Revisiting the Compensatory Theory as an explanatory model for relapse in obesity management

Catia Martins,[1,2,3] Gareth R Dutton,[4] Gary R Hunter,[3] and Barbara A Gower[3]

[1]Obesity Research Group, Department of Clinical Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [2]Centre for Obesity and Innovation, Clinic of Surgery, St. Olav University Hospital, Trondheim, Norway; [3]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL; and [4]Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

ABSTRACT

Weight regain remains the main challenge in obesity management, and its etiology remains elusive. The aim of the present review was to revise the available evidence regarding the "Compensatory Theory," which is an explanatory model of relapse in obesity treatment, and to propose alternative mechanisms that can contribute to weight regain. It has been proposed, and generally accepted as true, that when a person loses weight the body fights back, with physiological adaptations on both sides of the energy balance equation that try to bring body weight back to its original state: this is the Compensatory Theory. This theory proposes that the increased orexigenic drive to eat and the reduced energy expenditure that follow weight loss are the main drivers of relapse. However, evidence showing a link between these physiological adaptations to weight loss and weight regain is lacking. Here, we propose that the physiological adaptations to weight loss, both at the level of the homeostatic appetite control system and energy expenditure, are in fact a normalization to a lower body weight and not drivers of weight regain. In light of this we explore other potential mechanisms, both physiological and behavioral, that can contribute to the high incidence of relapse in obesity management. More research is needed to clearly ascertain whether the changes in energy expenditure and homeostatic appetite markers seen in reduced-obese individuals are a compensatory mechanism that drives relapse or a normalization towards a lower body weight, and to explore alternative hypotheses that explain relapse in obesity management. *Am J Clin Nutr* 2020;112:1170–1179.

Keywords: relapse, metabolic adaptation, hunger, ghrelin, weight loss, weight regain, energy expenditure, resting metabolic rate

Introduction

Obesity affects more than 650 million people worldwide, equating to approximately 13% of the world's population (1). It is a major risk factor for the ever-increasing incidence of several comorbid conditions, including type 2 diabetes, hypertension, coronary heart disease, and certain forms of cancer (2, 3). Obesity is, therefore, considered the 21st century public health threat (4, 5). Lifestyle interventions, including an energy-restricted diet, exercise, and behavioral therapy, are seen as the cornerstone in obesity treatment (6) and can lead to clinically relevant weight loss (WL; 5–10% of initial weight) (7) in the short term (8, 9). However, long-term results are disappointing (10), with the majority of individuals who initially achieve WL experiencing significant weight regain, and some relapsing to their original weight (11, 12). According to data from the National Health and Nutrition Examination Survey (NHANES, 1999–2006), only 1 in 6 individuals with overweight or obesity report ever having maintained a WL of at least 10% for 1 year after a lifestyle intervention (12). Therefore, relapse represents the biggest challenge in obesity management; as such, obesity should be considered a chronic, progressive, and relapsing condition (13).

It is well established that WL is accompanied by several physiological adaptations on both sides of the energy balance (EB) equation (14, 15), with an upregulated drive to eat (16, 17), despite a significantly reduced total energy expenditure (TEE) (18). These changes have been collectively known as "compensatory mechanisms" to WL, and proposed as the main drivers of relapse in obesity management (14, 15, 19).

The present narrative review explores the evidence regarding the potential role of the above-mentioned compensatory mechanisms as drivers of weight regain. In the absence of compelling and consistent data to support such a link, alternative explanatory pathways are proposed, along with existing theoretical and empirical support for these potential pathways. A systematic review on the impact of WL (achieved through lifestyle) on energy expenditure (at or below predicted values) and homeostatic appetite markers is outside of the scope of the present narrative review. However, we did perform a systematic search aimed at identifying all the studies looking at a potential association between energy expenditure (at or below predicted levels) or homeostatic appetite markers in obese-reduced individuals and weight regain. So, our aim was to identify studies that measured changes in energy expenditure and/or homeostatic appetite markers after WL induced by diet, exercise, behavioral therapy, or a combination (not bariatric surgery and/or pharmacotherapy), with measurements in the reduced-obese state performed outside ketosis (given that ketosis is well known to prevent the increase in hunger feelings and ghrelin secretion otherwise seen with WL) (20–22) and in a steady state (after a period of weight stabilization after WL). The following terms were used in our search: "energy expenditure" OR "total energy expenditure" OR "resting metabolic rate" OR "resting energy expenditure" OR "non-resting energy expenditure" OR "metabolic adaptation" OR "adaptive thermogenesis" OR "appetite" OR "hunger" OR "desire to eat" OR "prospective food consumption" OR "fullness" OR "ghrelin" OR "peptide-YY" OR "glucagon-like peptide 1" OR "cholecystokinin" AND "weight regain" OR "weight loss maintenance."

