Published in final edited form as:

Int J Obes (Lond). 2014 March ; 38(3): 388–396. doi:10.1038/ijo.2013.118.

Adaptations of leptin, ghrelin or insulin during weight loss as predictors of weight regain: a review of current literature

K Strohacker[1], **JM McCaffery**[1], **PS MacLean**[2], and **RR Wing**[1]

[1]Department of Psychiatry and Human Behavior, The Miriam Hospital and Warren Alpert School of Medicine at Brown University, Providence, RI, USA

[2]Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes, Center for Human Nutrition, University of Colorado Anschutz Medical Campus, Denver, CO, USA

Abstract

Numerous laboratory studies involving both animal and human models indicate that weight loss induces changes in leptin, ghrelin and insulin sensitivity, which work to promote weight regain. It is unclear, however, whether these biological changes serve as a biomarker for predicting weight regain in free-living humans in which biological, behavioral and environmental factors are likely at play. We identified 12 studies published between January 1995 and December 2011 that reported changes in leptin, ghrelin or insulin during intentional weight loss with a follow-up period to assess regain. Two of the nine studies examining leptin suggested that larger decreases were associated with greater regain, three studies found the opposite (smaller decreases were associated with greater regain), whereas four studies found no significant relationship; none of the studies supported the hypothesis that increases in ghrelin during weight loss were associated with regain. One study suggested that improvements in insulin resistance were associated with weight gain, but five subsequent studies reported no association. Changes in leptin, ghrelin or insulin sensitivity, taken alone, are not sufficient to predict weight regain following weight loss in free-living humans. In future studies, it is important to include a combination of physiological, behavioral and environmental variables in order to identify subgroups at greatest risk of weight regain.

Keywords

weight loss; weight regain; appetite hormones; review; free-living humans

INTRODUCTION

Sixty-eight percent of men and women in the United States are classified as overweight (body mass index ≥25 kgm^{-2}) or obese (body mass index ≥30 kgm^{-2}).[1] By promoting dyslipidemia, insulin resistance and systemic inflammation, excess adiposity increases risk for poorer health outcomes including cardiovascular disease or type 2 diabetes.[2,3] Moderate,

Correspondence: Dr RR Wing, Weight Control and Diabetes Research Center, The Miriam Hospital, 196 Richmond Street, Providence, RI 02904, USA. RWing@lifespan.org.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

but clinically significant weight losses of ~5–10% have been shown to reduce disease risk.[4,5] Although weight loss is achievable through a variety of programs (self-guided, commercial, behavioral or medically supervised), weight regain is common.[6–9]

Weight loss-induced adaptations in several humoral factors have been identified and substantial laboratory-based evidence supports that such adaptations promote weight regain. In rodent models of diet-induced obesity, weight loss triggers biological and metabolic adaptations that contribute to overfeeding and subsequent weight regain.[10–12] In humans, fasting concentrations of adiposity signals leptin and insulin, which are elevated with excessive adiposity, are substantially reduced during caloric restriction and subsequent weight loss.[13–26] Importantly, these reductions are disproportionately low relative to observed fat mass at a stabilized weight,[12,24,27–29] which is likely interpreted by the central nervous system as a considerable energy depletion that must be corrected.[30] Indeed, maintenance of a reduced body weight has been related to leptin-reversible neural activity in part of the brain responsible for energy homeostasis,[31] and leptin administration in weight-reduced subjects improves satiety.[32] In addition, caloric restriction and weight loss induce significant increases in the concentration of ghrelin,[33–35] a potent orexigenic hormone.[36,37] Elevations in ghrelin concentration, either endogenous[38] or exogenous,[39] are associated with feelings of hunger and increased food intake.

Given the substantial evidence that biological adaptations occur with weight loss in a manner that promotes overfeeding and weight regain in tightly controlled laboratory studies, it is important to determine whether any of the commonly measured biomarkers (leptin, insulin or ghrelin) are predictive of weight regain in free-living humans, in which non-homeostatic behavioral and environmental factors are also at play. Such a biomarker could have significant value in determining individual risk of weight regain in a clinical setting and in subsequently tailoring treatment programs to improve weight maintenance outcomes in previously overweight or obese individuals. Furthermore, determining a predictive biomarker could advance pharmacological prevention of weight regain. Therefore, the aim of the present review was to determine whether weight loss-induced changes in leptin, insulin or ghrelin have been demonstrated to predict human weight regain in the prior literature.

