ExEE, AEB, and CI) were tested for group differences using *t* tests. Our primary outcomes were CI, kcal compensated, percent body fat loss, and hormonal mediators or appetite with interest in how these variables related to exercise dose defined as sessions per week (randomized group), ExEE per week, time spent exercising per week, and exercise intensity (percent time spent exercising in HRR zones 3–5). Changes in concentrations of the hormonal mediators of appetite were assessed as pre–post differences in area under the curve (AUC) calculated via the trapezoidal rule. Differences in primary outcomes were tested via repeated measures two-way ANOVA to determine differences between groups, over time, and group–time interactions with sex and age included as covariates. Additional ANCOVA analyses were performed assessing changes over time and between groups for changes in body weight and FM, both as percent change and raw values. Bivariate correlation analysis was used to assess correlates of CI and body fat loss. Linear regression analyses were used to predict CI and percent body fat loss using leptin delta-AUC, ghrelin delta-AUC, exercise group (exercise frequency), time spent exercising per week, ExEE per week, and exercise intensity as independent variables. All analyses were performed in IBM SPSS Version 26 (IBM Corporation, Armonk, NY).

Power Analysis: We chose to power the present study to detect significant differences in body fat loss between groups to draw conclusions regarding energy compensation in a clinically relevant scenario, that is, a scenario in which individuals who are overweight to obese decrease body weight. Our previous study (18) demonstrated significant differences (1.7 kg) in body fat loss between groups exercising at 3000 kcal·wk^{-1} versus 1500 kcal·wk^{-1} for 12 wk with the 3000-kcal group decreasing significantly from baseline (−2.6 kg). Using an 80% power and 95% confidence level, 13 participants per group were needed to detect a significant change in body fat loss between groups with a standard deviation of 2.3. An alternative scenario would be to power the study based off of Rosenkilde et al. (15), who demonstrated significant differences between exercise groups in CI (−83% for high dose group and +20% for low dose group) with a pooled SD of 70.397. Using an 80% power and 95% confidence level, eight participants per group would be needed to detect significant differences in CI between groups.

RESULTS

Baseline characteristics are presented in Table 1, with no differences in BMI, age, VPA, REE/kg FFM, RQ, or $\dot{V}O_2$ max between groups. Participants in the 2-d·wk^{-1} group expended on average 745.33 ± 61.04 kcal per session, whereas the 6-d·wk^{-1} group expended 460.37 ± 26.04 kcal per session, mean ± SE, which was different ($P < 0.01$) between groups as expected. All exercise training-induced variables are presented in Table 2, with differences in weekly ExEE, time spent exercising, and percent body fat loss between groups. Both

TABLE 2. Resulting data from the exercise intervention between groups that exercised.

	6 d·wk^{-1} Group N = 15	2 d·wk^{-1} Group N = 17	All Participants N = 32
Exercise time/week[a] *	320.5 ± 20.40	188.8 ± 12.00	249.41 ± 16.85
% Time in zone 3–5[b]	47.73 ± 6.13	52.31 ± 4.62	50.32 ± 3.69
% Time in zone 1–2[c]	52.11 ± 5.68	47.69 ± 4.62	49.67 ± 3.69
ExEE/week[d]*	2753.5 ± 144.9	1490.7 ± 122.1	2041.68 ± 150.8
Kcal compensated/week[e]	1309.86 ± 274.5	715.42 ± 268.6	961.39 ± 198.7
Total exercise time[f]	3944.2 ± 242.8	2265.4 ± 143.4	2992.9 ± 202.2
Total ExEE[g]	33,091 ± 2112.8	17,562 ± 1547.7	24,291 ± 1895.0
Total kcal compensated[h]	15,718 ± 3294.1	8585.0 ± 3223.0	11,537 ± 2384.2
AEB[i]	–16,789 ± 3589.8	–8977.3 ± 3515.3	–12,363 ± 2586.7
CI[j]	55.43 ± 10.16	49.31 ± 20.56	50.25 ± 12.27
kg Weight loss[k]	–1.04 ± 0.45**	–0.76 ± 0.60	–0.59 ± 0.38
% Weight loss[l]	–1.48 ± 0.64**	–0.84 ± 0.66	–1.09 ± 0.45
kg Body fat loss[m,*]	–1.82 ± 0.39**	–0.64 ± 0.44	–0.58 ± 0.34
% Body fat loss[n,*]	–7.70 ± 2.04**	–1.86 ± 1.27	–4.43 ± 1.30
Delta REE/kg FFM[o]	1.06 ± 0.94	–1.45 ± 1.08	–0.38 ± 0.81
Delta RQ[p]	–0.11 ± 0.06	–0.09 ± 0.07	–0.09 ± 0.04

