Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Physiological Predictors of Weight Regain at 1-Year Follow-Up in Weight-Reduced Adults with Obesity

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Objective: This study aimed to assess whether changes in resting metabolic rate (RMR), exercise-induced energy expenditure (EIEE), and appetite following weight loss (WL) are associated with weight regain at 1 year.

Methods: Thirty-six adults with obesity underwent 8 weeks of a very-low-energy diet, followed by 4 weeks of refeeding and a 1-year maintenance program. RMR, EIEE, appetite ratings, and active ghrelin, peptide YY, glucagon-like peptide-1, cholecystokinin, and insulin concentrations were measured at baseline, week 13, and 1 year.

Results: A 17% WL (–20 ± 5 kg [mean ± SD]; range: –11.7 to –32.2 kg; $P < 0.001$) was achieved at week 13. After 1 year, weight regain was 2.5 ± 9.0 kg (not significant), ranging from –18.2 to 22.5 kg. Both fat mass and fat-free mass were reduced at week 13 (–17.9 ± 4.8 and –2.9 ± 2.7 kg, respectively; $P < 0.001$), while only loss of fat mass was sustained at 1 year. WL was associated with reduced RMR, EIEE, and fasting/postprandial insulin (all $P < 0.001$), as well as increased fasting hunger ($P < 0.01$) and fasting/postprandial active ghrelin ($P < 0.001$). There were no significant correlations between changes in RMR, EIEE, or appetite with WL and weight regain at 1 year.

Conclusions: No clear evidence emerged that changes in RMR, EIEE, or appetite following WL can predict weight regain at 1 year, but larger studies are needed to confirm these results.

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Introduction

The largest challenge in obesity management is not to achieve a clinically relevant weight loss (WL) but to maintain a reduced body weight in the long term (1). The majority of adults with obesity experience significant weight regain with some relapsing to their original weight (1-3). It is well established that diet-induced WL is accompanied by several physiological changes on both sides of the energy balance equation (4,5), with an upregulated appetite (6,7), despite a significantly reduced total energy expenditure (TEE) (8). Diet-induced WL was shown to reduce TEE because of a decrease in both resting and nonresting energy expenditure, as a result of reduced body mass and enhanced metabolic efficiency (8). Additionally, hunger feelings and the plasma concentration of the orexigenic hormone ghrelin increase, whereas satiety has been reported to be reduced (5,9). The reduction in resting metabolic rate (RMR) seen with WL may be attenuated after a period of weight stabilization (8). However, the reduction in TEE (falling below predicted values in some individuals, a mechanism known as adaptive thermogenesis), as well as the increase in hunger feelings and ghrelin secretion, appears to persist in the long term (6,10,11).

It has been repeatedly suggested that the physiological adaptations to WL are part of a compensatory response that opposes the reduced-weight state and stimulates weight regain (4,5,9,12,13). However, the weight-regain-promoting actions of the "compensatory mechanisms" are largely speculative because evidence demonstrating a causal relationship between the reduced energy expenditure, or increased appetite, seen with WL and weight regain is lacking. More studies are needed to elucidate whether the changes in appetite and energy expenditure that occur with WL contribute to weight regain in the long term. Therefore, the aim of this analysis was to assess whether changes in RMR, exercise-induced energy expenditure (EIEE), subjective appetite feelings, and plasma concentration of appetite-related hormones observed with WL are associated with weight regain at 1 year in adults who had undergone diet-induced WL.

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Methods

Participants

The study protocol initially included 54 adults with obesity (39 females; 40 ± 10 years; mean BMI 37 ± 4 kg/m^2) recruited from the local community of Trondheim, Norway, through blogging and advertisements in the local newspaper. The protocol used for this study was approved by the regional ethical committee (reference number 2012/1901), and the study was conducted according to the Declaration of Helsinki. All participants signed an informed consent before participation. Participants had to be weight stable (< 2-kg change over the previous 3 months), not be dieting to lose weight, and with a sedentary lifestyle. Exclusion criteria were pregnancy, breastfeeding, clinically significant illness (including diabetes), previous WL surgery, and/or taking medication known to affect appetite/metabolism or induce WL.

Study design

This was a longitudinal intervention study with repeated measurements. Participants underwent an 8-week supervised very-low-energy diet (VLED), followed by a 4-week refeeding phase and a 1-year weight-maintenance program. This analysis represents a secondary analysis of the main study (14).