Compensatory Responses to Weight Loss

Energy expenditure

WL has been shown to induce a significant reduction in TEE, driven by a decline in both resting and nonresting energy expenditure (EE) (18). Some (18, 23–27), but not all (28–31), studies report that the reduction in TEE and/or its components (resting and nonresting EE) is in excess of what would be predicted, given the measured alterations in fat mass (FM) and fat-free mass (FFM), a mechanism known as adaptive thermogenesis or metabolic adaptation. Moreover, a few studies have reported metabolic adaptation to be sustained in the long term, at up to 6 years of follow-up (23, 26, 27). Even though these compensatory changes in EE have been proposed to increase the risk of relapse, there is no evidence showing a link between the 2. From our knowledge, no single study has shown that the reduction in EE below the predicted levels that may accompany WL is a risk factor for weight regain in the long term.

Metabolic adaptation, in response to WL, is one of the most controversial issues in the obesity field, not only in terms of its existence, but also its clinical relevance as a potential driver of weight regain (relapse) (32–36). Some have argued that the claims around metabolic adaptation are exaggerated (37, 38), and others have shown that when weight-stable, weight-reduced individuals are compared with BMI-matched controls (28, 30, 39, 40) or against a prediction equation (31), no evidence of metabolic adaptation at the level of resting metabolic rate (RMR) exists. This is in strong contrast to longitudinal studies following

individuals over time in their WL journey, which report metabolic adaptation (18, 26, 41). There is growing evidence to suggest that differences among studies may be a result of inconsistencies related with the status of EB and/or weight stability of the participants when measurements are taken, with longitudinal studies being more likely to include EE measurements collected in conditions of negative EB. In line with this, we have previously shown that a 17% WL was not associated with metabolic adaptation, either at the level of resting or nonresting EE, when measurements were taken after 4 weeks of weight stabilization (42).

Results from the "Biggest Loser" competition in the United States showed metabolic adaptation to be sustained, and in fact augmented, at 6 years of follow-up. The authors reported a metabolic adaptation of 275 ± 207 kcal/day at the level of RMR after a WL of 58 kg, at the end of the 30-week program, and 499 ± 207 kcal/day at the 6 year follow-up despite a weight regain of 70% of the initial WL (26). However, metabolic adaptation at week 30 was not correlated with weight regain ($r = -0.1$; $P = 0.75$) at the 6 year follow-up in a group of 14 individuals with severe obesity at baseline (BMI = 49.5 ± 10.1 kg/m^2). In contrast, metabolic adaptation at 6 years was associated with both percentage weight gain ($r = 0.59$; $P = 0.025$; $n = 14$) and percentage weight change from baseline at the 6-year follow-up ($r = 0.54$; $P = 0.045$; $n = 14$), such that those with greater WL at 6 years were also those experiencing more metabolic adaptation, suggesting that metabolic adaptation may be a reflection of the magnitude of WL. The contestants were clearly in negative EB at the end of the 30-week program and, even though it was reported that participants were in EB over the 2 weeks before RMR assessment at the 6 year follow-up, there was a large day-to-day within-subject variation (-3 to $+3$ kg), and the slope of the line was clearly negative. The fact that some participants lost weight during the 2 weeks preceding the measurement, and were, therefore, in negative EB, might have led to a larger than expected reduction in RMR and distorted the overall results. Camps and colleagues (27) described similar results, with metabolic adaptation at the level of RMR after a 10 kg WL sustained at 1 year of follow-up despite a 44% weight regain. Metabolic adaptation was reported to correlate with the magnitude of WL both acutely and at the 1-year follow-up. However, no effort was made for measurements to be taken under EB, and metabolic adaptation was not reported to correlate with weight regain (27).

In the 1995 landmark paper by Leibel and colleagues (18), metabolic adaptation, both at the levels of resting and nonresting EE, was reported after both 10% and 20% WL. These findings are also most likely a result of negative EB. Even though participants were reported to be weight stable for 2 weeks before the measurements were taken, WL was induced by an 800 kcal dietary formula. Despite the absence of detailed information regarding the macronutrient composition of the diet, an 800 kcal/day diet using formula is most likely a ketogenic diet. Refeeding after a ketogenic diet leads to glycogen repletion and, with it, increased water content, and an average 2 kg increase in body weight should, therefore, be expected in conditions of EB (43, 44). The lack of the excess ~2 kg suggests that participants were likely in negative EB, despite being weight stable, which might explain why metabolic adaptation was found.