Data are mean ± SE, only individuals who completed intervention included.
*Significantly different between groups, $P \leq 0.05$.
**Significant change over time (change different from zero) $P \leq 0.05$.
Note: control group (N = 12) increased % weight change (+0.78 ± 1.19) and kg body weight (+0.40 ± 0.99) which was not different from exercise groups. The control group increased % fat change (+4.20 ± 2.82) and kg fat change (+0.98 ± 0.79) both different from 2- and 6-d groups ($P < 0.05$).
[a]Amount of time (in minutes) spent exercising per week.
[b]Percentage of time exercising spent in HR zones 3, 4, or 5 (70%–100% HRR).
[c]Percentage of time exercising spent in HR zones 1 or 2 (50%–69% HRR).
[d]Exercise energy expenditure (in kilocalories) per week.
[e]Energy (in kilocalories) compensated for each week calculated by adding AEB and total ExEE together and dividing by 12.
[f]Total amount of time spent exercising during the entire 12-wk intervention, in min.
[g]Total ExEE of the 12-wk intervention, in kcal.
[h]Total amount of kcal compensated, calculated by adding AEB and total ExEE together.
[i]Calculated from changes in bodily energy stores (changes in fat and lean mass) converted to kilocalorie equivalents.
[j]CI: percentage of kilocalories compensated for, calculated as (ExEE + AEB) / ExEE.
[k]kg of total body weight lost after the 12-wk intervention.
[l]kg of weight loss/baseline body weight in kg.
[m]kg of body fat lost after the 12-wk intervention.
[n]kg of body fat loss / baseline body fat in kg.
[o]Changes in REE per kg of FFM from baseline to post (post value minus baseline value).
[p]Changes in respiratory quotient during rest from baseline to post (post value minus baseline value).

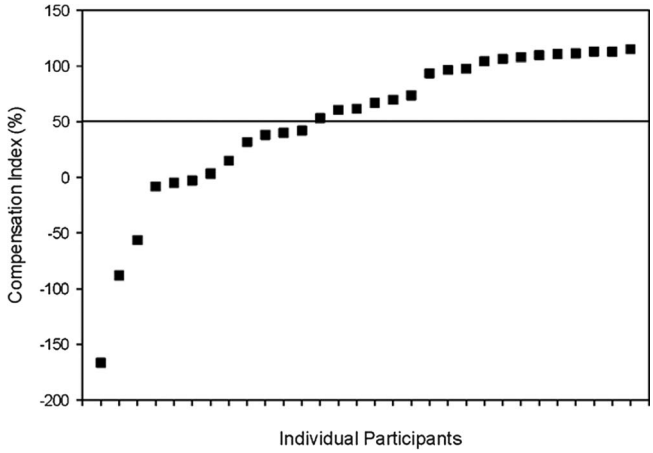

FIGURE 1—Plot of CI values. Each point represents an individual participant. Y values are CI expressed as a percentage (% kcal compensated for). The *solid black line* is the mean.