Detailed protocol

WL phase. For 8 weeks, participants followed a VLED (Allévo, Karo Pharma AS, Stockholm, Sweden) with 550 and 660 kcal/d for females and males, respectively (carbohydrates 42%, protein 36%, fat 18%, and fiber 4%), plus no-energy fluids and low-starch vegetables (maximum 100 g/d). For more information regarding this phase, please see Nymo et al. (14).

At week 9, participants were gradually reintroduced to normal food while withdrawing from the VLED products. An individual diet plan was prescribed by a trained dietician and was tailored to individual energy requirements (measured RMR × physical activity [PA] level [extracted from individual PA monitors used at week 8; SenseWear, BodyMedia, Pittsburgh, Pennsylvania]), with 15% to 20% protein, 20% to 30% fat, and 50% to 60% carbohydrates, according to the Nordic nutritional guidelines (15), aimed at weight stabilization. VLED products were stopped at the end of week 10.

Participants were asked not to change their PA levels during this phase of the study. To check for compliance, participants were asked to wear armbands (SenseWear) for 7 days at baseline and at weeks 8 and 12 (week 13). These data were considered valid if the participants wore the device for ≥ 4 days, including at least one weekend day, more than 95% of the time (16).

Weight-maintenance phase. A 1-year follow-up program aimed at WL maintenance (WLM) was offered from week 13. The diet plan provided at week 13 was revised and tailored to individual needs by a trained dietician taking into account individual energy requirements (measured RMR × PA level at week 12). The multidisciplinary follow-up program included regular individual and group-based sessions, focusing on nutritional counseling, PA, and cognitive behavioral therapy.

Measurements

All measurements were conducted after a 12-hour overnight fast. Participants were asked not to drink caffeine, to abstain from taking any nicotine for 12 hours, and not to perform moderate to vigorous PA for 24 hours prior to measurements. Data were collected at baseline, week 13, and 1 year for both weight and body composition (measured with air-displacement plethysmography [BOD POD, COSMED, Albano Laziale, Italy]) and at baseline and week 13 for other measures.

RMR. RMR was measured by indirect calorimetry (Vmax Encore 29N; Care Fusion, Baesweiler, Germany) using a canopy system and standard operating procedures (17).

EIEE. EIEE was measured by graded cycle ergometry (Monark Eromedic 839E; GIH, Vansbro, Sweden) 3 hours after a standardized breakfast. Participants pedaled at 60 rpm against graded resistance to generate 10, 25, and 50 W of power in sequential 4-minute intervals. Gas exchange was measured continuously using a fitted face mask by indirect calorimetry (Vmax Encore 29N), and the average of the last 2 minutes at each stage was used for analysis. Net EIEE was calculated by subtracting RMR (kilocalories per minute) from the gross EIEE as previously described (18).

Appetite measurements. Subjective appetite feelings (hunger, fullness, desire to eat, and prospective food consumption) were measured with a 10-cm visual analogue scale (19), and blood samples for the analysis of appetite-related hormones (active ghrelin [AG], active glucagon-like peptide 1 [GLP-1], total peptide YY [PYY], cholecystokinin [CCK], and insulin) were collected in fasting and every 30 minutes after a standardized breakfast (600 kcal: 17% protein, 35% fat, and 48% carbohydrates) for 2.5 hours. Plasma samples were analyzed for AG, active GLP-1, total PYY, and insulin using a Human Metabolic Hormone Magnetic Bead Panel (LINCOplex Kit; Millipore, St. Louis, Missouri) and for CCK using an "in-house" radioimmunoassay (RIA) method as previously described (20) (intra- and interassay coefficient of variation were < 10% and < 20% for AG, active GLP-1, and total PYY; < 10% and < 15% for insulin; and < 5% and < 15% for CCK, respectively).