MATERIALS AND METHODS

Search strategies

A systematic search was conducted through the PubMed electronic database. The database was searched for human studies from January 1990 to January 2012. The inclusion criteria were that studies (i) reported intentional weight loss with a follow-up period to assess weight regain, (ii) were published in English or with an English abstract, (iii) reported original research on the relationships between weight loss-induced changes in leptin, ghrelin and indices of insulin sensitivity (glucose clamp, fasting insulin, and so on) and weight regain or weight maintenance. Multiple keywords and word combinations were used in searches, including weight, regain, maintenance, leptin, ghrelin, insulin, insulin sensitivity, predict, future and weight change. The references of articles were also screened for potentially relevant studies. The study selection process is shown in Figure 1.

Data synthesis

The studies' diversity in sample, design, data analysis, variables and follow-up time-frame (3 months–4 years after weight loss) precluded meta-analysis. The data are summarized descriptively and synthesized in Tables 1–3. The tables are organized by author group and publication year from earliest to most recent, and then alphabetically. They include descriptions of the sample populations if available (age and body mass index upon entry to study and gender stratification) and descriptions of the intervention (approach to weight loss and durations of weight loss/maintenance phases). Initial weight loss is described referring to weight change during the initial weight loss phase compared with baseline. Follow-up weight loss is also described referring to weight change during the maintenance phase compared with baseline. If quantitative data for follow-up weights were not provided, the tables provide descriptive information on weight change patterns stratified by successful maintenance or quartiles. Finally, tables provide determinations ('yes', 'no' or 'not tested') on the basis of study outcomes of whether decreases in leptin, increases in ghrelin or increases in insulin sensitivity during weight loss were related to weight regain. Within the reviewed studies, we also determined whether low leptin, high ghrelin or high insulin sensitivity at baseline or post-weight loss were associated with weight regain. These data are also available on the provided tables.

RESULTS

Characteristics of the included studies

Twelve articles met the inclusion criteria, ranging in date published from 1995 to 2011. Nine articles assessed the relationship between changes in leptin and weight regain. Four studies assessed the relationship between changes in ghrelin and weight regain. Six studies assessed the relationship between changes in indices of insulin sensitivity and weight regain (seven experiments in total; Wing52 discussed two interventions in one publication).

Do reductions in leptin during weight loss predict weight regain?

The nine articles examining relationships between changes in leptin during weight loss and weight regain are summarized in Table 1. Overall, the results are mixed. Only two of nine studies supported the hypothesis that decreases in leptin predict weight regain in free-living humans. Erez *et al.*[40] found that weight regain was greatest in individuals with larger decreases in leptin during weight loss, supporting the hypothesis that decreases in leptin may be a determinant of weight regain. Soni *et al.*[41] provided mixed support of their hypothesis. Decreases in leptin during the weight-loss phase were associated with weight regain during the maintenance phase; however, this association was lost when analyses were limited to participants who lost ≥10 lbs during the initial weight-loss phase.[41] Three studies reported opposite results, such that a smaller decline in leptin during weight loss was associated with a larger weight regain.[42–44] In the largest and most recent of these studies,[43] the authors found that smaller decreases in leptin were significantly related to regain among men and women who had lost on average 5% of their weight during a low-calorie diet.[43] Finally, four additional studies reported no association between leptin reductions during weight loss and subsequent weight change.[45–48]

A number of these studies also examined the association between baseline and/or post-weight loss leptin and weight regain; these findings are also mixed (Table 1). One study found that low baseline leptin levels were associated with weight regain.[44] However, two studies demonstrated opposing findings, such that relatively higher baseline leptin concentrations were associated with greater weight regain.[42,43] Four additional studies found no association between baseline leptin and subsequent weight change.[41,45,46,48] The relationship of post-weight loss leptin with weight change was less frequently assessed. Two studies reported no correlation with subsequent weight change,[47,48] whereas another found that higher end point leptin was associated with greater weight regain.[43]

Do increases in ghrelin during weight loss predict weight regain?