Additional support for the importance of EB in determining metabolic adaptation comes from a recent analysis performed by our research group. We measured RMR after 4 weeks of

controlled feeding and weight stabilization in 171 European American (EA) and African American (AA; race was self-reported) women with overweight at baseline (BMI = 28.3 ± 1.3 kg/m^2), after WL, and at 1- and 2-year follow-ups. Minor metabolic adaptation (approximately 50 kcal/day difference between measured and predicted RMR) was found after a 12 kg WL, but was not sustained at 1- or 2-year follow-ups (with 50 and 90% weight regain, respectively). This minor gap between measured and predicted RMR is, again, most likely a result of the participants being in negative EB, despite being weight stable, due to repletion of glycogen and water (as an 800 kcal/day diet was used to induce WL). Moreover, metabolic adaptation after WL was positively correlated with FM loss in all women, both EA and AA; was positively correlated with WL in AA; and was negatively correlated with weight regain at both 1 and 2 years in AA [r = 0.258 (P = 0.031; n = 70) and r = 0.278 (P = 0.067; n = 44), respectively] (45). This was confirmed in another study by our group in adult Caucasians with obesity at baseline (34.6 ± 3.4 kg/m^2) who followed ketogenic 1000 kcal/day diets for 8 weeks, followed by a 4-week weight stabilization phase and a 1-year follow-up program, with RMR being measured at all time points (baseline, week 9, week 13, and 1 year). A metabolic adaptation (at the level of RMR) of approximately 110 kcal/day (below predicted levels) was seen immediately after a 14 kg (13%) WL, which then was reduced to less than half (49 kcal/day) after 4 weeks of weight stabilization (week 13) and disappeared at the 1-year follow-up (29% weight regain). Moreover, in those with weight gain between week 9 and week 13, no metabolic adaptation was seen at week 13. Metabolic adaptation after WL was also not correlated with weight regain at the 1-year follow-up (r = 0.034; P = 0.824; n = 45) (46). These 2 studies clearly show that metabolic adaptation at the level of RMR is minimal when measurements are taken under conditions of weight stability, and most likely not present under conditions of EB, and does not predict weight regain long term.

The reduction in non-resting EE below the predicted values described by some studies (18, 23) has been proposed to be a result of increased exercise efficiency (47). However, this has been highly debated, and several studies have failed to find increased exercise efficiency with WL (29, 48–50), even when the magnitude of WL is very large (17%) (42). Moreover, no metabolic adaptation was found in nonresting EE (29, 48–50) following a 10–12 kg WL in premenopausal women with overweight when measurements were done in conditions of weight stability. Improved locomotion economy/efficiency may actually reduce the risk of weight regain. Several studies have shown that increases in exercise economy induced by exercise training are associated with increased ease of locomotion (51–54), which in turn is associated with increased participation in free living physical activity and reduced weight regain (55–59), not the opposite.

The evidence linking a reduction in EE, both resting and nonresting, seen with WL with subsequent weight regain is scarce and conflicting. On one hand, Wang et al. (60) reported that the reduction in measured RMR that accompanies WL was not predictive of weight regain at 12 months of follow-up in women who underwent an initial 20-week hypocaloric diet with or without exercise. Pasman et al. (61), on the other hand, reported that the amount of weight regained at 14 months of follow-up in premenopausal women with obesity was larger in those who

experienced the greatest decrease in measured RMR and physical activity EE (measured with an activity monitor) in response to a 2-month low-energy diet. We have recently shown that the reductions in RMR and exercise-induced EE that are observed with a 17% WL (followed by 4 weeks of weight stabilization) were not predictive of weight regain at a 1-year follow-up (62). Moreover, as previously discussed, even the studies showing metabolic adaptation fail to report an association between this phenomenon and weight regain (26, 27). A recently published study by Thom and colleagues (63) showed again no association between metabolic adaptation 6 months after diet-induced WL (14 kg, 14%) and weight regain between 6 and 24 months (r = 0.19; P = 0.51; n = 15), in a population with obesity at baseline (BMI = 39.4 ± 4.3 kg/m^2). In summary, the evidence available at present (and discussed above) suggests that 1) the reduction in measured EE, both at rest and during exercise, does occur with WL; 2) metabolic adaptation, defined as a measured EE below predicted values, is most likely an illusion, only present when measurements are done under negative EB; 3) metabolic adaptation at the level of RMR reflects the magnitude of WL, both in the short and long term; and 4) metabolic adaptation has not been shown to predict weight regain. Failure to establish EB after WL can lead to misleading impressions that weight-reduced individuals suffer from metabolic adaptation, and this likely explains the large discordance among studies.