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 23 (IBM Corp., Armonk, New York), and data are presented as mean ± SD. Statistical significance was set at $P < 0.05$ for changes over time in energy expenditure and appetite variables. For correlation and regression analysis, a more conservative significance value of $P < 0.01$ was used to account for the large number of tests performed and to reduce the likelihood of false positives. Area under the curve (AUC) for fullness feelings and secretion of appetite-related hormones was calculated with the trapezoid rule from 0 to 150 minutes after the standardized breakfast. Changes in appetite and energy expenditure variables with WL (baseline to week 13) were assessed by paired *t* tests or nonparametric alternatives for non-normal distributed data. Correlation analysis between weight regain (calculated as percent change in body weight between week 13 and 1 year) and percent changes in energy expenditure and appetite variables as a result of WL (baseline to week 13) were performed by Pearson or Spearman correlation for normal and non-normal distributed variables, respectively. In addition, linear regression assessed the potential predictive factors concerning weight regain, using weight regain (percentage) as outcome variable and percent changes in energy expenditure and appetite variables with WL as potential predictors. The results are presented as regression coefficients (β), with a 95% confidence interval (CI) and *P* value for

linear regressions of weight regain on each predictor separately, after adjusting for age, sex, and magnitude of WL (baseline to week 13 [kilograms]). All analyses are for completers only, as defined by participants with data at baseline, week 13, and 1 year.

Results

Of the 54 participants who started the study, 48 provided data at week 13 (2 withdrew due to family-related illness, 2 did not tolerate the VLCD, 1 was excluded because of consumption of extra foods, and 1 was lost to follow-up). A total of 36 (26 males) provided data at the 1-year follow-up (1 withdrew for personal reasons, 2 withdrew because of their own or family-related illness, 2 withdrew because of work constraints making it difficult to return for measurements, and 7 were lost to follow-up). No differences in baseline characteristics were found between those who completed and those who withdrew from the study. Changes in body weight and body composition are shown in Table 1. A 17.1% ± 2.9% WL (–20.0 ± 5.0 kg; $P < 0.001$) was measured at week 13, with no significant weight regain between week 13 and 1 year at the group level (2.5 ± 9.0 kg; $P = 0.112$); however, there was substantial individual variability (range: –18.2 to 22.5 kg). At 1-year follow-up, 30 out of the 36 participants had WL of at least 10% of baseline weight. Fat mass was significantly reduced at week 13 (–17.9 ± 4.8 kg; –10.3% ± 4.6%; $P < 0.001$ for both), with no significant change between week 13 and 1 year. Fat-free mass (kilograms) decreased between baseline and week 13 (–2.9 ± 2.7 kg; $P < 0.001$) and increased between week 13 and 1 year (1.1 ± 2.0 kg; $P < 0.01$). Fat-free mass (percentage) was significantly increased at week 13 (10.3% ± 4.6%; $P < 0.001$), with no significant change between week 13 and 1 year.

Changes in energy expenditure and appetite variables with WL are reported in Table 2. WL was accompanied by a significant reduction in RMR and EIEE at 10 and 50 W (all $P < 0.001$) but not at 25 W. An

TABLE 1 Body weight and composition at baseline and changes over time

	Baseline	Δ Baseline to week 13	Range of Δ	*P* value	Δ Week 13 to 1 year	Range of Δ	*P* value
Weight (kg)	116.80 ± 19.95	–20.00 ± 5.00	(–11.70 to –32.20)	< 0.001	2.49 ± 9.02	(–18.20 to 22.5)	0.112
Weight (%)		–17.1 ± 2.93	(–9.22 to –22.9)	< 0.001	2.33 ± 8.93	(–21.66 to 21.11)	0.126
BMI (kg/m^2)	36.63 ± 4.33	–6.25 ± 1.28	(–3.46 to –9.61)	< 0.001	0.67 ± 2.73	(–6.33 to 6.29)	0.150
FM (kg)	48.39 ± 12.81	–17.9 ± 4.80	(–12.23 to –34.14)	< 0.001	2.33 ± 7.59	(–16.9 to 17.84)	0.083
FM (%)	41.69 ± 6.90	–10.27 ± 4.62	(–5.20 to –27.10)	< 0.001	1.11 ± 4.96	(–9.50 to 10.6)	0.195
FFM (kg)	67.08 ± 11.55	–2.91 ± 2.66	(2.83 to –7.99)	< 0.001	1.06 ± 1.98	(–3.24 to 5.65)	< 0.01
FFM (%)	58.30 ± 6.90	10.30 ± 4.60	(5.20 to 27.10)	< 0.001	1.13 ± 4.97	(–9.50 to 10.6)	0.188

Results presented as mean ± SD. $N = 36$ for all time points. Range: minimum and maximum values.
FM, fat mass; FFM, fat-free mass.