total and percent body fat and body weight changed (decreased) over time for the 6-d·wk^{-1} group but not in the 2-d·wk^{-1} group or control. These changes held when controlling for age and sex (ANOVA) and when controlling for baseline values (ANCOVA). The control group gained 0.98 ± 0.79 kg (4.20% ± 2.82%) body fat, which was significantly different ($P < 0.04$) from both exercise groups. The increases in total body weight of the control group (0.40 ± 0.99 kg and 0.78% ± 1.19%) were not significantly different from either exercise group. These results did not change when covarying for baseline body fat or total mass, sex, or age. Changes RQ and REE were not different between groups or over time when assessed as raw values or per kg FFM. Neither CI nor total kcal compensated per week was different between groups. Figure 1 presents a plot of individual CI values, indicating a large individual variation and a mean CI of 50%. Table 3 presents changes in AUC for the hormonal mediators of hunger, with only leptin demonstrating significant changes between groups and over time. Compensation index was positively correlated with leptin delta AUC. Percent body fat loss was positively correlated with ghrelin and leptin delta AUC, and percent time spent exercising in HR zones 3 to 5. Percent body fat loss was negatively correlated with ExEE and time spent exercising per week.

Linear regression results are presented in Tables 4 and 5 predicting CI and percent body fat lost, respectively. Full models include all dosing variables and others correlated with the dependent variable. Reduced models are presented with only significant predictors. Leptin delta AUC was the only independent predictor of CI, whereas ExEE per week and ghrelin delta AUC were the only independent predictors of percent body fat loss.

DISCUSSION

The present study's hypothesis that less frequent exercise would evoke a reduced compensatory response compared with frequent exercise did not hold, in that both groups compensated similarly. The ever-present obesity epidemic is indication that weight loss and weight loss maintenance will continue to be of prime importance as the vast majority of individuals are not meeting these weight loss needs. Compensatory responses that defend against a negative energy balance can be dichotomized into two types, behavioral or automatic (5). Automatic compensatory responses are those in which humans have little control over, such as lowering metabolic rate, or REE, when faced with an energy deficit. Behavioral

TABLE 3. Changes in AUC calculations (12-wk minus baseline) for concentrations of acylated ghrelin, leptin, insulin, and GLP-1 from prebreakfast (fasting) to 3 h postprandial with samples taken before eating and every 15 min thereafter for the first hour and every 30 min for the second hour.

	6 d·wk^{-1} Group	2 d·wk^{-1} Group	Control
Ghrelin ΔAUC	–5321.99 ± 4304.09	1778.38 ± 2114.07	–4028.67 ± 2440.11
Leptin ΔAUC	–998.57 ± 414.16*,**	–604.53 ± 617.98*	1118.31 ± 650.77*
Insulin AUC	–1090.49 ± 759.40	410.80 ± 625.16	315.39 ± 1184.69
GLP-1 AUC	–27.10 ± 20.85	–19.12 ± 22.86	–25.90 ± 12.85

*Significant differences between groups, $P \leq 0.05$.
**Significantly different from zero (change from baseline is significant) $P \leq 0.05$.
GLP-1, glucagon-like peptide 1.

TABLE 4. Regression models predicting CI among participants who exercised as control participants did not have values for CI.

Effect	β	SE	P	Partial Correlation[a]
Full model of all predictors				
Intercept	47.87	27.85	0.10	
Leptin[a] ΔAUC	0.01	<0.01	<0.01	0.60*
Exercise frequency[b]	23.98	23.01	0.17	0.31
Exercise time/week[c]	–0.13	0.11	0.24	–0.27
ExEE/week[d]	0.13	0.02	0.47	0.17
% Time in zones 3–5[e]	0.09	0.35	0.81	0.06
% body fat lost[f]	5.79	1.25	<0.01	0.73*
Reduced model of significant predictors				
Intercept	86.42	7.05	<0.01	
Leptin[a] ΔAUC	0.01	<0.01	<0.01	0.64*
% body fat lost[g]	4.28	0.88	<0.01	0.71*

Partial correlations also displayed.
*Significant correlation.
[a]Partial correlation coefficient between each independent variable and CI, controlling for other independent variables.
[b]Changes in AUC for changes in concentrations of leptin premeal (fasting) to 2 h postprandial.
[c]Participants were randomly assigned to exercise 6 or 2 d·wk^{-1}.
[d]Amount of time (in minutes) spent exercising per week.
[e]Exercise energy expenditure (in kilocalories) per week.
[f]Percentage of time exercising spent in HR zones 3 to 5 (70%–100% HRR).
[g]kg of FM lost/baseline kg fat mass.