Appetite

WL has consistently been shown to lead to an increased drive to eat, with an upregulation in the secretion of the hunger hormone ghrelin and subjective feelings of hunger, desire to eat, and prospective food consumption (16, 17, 21, 64–67). These increases have been shown to be sustained in the long term (16, 64), even after partial weight regain (16). Moreover, WL has also been shown to lead to a reduction in the postprandial secretion of satiety peptides, such as active glucagon-like peptide 1 (GLP-1), total peptide YY (PYY), and cholecystokinin (CCK) (16, 68). However, the weight regain–promoting actions of these "compensatory" changes in appetite remain largely speculative, as evidence demonstrating a causal relationship between changes in either subjective feelings of appetite or plasma concentrations of appetite-related hormones concomitant with WL and the risk of weight regain is lacking.

In the landmark paper of Sumithran and colleagues (16), the authors concluded that strategies to counteract the sustained increase in ghrelin secretion and hunger feelings and the reduction in the postprandial release of total PYY and CCK seen with WL (14 kg and 14%, respectively) were needed to prevent weight regain in a population of individuals with overweight or obesity at baseline (BMI = 34.4 ± 2 kg/m^2). However, in their Supplementary Material, they reported no association between the changes in the plasma concentrations of appetite-regulating hormones or in the subjective feelings of appetite observed with WL and weight regain at a 1-year follow-up (no correlation coefficients or significance level provided in the Supplementary Appendix) (16). Adding to this, Strohacker and colleagues (69) found no evidence in their 2014 review that the increase in ghrelin secretion observed with WL was associated with weight regain. We have also recently published evidence that the increased hunger feelings in fasting (r = -0.099; P = 0.564; n = 36) and

basal and postprandial ghrelin secretion [$r = -0.328$ ($P = 0.058$) and $r = -0.333$ ($P = 0.055$), respectively; $n = 36$] seen with diet-induced WL (20 kg, 17%) are not associated with weight regain at 1 year of follow-up in a group of individuals with obesity at baseline (BMI = 36.6 ± 4.3 kg/m^2) (70). A recently published study by Thom and colleagues (63) showed again no association between the increase in basal plasma ghrelin concentration at 6 months after diet-induced WL (14 kg, 14%) and weight regain between 6 and 24 months of follow-up (no correlation coefficient or significance level provided) in a group of individuals with obesity (BMI = 39.4 ± 4.3 kg/m^2). In fact, we have previously reported a trend [$r = -0.328$ ($P = 0.058$) and $r = -0.333$ ($P = 0.055$), respectively; $n = 36$] for a larger increase in basal and postprandial ghrelin secretion with diet-induced WL to be associated with less weight regain at 1 year of follow-up (70). Crujeiras and colleagues (71) reported a similar pattern, with a decrease in ghrelin secretion after an 8-week hypocaloric diet (4.5 kg, 5% WL) being associated with an increased risk for weight regain [odds ratio = 3.109 ($P = 0.008$) and $r = -0.18$ ($P = 0.061$), respectively] in individuals with overweight or obesity at baseline (BMI = 30.7 ± 2.4 kg/m^2). Another study recently published by Hansen and colleagues (72) in individuals with overweight or obesity at baseline (BMI = 27.7 ± 2.1 kg/m^2) who had lost an average 9.6 kg (10.8%) also showed that a high level of appetite (assessed by visual analogue scales) after WL was not associated with WL maintenance at 3 months of follow-up ($\beta = -0.02$; $P > 0.22$; $n = 181$). However, the authors found that suppression of self-reported appetite (assessed with visual analogue scales) during the weight maintenance phase, by the consumption of food products high in fiber and/or protein, was associated with improved WL maintenance, making appetite-reducing food products an interesting strategy for the prevention of weight regain (72). Additionally, the marked reduction in leptin concentration that occurs with WL has also been reported not to be associated with weight regain in the long term in free-living humans (69).

The previously described findings weaken the hypothesis that the changes in appetite seen with WL are part of a compensatory response that drives relapse. Two reasons might explain the unexpected inverse association between changes in ghrelin secretion with WL and weight regain. Crujeiras and colleagues (71) have suggested that maybe these findings are consistent with a disruption in the sensitivity to ghrelin at the level of the central nervous system. However, our data (62) suggest that this inverse association might reflect the fact that ghrelin is an inverse adiposity signal (73), and as a larger initial WL is usually associated with a better WL maintenance, a larger increase in ghrelin secretion in response to WL tends to be also associated with a lower weight regain (or lower BMI) at 1 year.