TABLE 2 Changes in energy expenditure and appetite variables from baseline to week 13 and from week 13 to 1 year

	Baseline	Δ Baseline to week 13	*P* value	Δ Week 13 to 1 year	*P* value
RMR (kcal/d)	1,730 ± 323	–146 ± 169	**< 0.001**	76 ± 181	0.016
RMR/FFM (kcal/d × kg)	25.63 ± 2.90	–1.11 ± 2.58	**0.015**	0.72 ± 2.68	0.121
Net EIEE 10 W (kcal/min)	2.78 ± 0.66	–0.60 ± 0.51	**< 0.001**	0.12 ± 0.40	0.103
Net EIEE 25 W (kcal/min)	3.46 ± 0.69	–0.14 ± 2.59	0.764	–0.25 ± 2.42	0.545
Net EIEE 50 W (kcal/min)	4.74 ± 0.78	–0.55 ± 0.70	**< 0.001**	0.11 ± 0.55	0.266
Fasting hunger (cm)	3.64 ± 2.02	1.39 ± 2.28	**< 0.010**	–0.49 ± 3.0	0.327
Fasting DTE (cm)	4.59 ± 1.98	0.57 ± 2.07	0.109	–0.72 ± 2.83	0.134
Fasting PFC (cm)	6.09 ± 2.35	–0.32 ± 2.55	0.457	–0.55 ± 2.31	0.164
AUC fullness (cm/min)	865.83 ± 258.4	74.58 ± 279.32	0.118	7.52 ± 230.00	0.845
Fasting AG (pg/mL)	85.61 ± 45.60	58.55 ± 55.48	**< 0.001**	–14.11 ± 49.79	0.113
Fasting insulin (pg/mL)	1,175 ± 587	–674 ± 568	**< 0.001**	26 ± 268	0.582
AUC AG (pg/mL × min)	8,539 ± 4,828	6,103 ± 6,231	**< 0.001**	–1,006 ± 4,808	0.245
AUC active GLP-1 (pg/mL × min)	1,181 ± 614	–32 ± 773	0.812	168 ± 6,948	0.182
AUC total PYY (pg/mL × min)	9,877 ± 5,445	–476 ± 4,251	0.581	–2,602 ± 5,429	0.028
AUC CCK (pmol/L × min)	3,359 ± 1,319	–29 ± 103	0.111	74 ± 134	**0.003**
AUC insulin (pg/mL × min)	581,771 ± 222,606	–266,895 ± 196,496	**< 0.001**	–12,732 ± 133,874	0.600

Results presented as mean ± SD. $N = 36$ at all time points. "Net": after subtracting RMR/min. Bold font indicates statistically significant findings.
AG, active ghrelin; AUC, area under the curve; CCK, cholecystokinin; DTE, desire to eat; EIEE, exercise-induced energy expenditure; GLP-1, glucagon-like peptide-1; PFC, prospective food consumption; PYY, peptide YY; RMR, resting metabolic rate; FFM, fat-free mass.