compensatory responses, on the other hand, are those in which individuals have control over, such as increasing energy intake, which many agree to be the primary compensatory responses when the body is faced with an energy deficit induced by exercise (5). Limiting the compensatory responses induced by exercise would, in effect, make exercise a more viable option for weight loss and reduce the prevalence of obesity, although there are still questions regarding the mechanisms controlling these responses and their overall contribution to the total compensatory response. We are also uncertain how different parameters of an exercise program may influence mechanisms proposed to control these responses and their relative contribution to the overall compensatory response. The present investigation provides insight into some of these questions, with the primary finding that energy compensation is not influenced by exercise dose, rather, greater energy expenditures (approaching 3000 kcal·wk^{-1}) are needed to overcome this compensatory response to produce significant reductions in body fat. We have also demonstrated important roles reducing leptin and ghrelin concentrations may have on energy compensation and body fat loss.

In agreement with our previous study (18), the current findings indicate that individuals compensate for approximately 50% of the kcal they expend through exercise, regardless of exercise dose. Exercise dose, in the present analysis, was conceptualized as frequency (number of sessions per week), duration of exercise (time spent exercising per week), exercise intensity (% time spent exercising at HR zones 3–5), and weekly ExEE. When including each of these variables as an independent variable in a regression model predicting CI or total kcal compensated, none of these exercise dose variables influenced the compensatory response. This finding was very similar to our previous work, where participants compensated for approximately 50% of their kcal, equating to 1000 kcal·wk^{-1}, with no difference between groups that differed in ExEE (18). In the present study, we also demonstrated the compensatory response not relative to exercise energy expenditure (total kcal per week) was not different between groups, averaging 961 kcal·wk^{-1}, which was similar to our previous work where groups differing in ExEE compensated 943 and 1007 kcal·wk^{-1} (18). However, in the present study, the between-group differences in kcal compensated per week (594 kcal) was much larger than the 64-kcal·wk^{-1} difference between groups observed in (18). This difference between groups in the present study would equate to 84.9 kcal·d^{-1}, which may be clinically significant, likely influencing changes in body FM if the intervention was longer than 12 wk. Another possibility, due to the variance of over 200 kcal for each group, is that a greater sample size would be needed to determine differences in this metric. Future studies assessing energy compensation may improve on this by using longer interventions and a greater sample size to better answer these questions.

Because groups in the present study differed in both exercise frequency and ExEE, we are not able to draw conclusions on between group differences on either of these variables in isolation. Although similar to our previous work, only the group with greater ExEE lost significant amounts of body fat, indicating that greater energy expenditures are able to overcome, at least partially, the compensatory response to an exercise-induced energy deficit to produce weight loss. This is at odds with Rosenkilde et al. (15), who demonstrated that expending either 1800 or 3600 kcal during exercise per week produced nearly identical energy deficits after 12 wk due to the greater CI observed in the 3600-kcal group. Results from the large Examination of Mechanisms of Exercise-Induced Weight Compensation (E-MECHANIC) study offers additional insight with high-volume group (ExEE of 20 kcal·kg^{-1} body weight) compensating significantly more than the low-volume group (8 kcal·kg^{-1} body weight); however, weight loss was greater in the 20-kcal·kg^{-1} group compared with the 8-kcal·kg^{-1} (−1.6 vs −0.4, respectively, $P = 0.02$) (27). These

TABLE 5. Regression models predicting percent body fat loss among participants who exercised as control participants did not have values for many independent variables/predictors.