Several studies have looked at the impact of diet-induced WL on the postprandial release of satiety peptides, and the results are similarly divergent (16, 17, 64, 74), likely due to methodological differences related to the method of hormonal analyses and the specific fractions measured. For example, some report an increase in total GLP-1 (17, 74) and PYY$_{3-36}$ (17) secretion in the postprandial state with WL, while others reported a decrease in total PYY and no changes in active GLP-1 (17, 64). Total PYY is a measure of secretion, whereas only PYY$_{3-36}$ resulting from dipeptidyl peptidase 4 metabolism inhibits food intake (75). Similarly, total GLP-1 is the adequate measure of L-cell secretion, whereas active GLP-1 only provides information about the "endocrine" part of the GLP-1 action, but not about the afferent signals (which total GLP-1 reflects) (76, 77). In line with these findings, and contrary to the generalized belief, no single study has reported that WL leads to a reduction in the feelings of postprandial fullness. Most report no change (16, 21, 65–67, 78), and in the largest study ($n = 71$) in this field, we were able to show that both acute and sustained WL as high as 17% of baseline weight was associated with increased postprandial feelings of fullness, suggesting that lack of power may have prevented this finding from being detected in previous studies.

Collectively, all of these findings contradict the Compensatory Theory (26–29), which suggests that the body fights against WL by upregulating ghrelin secretion and hunger feelings, leading to overeating and a relapse in obesity management (weight regain). We have recently shown that the increased hunger feelings and ghrelin secretion seen after WL in weight-reduced individuals are no different than what is seen in a control group matched for FM and FFM who had never lost weight (79). Postprandial total GLP-1 secretion has also been reported to increase towards the levels seen in lean controls (74), and postprandial fullness, generally reported to be blunted in obese compared with normal-weight individuals (80), increases with WL (64). Therefore, it seems that the increased drive to eat observed after WL is in fact a "normalization" towards the expected levels at a lower body weight and FM.

In fact, some individuals with obesity report that their own eating patterns bear no relation to feelings of hunger or fullness, suggesting an altered or weakened recognition and response to these internal sensations (81). Even though the available evidence regarding the potential association between BMI and the release of appetite-related hormones remains conflicting (82–84), the majority of the studies show a blunted release of satiety peptides after a meal in individuals with obesity, compared with nonobese controls (68, 80, 85–88), as well as impaired attenuation of ghrelin secretion (the expected postprandial drop in ghrelin secretion is absent or reduced) in individuals with obesity when compared with nonobese controls (68, 88). This would then lead to a lower satiation, manifested as a higher volume intake to reach fullness (85), and lower satiety, manifested as a higher energy intake at ad libitum test meals (85), as well as lower postprandial fullness feelings in response to a standardized test meal (80). This impaired satiation and satiety response in individuals with obesity would then result in increased energy intake, reinforcing their obesity.

Differences in sample sizes, BMIs between groups, macronutrient compositions, and energy loads of the test meals and hormonal fractions measured can potentially account for the majority of the inconsistencies seen among studies. While ghrelin secretion and hunger feelings in the fasting state increase, feelings of fullness after a meal also increase with WL (64) and might reflect a normalization towards what is expected at a healthy normal body weight and, overall, a more accurate appetite control system in the reduced-obese state.