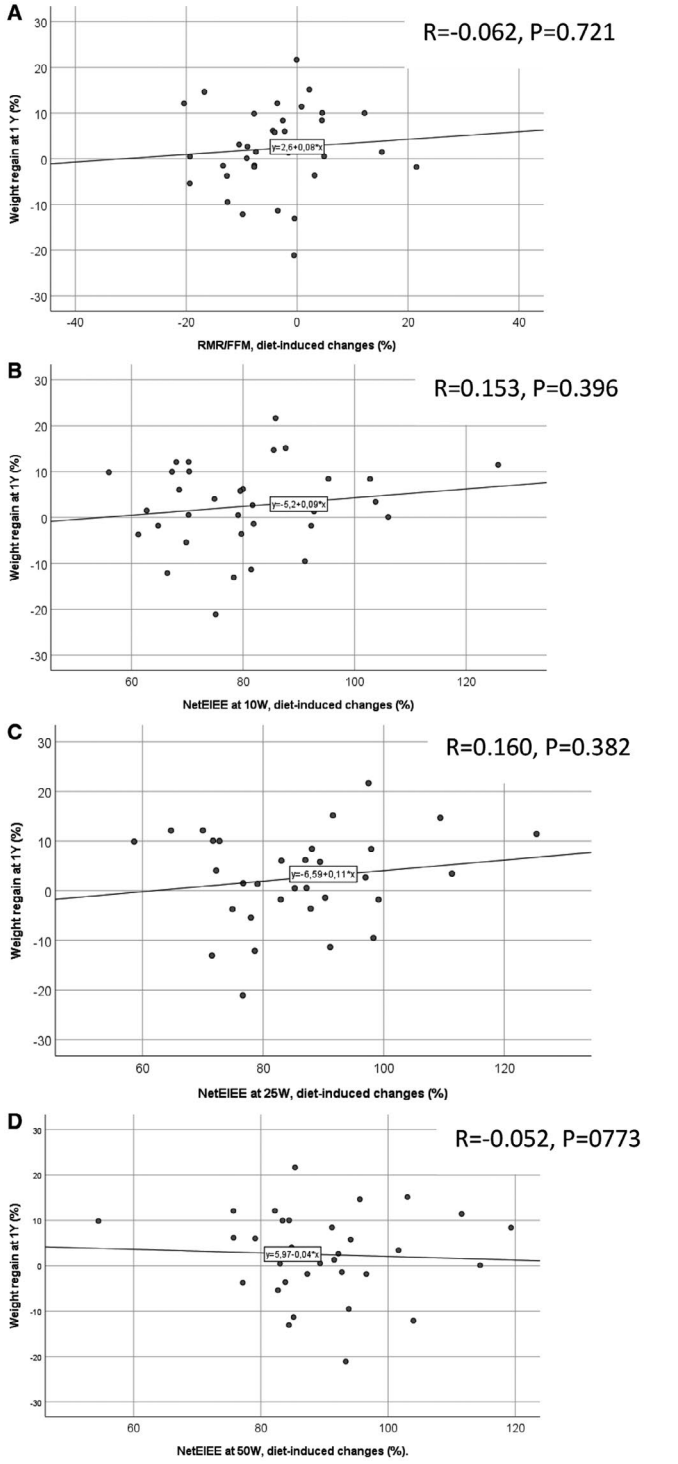

Figure 1 Association between diet-induced changes (%) in (**A**) hunger feelings in fasting, (**B**) fasting AG plasma concentration, (**C**) AG AUC, and (**D**) CCK AUC and percent weight regain at 1-year follow-up ($n = 34$). AG, active ghrelin; AUC, area under the curve; CCK, cholecystokinin.