Effect	β	SE	P	Partial Correlation[a]
Full model of all predictors				
Intercept	5.62	4.78	0.26	
Leptin[a] ΔAUC	<0.01	<0.01	0.07	0.43
Ghrelin[b] ΔAUC	<0.01	<0.01	0.03	0.50*
Exercise frequency[c]	0.23	4.00	0.95	0.01
Exercise time/week[d]	0.02	0.02	0.22	0.29
ExEE/week[e]	–0.01	0.03	0.05	–0.45*
% Time in Zone 3–5[f]	0.07	0.06	0.31	–0.25
Reduced model of significant predictors				
Intercept	5.80	3.19	0.08	
Ghrelin[b] ΔAUC	<0.01	<0.01	<0.03	0.44*
ExEE/week[e]	–0.01	<0.01	0.01	–0.54*

Partial correlations also displayed.
*Significant correlation.
[a]Partial correlation coefficient between each independent variable and CI, controlling for other independent variables.
[b]Changes in AUC for changes in concentrations of leptin premeal (fasting) to 2 h postprandial.
[c]Changes in AUC for changes in concentrations of Acylated Ghrelin premeal (fasting) to 2 h postprandial.
[d]Participants were randomly assigned to exercise 6 or 2 d·wk^{-1}.
[e]Amount of time (in minutes) spent exercising per week.
[f]ExEE (in kilocalories) per week.
[g]Percentage of time exercising spent in HR zones 3 to 5 (70%–100% HRR).

results partially support both present findings, that greater exercise energy expenditures are needed to produce weight loss, and those of Rosenkilde et al. that greater ExEE instigates greater compensation. The ExEE of E-MECANIC study participants was about 1760 and 700 kcal·wk^{-1} for the 20- and 8-kcal·kg^{-1} groups, respectively, much lower than the current study which averaged 2753 and 1491 for the 6-d and 2-d groups, respectively, and the 3000 and 1500 ExEE groups as in Flack et al. (18). The larger dose (3600 kcal·wk^{-1} vs 1800 kcal·wk^{-1}) and larger differences in ExEE between groups (1800 kcal) Rosenkilde et al. (15) used may explain some of the discrepancies. It is possible that there may be a point at which greater levels of ExEE do not additionally contribute to weight loss, rather, disproportionately influence energy compensation. Future research may benefit from assessing the compensatory responses to 4000 to 5000 kcal·wk^{-1} to investigate this possibility.

An additional objective of the present study was to investigate possible mechanisms contributing to the compensatory response, focusing on automatic metabolic adaptations (changes in REE and substrate utilization) and factors that may influence energy intake (concentrations of hormonal mediators of hunger/satiety both fasting and in response to a meal). Correlation analysis indicated that CI was positively correlated with leptin delta AUC, indicating that less compensation was linked to greater reductions in leptin AUC. Because leptin is an anorexigenic hormone, greater reductions in leptin concentrations would be expected to produce less satiety and promote greater energy intake. However, the present results demonstrate that reductions in leptin predict less energy compensation even when controlling for ExEE, exercise intensity, weekly exercise time, exercise frequency (group), and body fat loss (Table 4). These findings, what may seem to be counterintuitive, actually support recent work by Zhao et al. (28), who through a series of experiments using a rodent model demonstrated partial leptin reductions restore leptin sensitivity in hypothalamic neurons, reducing food intake and protecting mice from diet-induced obesity. It is possible that greater leptin sensitivity resulted from exercise- or weight loss-induced reductions in leptin to promote less energy compensation in our sample. This is, as far as we know, is the first study to demonstrate such an effect in humans, supporting findings from animal literature and potentially opening new research questions and treatment options that may work to reduce energy compensation with exercise.

There were no other correlations with CI, which was reflected in none of the variables for exercise dose (frequency, weekly exercise time, ExEE, exercise intensity) being a significant predictor or interfering with the predictive ability of leptin delta AUC. Changes in REE or RQ were not correlated nor different between exercise groups or sedentary control, supporting work from the E-MECHANIC study (27) and our previous findings that changes in REE or RQ do not significantly contribute to the compensatory response with exercise (18). These findings seem to undermine the impact of automatic metabolic compensatory mechanisms on the overall compensatory response; however, these negative findings may also be due to methodological shortcomings. Work by Weigle et al. (29) demonstrated that, after weight loss, REE was 97% of that predicted, whereas non-REE was only 76%, indicating the energy saving metabolic effects in the reduced obese state occurred primarily through non-REE. It, therefore, appears metabolic compensatory responses need to be assessed by more than REE and include assessments of skeletal muscle efficiency during physical activity and total energy expenditure. Indeed, many have demonstrated changes in skeletal muscle metabolism after weight loss that coincide with lower energy expenditures for a given workload as a mechanism to conserve energy expenditure after weight loss (14,30). Future studies would, therefore, benefit from these additional assessments to further eludicate metabolic adaptations caused by a negative energy balance.