Compensation Versus Normalization

The Compensatory Theory proposes that reduced-obese and nonobese BMI-matched controls are physiologically different in
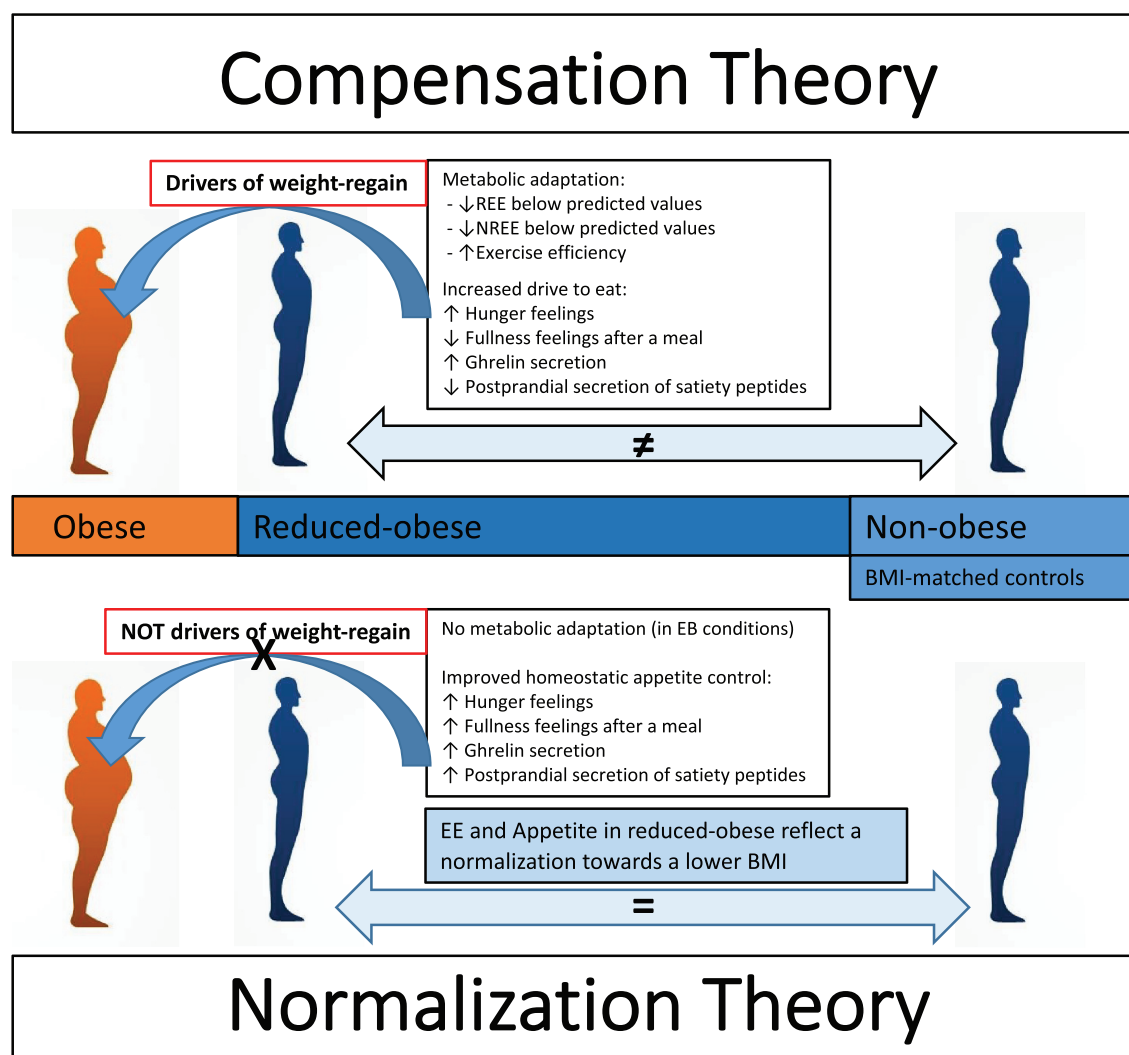
FIGURE 1 Compensation Theory versus Normalization Theory, as explanatory models for the changes in energy expenditure and appetite markers concurrent with weight loss and their role as drivers of weight regain. Abbreviations: EB, energy balance; EE, energy expenditure; NREE: non-resting energy expenditure; REE, resting energy expenditure.

regard to EE and homeostatic appetite markers. However, and as previously discussed, metabolic adaptation is likely due to individuals being in negative EB, and there is no evidence that the physiological adaptations at the level of EE or homeostatic appetite markers drive weight regain. Therefore, we propose a new theory (the Normalization Theory), by which the reduced-obese state is characterized by no metabolic adaptation (in EB conditions) and improved appetite control (with increased orexigenic signals, but also improved satiety). As such, this new theory proposes that reduced-obese and nonobese BMI-matched controls are identical when it comes to homeostatic appetite markers and EE physiology, and that the reduction in EE and increase in hunger seen in reduced-obese individuals reflect a normalization towards a lower body weight (see **Figure 1**).

FFM is an important determinant of both EE (89, 90) and appetite regulation (91). As such, obese-reduced individuals should be compared with FFM-matched controls. In our study showing a normalization in appetite in obese-reduced individuals after a sustained 17% weight loss, controls were matched for

FFM (79). Moreover, in the cross-sectional studies comparing RMR between obese-reduced individuals and BMI-matched controls, all had adjusted for FFM in their statistical analysis (28, 30, 39, 40), and in 1 study the controls were matched for FFM (29). This strengthens our conclusion that the reduced TEE and the increased drive to eat seen with WL seem to represent a normalization towards lower body weight, FM, and FFM. More importantly, a larger reduction in TEE, and in some cases metabolic adaptation, and a larger increase in hunger are not associated with more weight regain long term. In fact, a larger metabolic adaptation (26, 45) and an increase (71), or larger increase, in ghrelin secretion (62) with WL have been shown to be associated with better long-term WL maintenance, likely because they are a reflection of the magnitude of WL, both short term and long term.

It needs to be acknowledged that the available studies on the potential association between changes in EE and homeostatic appetite markers that occur with WL and weight regain have not adjusted for baseline body weight and total WL. Future studies

need to adjust for this and other potential confounders in their statistical models.