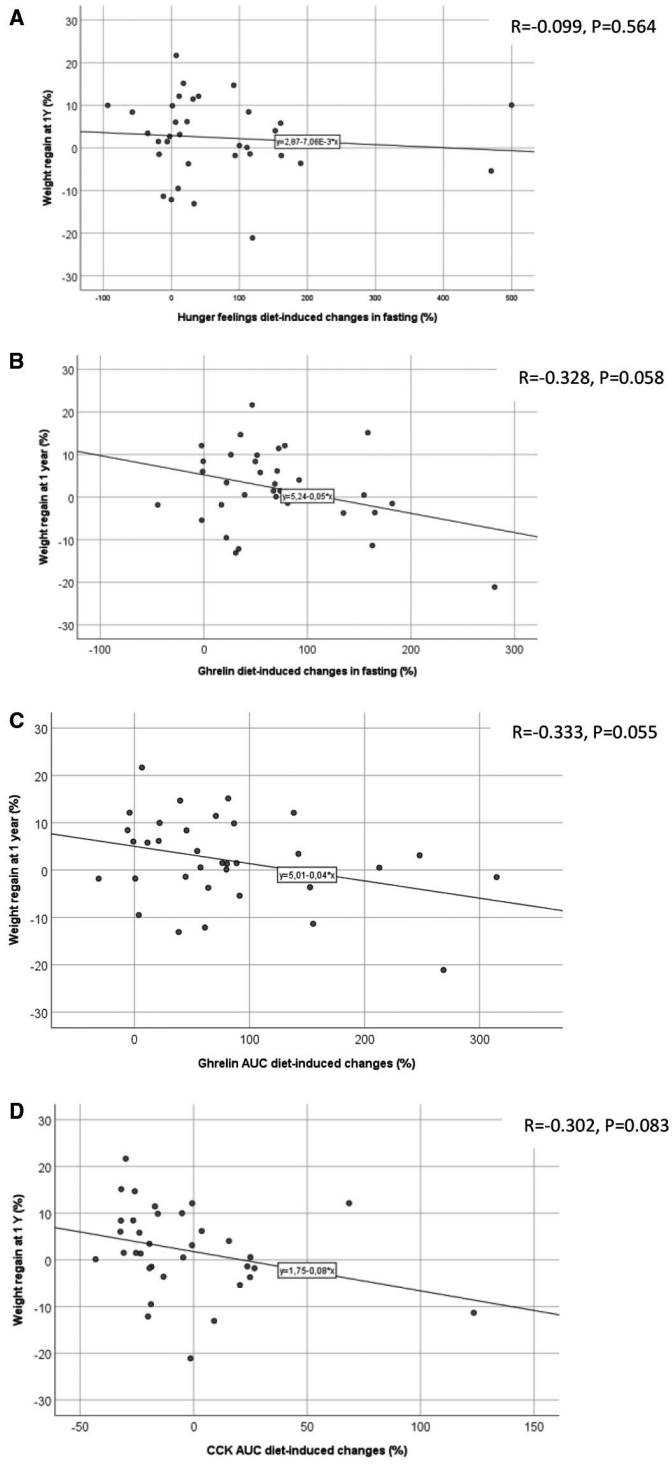

Figure 2 Association between diet-induced changes (%) in (**A**) RMR (kcal/kg FFM/d) and (**B–D**) EIEE and percent weight regain at 1-year follow-up ($n = 34$). EIEE, exercise-induced energy expenditure; FFM, fat-free mass; RMR, resting metabolic rate.

increase in hunger ratings in fasting ($P < 0.01$) and fasting and postprandial AG concentrations, as well as a reduction in fasting and postprandial insulin (all $P < 0.001$), was also seen with WL.

No significant correlations were found between changes in RMR, EIEE, or appetite with WL and WLM at 1 year (Figures 1 and 2). However, there was a tendency for a negative association between the

TABLE 3 Potential predictors of weight-loss maintenance at 1-year follow-up

	β	95% CI	*P*
ΔRMR	0.096	−0.301 to 0.494	0.625
ΔNet EIEE 10 W	−0.049	−0.205 to 0.108	0.529
ΔNet EIEE 25 W	−0.013	−0.153 to 0.127	0.852
ΔNet EIEE 50 W	0.088	−0.104 to 0.281	0.356
ΔFasting hunger	−0.007	−0.035 to 0.021	0.620
ΔAUC fullness	−0.061	−0.150 to 0.029	0.178
ΔFasting AG	**−0.061**	**−0.121 to −0.001**	**0.046**
ΔFasting insulin	−0.042	−0.207 to 0.123	0.607
ΔAUC AG	−0.045	−0.094 to 0.003	0.064
ΔAUC insulin	0.150	−0.053 to −0.262	0.183
ΔAUC PYY	−0.052	−0.144 to 0.040	0.249
ΔAUC GLP-1	−0.009	−0.063 to 0.044	0.727
ΔAUC CCK	**−0.120**	**−0.229 to −0.012**	**0.031**

Results given as regression coefficients (β), with 95% CI and *P* value for linear regressions of weight-loss maintenance at 1 year on each predictor separately, after adjusting for age, sex, and magnitude of weight loss (week 13 – baseline [kg]). Δ = Percentage change with weight loss (week 13 – baseline). Bold font indicates statistically significant findings.
AG, active ghrelin; AUC, area under the curve; CCK, cholecystokinin; EIEE, exercise-induced energy expenditure; GLP-1, glucagon like peptide-1; PYY, peptide YY; RMR, resting metabolic rate.

dietary-induced changes in CCK AUC and fasting and AUC for AG and WLM at 1 year. More specifically, there was a tendency for a reduction in CCK AUC with WL to be associated with poorer WLM at 1-year follow-up ($r=-0.404$; $P=0.022$) and for increased AG plasma concentrations with WL both in fasting and after a meal to be associated with improved WLM at 1 year ($r=-0.328$, $P=0.058$ and $r=-0.332$; $P=0.055$, respectively). After adjusting for age (β = −0.019; $P=0.913$), sex (β = −4.313; $P=0.222$), and magnitude of WL (kilograms) at week 13 (β = −0.240; $P=0.683$), no significant predictors of weight regain were found. However, there was a tendency for percent changes in fasting AG and CCK AUC with WL to be associated with weight regain at 1 year ($P=0.046$ and $P=0.031$, respectively) (Table 3). No significant correlations were observed between energy expenditure (RMR and EIEE) or appetite variables at baseline and weight regain at 1-year follow-up (data not shown).