Percent body fat loss was positively correlated with ghrelin and leptin delta AUC, indicating greater increases in ghrelin and leptin AUC were correlated with increasing changes in percent body fat (less negative losses or gains in body fat). Percent body fat loss was also positively correlated with percent of exercise time spent in HR zones 3 to 5 and negatively correlated with ExEE and time spent exercising per week. The finding that percent body fat loss decreased (more negative) as time spent exercising and ExEE increased supports what we deduced from the between group differences and regression models predicting CI as discussed, that greater energy expenditures are not completely compensated for and thus promote body fat loss. This is further supported in the regression analysis where weekly ExEE was a significant independent predictor after accounting for all other relevant variables, including time spent exercising and exercise frequency. It is not surprising that weekly ExEE is the only dose variable that independently predicts body fat loss as ExEE is a product of the all the other dose variables. It is interesting that a greater percentage of exercise time spent in HR zones 3 to 5 are associated with a less favorable change in percent body fat; however, this dosing variable was no longer a significant predictor when included in the linear regression analysis, which was also the case with leptin delta AUC leptin. Ghrelin delta AUC, on the other hand, proved to be an independent predictor of percent body fat loss when included in the both the full and reduced regression models (Table 5), indicating that greater attenuation in ghrelin concentrations from fasting to 3 h postprandial independently predicts greater percent body fat loss. Similar findings have been observed, where reductions in postprandial ghrelin concentrations resulted from exercise-induced weight loss (7); however, we believe this is the first time reductions in ghrelin have been subscribed to exercise-induced body fat loss while controlling for exercise dose. There are a few possible explanations for this result, one being centered on ghrelin's well-known role as an orexigenic hormone. Individuals who experienced greater declines in ghrelin are likely to be less hungry, especially postprandially, and more likely to curb their energy intake. An additional mechanism that may be at play may involve ghrelin's role in reward-based feeding (31), increasing the

neural response to food in the amygdala, orbitofrontal cortex, hippocampus, striatum, and ventral tegmental area (32–34). These brain regions are involved in reward processing and hedonic feeding, influencing central dopamine release to modulate the rewarding value of food (32). Ghrelin may also shift food preferences toward diets rich in fat (35,36) or high in sugar (37), which is in line with the fact that foods considered highly reinforcing, that is, able to promote feelings of craving or wanting, are high in fat and/or sugar (38). The current study cannot determine which (homeostatic drive for eating or hedonic/reward-mediated feeding) or if a separate, not yet understood, role of ghrelin is at play. Additionally, much of the literature on ghrelin's role in reward-driven feeding has been specific to animal models and yet to be translated to humans. The present study serves as initial evidence that reducing concentrations of ghrelin are important for successful body fat loss from an exercise program. This could promote future research involving dopamine antagonists to be used in conjunction with exercise as a weight control strategy.

This study is not without limitations. Use of doubly labeled water would be the most robust method to evaluate energy expenditure and deduce energy intake from comparing expected to actual body composition changes. Similarly, *ad libitum* energy intake would be best assessed in an inpatient feeding design where all of participants' meals and snacks are consumed in a controlled environment and recorded by research staff to prevent the known underreporting that often occurs with self-reported dietary intake. Without an assessment of dietary intake, the present study does not have an exact amount of energy participants compensated with via increases in dietary intake. As noted previously, the present study, and many others, only assessed REE and resting RQ to deduce the metabolic compensatory response. Additional assessments of the thermic effect of food and skeletal muscle efficiency would be valuable assessments to include in future studies. Because the present study lacked these assessments, it is not equipped to determine the exact amount of energy compensation resulting from automatic/metabolic responses or volitional/behavioral responses. Large-scale, controlled feeding studies utilizing doubly labeled water are needed to quantify the exact amount of energy compensated for by specific mechanisms, an exciting area for future research.