Other Physiological Mechanisms

In light of the conflicting findings offering limited support to the compensatory hypothesis of weight regain, other physiological mechanisms warrant further examination for their potential role in relapse in weight management. For example, WL is followed by marked changes in sympathetic activity, which could potentially play a role in long-term weight regain. Even though low sympathetic activity to some regions—namely, skeletal muscle and adipose tissue—may be a risk factor for weight gain and obesity development, the contribution of the sympathetic nervous system seems to be rather small (92). Moreover, to our knowledge no study has directly assessed whether the alterations in sympathetic activity that parallel WL modulate weight regain long term in free-living individuals. The potential roles of insulin sensitivity, gut microbiota, and brain functions in modulating relapse are summarized below.

Insulin sensitivity

It has been proposed that increased insulin sensitivity may exacerbate the risk of weight gain in the present obesogenic environment (93). However, in the 2014 review from Strohacker and colleagues (69), it was shown that changes in insulin sensitivity with WL do not predict weight regain in free-living humans. Only 1 out of the 6 studies included in the review reported that increased insulin sensitivity after WL increased the risk of weight regain at both 12 and 18 months of follow-up (94). Thus, the evidence for the increase in insulin sensitivity with WL promoting weight regain is weak.

However, in weight-reduced women with a family history of overweight/obesity, those who had the combination of high insulin sensitivity and high acute insulin response regained more body fat after 1 year than those with low insulin sensitivity and low acute insulin response to glucose (AIRg) (95, 96). This was particularly true among women who consumed a diet with a relatively high glycemic load. However, this observation may speak more to the inherent physiologic characteristics of a subset of women with obesity than to compensation for WL. In this case, the relatively high insulin sensitivity and AIRg were not considered compensatory responses to WL. Thus, it is important to distinguish between the inherent characteristics of some individuals prone to obesity that may promote both initial weight gain and weight regain following WL and the acquired characteristics that occur solely in response to negative EB.

Gut microbiota

The gut microbiota has emerged as an important factor underlying changes in the metabolic processes of the host. Recent works have indicated that the gut microbiota may mediate some of the inter-individual differences seen in long-term WL maintenance after bariatric surgery, particularly Roux-en-Y gastric bypass (97–99). It has also been found that microbiota differences at baseline (pre-WL) might allow for discrimination between those successful and unsuccessful in maintaining WL in the long term after a lifestyle intervention (100). The potential impact of the gut microbiota on body weight regulation is likely mediated, at least partially, by its capability to regulate different aspects of appetite and eating-related behavior (101).

Damms-Machado et al. (102) showed that an identical WL induced by sleeve gastrectomy and a low-calorie diet over a 6-month period had opposite effects on the gut microbiota. Sleeve gastrectomy was associated with an increase in the Bacteroidetes/Firmicutes ratio and a decrease in butyrate-producing bacterial species, while diet-induced WL was associated with the opposite. An increase of bacterial taxa that are important butyrate producers, such as Faecalibacterium and Butyricicoccus, has also been reported in another study after diet-induced WL (100). This suggests that diet-induced WL may lead to adaptations at the level of gut microbiota toward more energy-efficient species, favoring a positive EB. However, the studies were relatively small and the macronutrient composition of the diet with a small fiber content (total meal replacements were used) may have biased the results. Even though larger and better-controlled studies are needed to elucidate the exact role of gut microbiota in modulating long-term WL maintenance after lifestyle interventions, the preliminary findings described above are promising.

Brain function

Using functional magnetic resonance imaging, Cornier and collaborators (103) showed that in the eucaloric state, food images (as compared to nonfood images) elicited significantly greater activation of the insula and inferior visual cortice in thin individuals, as compared to reduced-obese individuals. More importantly, 2 days of overfeeding resulted in significant attenuation of the response (at the level of the insula, visual cortex, and hypothalamus) to visual foods cues in thin (but not reduced-obese) individuals (103). This suggests that there are important differences in the response to visual food-related cues between thin and reduced-obese individuals that place the latter group at an increased risk of weight regain.

Overall, in the review by Cornier et al. (103), it was concluded that weight-reduced individuals present with significant changes in the neuronal response to food-related cues, which is associated with a dysregulation of EB. Again, even though this milieu would favor weight regain, no study has reported a link between the 2, and more research is clearly needed in this field.

As previously discussed, at present, the exact physiological mechanisms driving weight regain remain unknown. Nevertheless, relapses in obesity treatment can be minimized if patients are supported in the long term (104, 105).