Discussion

The prevention of weight regain is the most clinically relevant challenge after diet-induced WL, and therefore, it needs to be better understood if we are to succeed in tackling obesity at an individual level. The novel findings of this study suggest that the physiological adaptations to WL, both at the level of energy expenditure (changes in RMR and EIEE) and appetite (changes in hunger and ghrelin), are not significant predictors of weight regain at 1-year follow-up. These findings contradict the globally accepted "compensatory mechanism theory," which proposes that the reduction in energy expenditure and increase in drive to eat seen with WL are drivers of weight regain in the long term (4,5,9,12,13).

The data that are available are conflicting regarding whether the initial fall in RMR with WL is predictive of weight regain. Wang et al. found lower RMR after WL not to be predictive of greater weight regain at 12-month follow-up in women who underwent an initial 20-week hypocaloric diet with or without exercise (21). Pasman et al., on the other hand, reported that the amount of weight regained at 14-month follow-up in premenopausal women with obesity was larger in those who experienced the greatest decrease in RMR in response to a 2-month low-energy diet (22).

Currently, we lack information on whether there is an association between a decrease in EIEE, in response to a standardized volume of exercise, and WL and weight regain. In 2008, Wang et al. reported the magnitude of weight regain during follow-up of weight-reduced women to be associated with decreased PA energy expenditure, measured with an activity monitor (21).

Sumithran et al. showed in their landmark paper that the upregulated appetite hormones and peptides associated with diet-induced WL were sustained at 1-year follow-up and claimed that these stimulated weight regain and therefore needed to be counteracted if weight regain is to be prevented (6). However, they reported no significant correlations between the increase in appetite (either subjective appetite feelings or plasma concentration of AG, CCK, total PYY, active GLP-1, and insulin) seen with WL and weight regain at 1-year follow-up in their Supporting Information (6). We recently reported that, in adults with 15% sustained WL at 1-year follow-up, the drive to eat (subjective hunger feelings and ghrelin plasma concentrations) were increased, but postprandial fullness feelings were also increased (11). In their systematic review, Strohacker et al. reported that the increase in ghrelin and reduction in insulin and plasma concentrations seen with WL were not predictive of weight regain in free-living humans (23).

Our finding showing a tendency for a larger increase in ghrelin to be associated with greater weight regain at 1 year (after adjusting for age, sex, and magnitude of WL) was unexpected, but some support for this finding was published by Crujeiras et al. in 2010, who showed a significant negative association between ghrelin changes and WL and weight regain 6 months later (24). In fact, they reported that a fall in ghrelin after the 8-week hypocaloric diet was related to an increased risk for weight regain (odds ratio = 3.109; $P=0.008$). These authors proposed that these unique findings may be due to central or peripheral resistance to this hormone and/or with a putative proinflammatory state (24). However, an alternative explanation for the positive association between ghrelin and weight regain is that it may reflect a normalization toward what is seen in individuals with lower body weight rather than being part of an overall "compensatory" response. Indeed, individuals with obesity present with lower fasting ghrelin concentrations (25,26), as well as reduced postprandial release of satiety peptides, such as GLP-1 and PYY, compared with healthy-weight controls (25). A lower weight regain at 1 year would mean that BMI would be nearer to a "healthy weight" and theoretically should be associated with a more normalized ghrelin profile. Our findings would support this, because the less weight regained, the lower the BMI was at 1 year ($r=0.5$; $P=0.002$). Unfortunately, studies comparing the plasma concentration of appetite-related hormones between reduced-weight individuals with obesity and normal-weight individuals have been scarce. Verdich et al. showed that WL in individuals with obesity led to a partial normalization of the postprandial release of GLP-1, with concentrations rising with WL to a level between that of lean individuals and those with obesity (27). More research is clearly needed in this area to ascertain whether this new hypothesis is valid and to explore further using body composition measures rather than relying on body weight alone.