Additionally, stage of menstrual cycle was not accounted for among female participants, which may be important as recent reports indicate that, relative to the follicular phase, energy intake is increased during the luteal phase when progesterone levels are increased (39). This may have influenced energy intake and caused unaccounted for variations in energy expenditure, thus altering the calculated compensatory response for some participants. Twelve of the 36 female participants randomized at baseline reported taking oral contraceptives, although differences in dose, classification and unknown compliance make it difficult to draw conclusions on the true influence varying levels of progesterone and estrogen may have had in the compensatory response. Future research may include assessments of these hormones to determine if they could be a factor in energy compensation to aerobic exercise. The unsupervised nature of the exercise program may also be considered a limitation as participants could have exercised for additional time while not recording it (did not start watch), although we have no reason to believe this occurred. Lastly, of the 44 participants who completed the current study, 40 were white (one Pacific Islander, one Asian, two African American), thus limiting the generalizability to other race/ethnic groups. This study also was not designed to detect sex differences and included an unbalanced sample of women; thus, sex effects cannot be drawn.

CONCLUSIONS AND FUTURE DIRECTIONS

There are three primary findings from the present study that may set forth additional research in the realm of obesity treatment through exercise. First, in agreement with our previous work (18), this study demonstrates individuals do not increase their energy compensation with greater doses of exercise. This lack of significant compensation was observed as neither CI (energy compensation proportional to energy expended) or total energy compensated differed between groups. Rather, the greater dose of the 6-d·wk^{-1} group was needed to produce appreciable fat loss with exercise. This is an important consideration for exercise prescription when the goal is to reduce body fat. Current recommendations state that exercise programs should exceed 225 min·wk^{-1} to induce clinically significant weight loss (40); however, the average weekly exercise time for all participants was just over 249 min, producing nonsignificant decreases in percent body fat loss. The 6-d·wk^{-1} group exercised more than 320 min·wk^{-1} to experience significant decreases in body fat. Therefore, the results of the present study suggest current recommendations for exercise to promote weight loss may be inadequate and should be closer to 300 min·wk^{-1} to overcome the approximately 1000-kcal·wk^{-1} compensatory response that accompanies exercise. Although more research in this area is needed to definitively make such recommendations. Future research could involve using greater doses of exercise as it is uncertain if exercise energy expenditures greater than 3000 kcal·wk^{-1} range would instigate a different compensatory response or act on a different mechanism for energy compensation.

The second and third primary findings revolve around important predictors of energy compensation and body fat loss with exercise. For the first time, we demonstrated that reductions in postprandial leptin concentrations influence energy compensation when controlling for all relevant exercise dose variables. This supports what has only recently been observed in rodents, that reducing leptin concentrations can restore leptin sensitivity in hypothalamic neurons and reduce food intake (28), this is a novel mechanism that has yet to be investigated further in humans but may offer potential for future pharmacological treatment that may be used in conjuncture with exercise. Additionally, it appears reductions in postprandial ghrelin concentrations are an important predictor of body fat loss, regardless of exercise dose. It is uncertain if reductions

in ghrelin are working to reduce the appetitive drive to consume food or acting on the reward centers in the brain to decrease the rewarding value of eating. In either case, and similar to leptin, pharmacological treatments that reduce ghrelin may exert additional benefits when coupled with exercise, and thus offering an area for future research.

It is evident, based on the lack of improvement in the present obesity epidemic, that more effective weight-loss treatment strategies are needed. Exercise is commonly prescribed as a treatment option; however, the multi-faceted, complex nature of exercise necessitates careful prescription and consideration for all and interacting variables that may influence the weight loss response. The current findings provide some clarity on relevant variables and set the stage for future research that may further elucidate the role exercise may have or increase its utility in obesity treatment.

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