Motivation and Behavioral Aspects

In addition to several intriguing physiological processes that may impact weight regain, there are potential behavioral and psychological factors relevant to long-term WL maintenance as well. For instance, self monitoring of dietary intake, physical activity, and body weight is a fundamental behavioral strategy to obesity interventions, and it is well documented that more consistent adherence to self monitoring is associated with greater initial WL (106) and better maintenance of lost weight (107, 108). However, self-monitoring adherence declines over time

(106, 109, 110), and these declines in adherence are associated with weight regain (108, 110, 111). In fact, in 1 study, those participants who reported continued high levels of dietary self monitoring during extended care actually continued to lose weight, while the other participants demonstrated the more common pattern of weight regain following initial treatment (111).

Of note, the benefit of dietary self-monitoring adherence for WL maintenance was mediated by better adherence to energy intake goals (110). Similarly, the benefit of self weighing for better weight management was partially mediated by the improved adherence to energy intake and EE goals (109). These findings on the mechanisms by which self-monitoring adherence influences weight outcomes highlight the importance of self monitoring in impacting other lifestyle behaviors (i.e., eating and physical activity) that are critical for successful WL maintenance.

In addition to self monitoring, adherence to other behavioral strategies is relevant for the prevention of weight regain. Not surprisingly, more frequent dietary lapses (i.e., eating a larger portion than intended, eating an unplanned meal or snack, eating a food one was trying to avoid) are associated with attenuated short-term and extended WL (112). However, several psychological and environmental factors may be related to these dietary lapses. In 1 study, for instance, dietary lapses were more likely to occur at home, on weekends, in the evenings, and when exposed to certain desirable foods (112). Further, higher levels of negative emotional states, including sadness, loneliness, boredom, and irritation, were also associated with subsequent dietary lapses (112). These findings highlight the relevance of external factors (e.g., location, schedule, access to certain foods), as well as internal psychological states that impact dietary lapses, which may lead to weight regain.

Diminished motivation for long-term engagement in lifestyle modifications contributes to the challenge of sustained behavioral adherence and avoidance of behavioral lapses. Decision theory posits that immediate consequences (rewards and/or costs) are more powerful than delayed consequences in influencing behavior (113, 114). For example, the immediate reward for consuming an energy-dense snack (or the immediate cost of depriving oneself of the snack) outweighs the delayed consequences (e.g., weight regain) of this behavioral choice. In the context of WL maintenance, perceived long-term rewards are further diminished by individuals' concerns that weight regain will occur despite the behavioral effort expended to maintain lost weight (115). Further, individuals may lose interest in WL efforts due to the monotony and behavioral demands required to maintain lost weight (116). In addition, the prevention of weight regain is inherently less reinforcing than the initial WL, so the balance between perceived costs and rewards for maintaining weight tends to shift over time for many individuals (117, 118).

Perceptions that the behavioral demands of WL maintenance are too costly may be further influenced by individual differences in disposition. For instance, individuals who exhibited a "prevention-focused" disposition, characterized by greater vigilance and motivation to avoid undesired outcomes, did better with maintaining lost weight than those who did not have this type of self-regulatory disposition (119). While a comprehensive summary of other individual characteristics associated with weight regain is beyond the scope of this review, additional psychological and behavioral characteristics predicting weight regain may include higher levels of dietary disinhibition (i.e., perceived loss of control while eating), the presence of binge eating (105, 120), eating in response to negative emotions and stress, more passive reactions to problems (105), and elevated depressive symptoms (120). Another variable worthy of further investigation for its effects on weight regain is cognitive functioning (118). This includes cognitive domains, such as executive functioning (e.g., decision-making, inhibitory control), attention, and memory, as lower levels of these cognitive variables have been predictive of poorer short- and long-term weight outcomes in obesity treatment (121–123).

Conclusions

The majority of the evidence discussed in this review seems to point to the fact that body weight is not defended by physiological adaptations at the level of the homeostatic appetite control system or EE that occur with WL. Instead, it seems more plausible that such physiological changes reflect a normalization towards a lower body weight. Even though other biological pathways may be involved in weight recidivism—namely, the hedonic appetite control system (124) or gut microbiota (100, 102)—it is also possible that it represents, at least partially, the struggle of weight-reduced individuals in adhering to a healthy lifestyle long term. It has been consistently shown that relapse can be minimized if patients are supported in the long term and obesity is treated as what it is: a chronic disease (104, 105). However, we need to recognize that individuals prone to obesity have intrinsic physiological characteristics that predispose them to both obesity (weight gain) and weight regain following WL. These intrinsic characteristics must be addressed, or weight regain will follow. Despite this, more research is needed to clearly ascertain whether the changes in EE and homeostatic appetite markers seen in reduced-obese individuals are a compensatory mechanism that drives relapse or a normalization towards a lower body weight. Further research should also explore alternative mechanistic pathways that can explain weight regain and include both physiological and behavioral aspects.

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