The impact of WL on fullness feelings and the release of satiety hormones remains highly controversial, and outcomes for satiety peptides seem to be largely dependent on the hormonal fractions measured. Studies measuring total GLP-1 and PYY_{3-36}, fractions that better reflect the physiological actions of these hormones on appetite (28,29), have reported an increase in the postprandial release of these peptides with WL (7,27). This is in contrast with studies that have measured active GLP-1, in which no change with WL was found (6,11), and those measuring total PYY, in which either no change (11) or a reduction (6) was reported. This again adds evidence to our new hypothesis by showing that WL would lead to a normalization of the secretion of GLP-1 and PYY, two satiety hormones, toward what is seen in those with a lower healthier body weight, in this case by increasing their secretion, which is well known to be blunted in individuals with obesity (25,27). In line with this, postprandial fullness has been reported not to change (6) or to increase in response to diet-induced WL (11).

Eating behavior is extremely complex, and energy intake in free-living conditions is likely to be determined by an interplay between environmental factors, such as food availability and sensory stimuli, and physiological cues (30,31). It is generally accepted that physiology can be easily overridden by the environmental cues (32). Therefore, even though we found a tendency for a reduction in CCK AUC with WL to be associated with more weight regain at 1-year follow-up, there was also a tendency for a larger increase in ghrelin, an orexigenic hormone, to be associated with less weight regain at 1 year. Moreover, and more importantly, dietary-induced changes in subjective feelings of appetite were not predictors of weight regain.

Therefore, the challenge of weight regain after diet-induced WL remains to be fully understood. It may be that other, still unexplored factors may be involved, such as changes in gut microbiota following WL, which could favor energy harvesting. At least two studies have shown that diet-induced WL leads to an increase of bacterial taxa that are important butyrate producers, such as *Faecalibacterium* and *Butyricicoccus* (33,34). This suggests that diet-induced WL, and indeed the type of dietary pattern utilized, may lead to adaptations at the level of gut microbiota toward more energy-efficient species, favoring a positive energy balance.

Despite the fact that, in the present study, all of the measurements were performed using robust and validated methods, there are some limitations. The multiplex assay used for the measurements of appetite hormones (except for CCK) is likely to result in less accurate and precise measurements compared with optimized assays for each individual hormone. In addition, potential changes in central sensitivity to appetite-related hormones were not taken into consideration. Finally, because it is a secondary analysis of data, it is likely underpowered to examine the relatively large number of predictors associated with weight regain that were deemed necessary to explore. More studies, with larger sample sizes, are needed to confirm these findings.

The lack of significant changes in postprandial fullness feelings reported here are likely to be due to lack of power, as we recently published (with a sample of $n = 71$) a significant increase in postprandial fullness ratings after a 16% WL, which was sustained at 1-year follow-up (11). Therefore, the increased feelings of hunger in fasting, and the increased fullness feelings after a meal, observed with WL may potentially reflect a more accurate and normalized appetite control system. If we take these findings into account, that the increase in hunger feelings seen with WL is sustained in the long term (6,11), weight-reduced individuals should get support from their health professional on how to cope with this response in order to optimize their food choices aiming at an energy-restricted diet, in line with their reduced energy needs. Results from this study do have important practical implications. Even though participants with obesity should expect a significant reduction in both RMR and EIEE after WL and, despite that, an increase in the drive to eat, those adaptations are not predictive of weight regain in the long term. This likely reflects the complexity of body weight regulation (35,36). Overall, if weight-reduced individuals want to succeed in the long term, they need to adjust to their newer lower-energy needs by sustaining a reduced energy intake and, ideally, also increasing their PA levels. PA has the potential to not only increase TEE but also improve the sensitivity of the appetite control system (37,38). Overall, our findings are good news if translated into practice appropriately, and weight regain should not be seen as an inevitable outcome. Christensen et al., for example, showed recently that it is possible to maintain a 10% WL over a 3-year period if measures are taken to keep a reduced energy intake over time (39).

Conclusion

The physiological adaptations that occur with WL, both at the level of energy expenditure and appetite, do not seem to predict weight regain in the long term. However, more studies, with larger sample sizes, are needed to confirm these findings.

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