Four studies have directly tested relationship between ghrelin and weight regain.[40,43,49,50] None of the available studies support hypothesis that higher levels of ghrelin predict weight regain (Table 2). Three studies found no association between weight loss-induced increases in ghrelin and weight regain,[41,47,49] whereas one study by Crujeiras *et al.*[43] found that decreases in ghrelin during weight loss increased the risk of regain. However, it should be noted that in the study by Crujeiras *et al.*,[43] post-weight loss increases in ghrelin were small (12 pg ml^{-1}) and statistically nonsignificant (P=0.461) and the average weight loss was relatively small (average 4.8 kg lost, regaining 10% of lost weight), suggesting that this finding should be interpreted with caution. Lower levels of ghrelin at baseline were found to be associated with greater weight regain in two studies,[43,49] whereas no association between baseline ghrelin and weight change was noted in the third.[41] Two studies found that lower post-weight loss ghrelin after weight loss was associated with weight regain.[43,49] A third study found no relationship between post-weight loss ghrelin and weight regain.[47] Taken together, almost no studies found that higher ghrelin measured at any time point during weight loss predicted more difficulty with weight loss maintenance.

Do improvements in insulin sensitivity during weight loss predict weight regain?

As with both leptin and ghrelin, improvements in insulin sensitivity via weight loss do not seem to predict weight regain (Table 3). The earliest published study[51] found that improvements in insulin sensitivity with weight loss predicted weight regain. However, results from five subsequent experiments do not confirm these results.[41,43,47,52] For example, Wing52 reported that changes in insulin sensitivity did not predict weight regain in two separate experiments carried out in non-diabetic and type 2 diabetic subjects, respectively, following behavioral weight loss treatment that consisted of 6 months of weight loss and relatively long (2+ years) follow-up period to assess weight regain.[52] Neither baseline[41,43] nor end point[43,47,52] measures of insulin sensitivity predicted weight regain.

DISCUSSION

This systematic review identified studies that assessed changes in leptin, ghrelin and insulin sensitivity during weight loss, and tested the relationship between such changes and weight regain. Strong evidence assert that biological adaptations of these factors to weight loss increase the propensity for weight regain.[47,53–56] Yet, in reviewing clinical weight loss trials that assessed pre-post changes in leptin, ghrelin, and insulin sensitivity and weight regain,

neither decreases in leptin or insulin sensitivity nor increases in ghrelin consistently predicted subsequent weight regain. Further, little evidence within the reviewed studies support pre- or post-weight loss leptin, ghrelin or insulin sensitivity as predictors of regain. These findings suggest that, despite the important roles that leptin, ghrelin and insulin seem to exert in energy homeostasis, their changes during weight loss, taken alone, are not sufficient predictors of weight regain in free-living humans.

Although leptin, ghrelin or insulin are typically measured and assessed throughout the literature as though they may singularly be predictive of weight regain, this is an unlikely scenario. Circulating hormones represent just one facet of a highly complex, systemic response that involves interactions between the central nervous system, the gut, adipose tissue, muscle tissue and the liver.[30] Sex differences are also likely important, as the strongest evidence for leptin reduction as a predictor of weight regain was shown in a study consisting mainly of men,[40] whereas women were more strongly represented in the majority of studies with nonsignificant results. Furthermore, the magnitude of change in leptin with weight loss differs by sex,[57,58] as does hypothalamic sensitivity to leptin.[59,60] Genetic variability also may alter such changes in and interactions between leptin, ghrelin or insulin, influencing the predictive ability of these biomarkers regarding weight regain.[30,61]

In addition, non-biological inputs can also influence the degree of weight maintenance or regain. An obesogenic environment is characteristic of many modern nations, marked by fast food promotion, high availability of sugar-sweetened beverages, large serving sizes paired with decreased opportunities for active transportation and recreation,[62] in addition to other emerging factors that may have a role in obesity or weight regain.[63–65] Such environmental pressures may overshadow biological or genetic control of body weight.[66] In this case, teaching individuals how to successfully navigate food cravings or an obesogenic environment is necessary. Successful prevention of weight regain has been related to behaviors such as strictly adhering to a low-calorie, low-fat diet, performing high levels of physical activity (~2800 kcal energy expenditure per week), frequent self-weighing and breakfast consumption.[67] Psychological variables, such as disinhibition, or self-reported loss of control over eating, have also been shown to predict weight regain.[68] In addition, continued clinical contact has also been demonstrated to help prevent weight regain.[69]

Future directions

On the basis of our findings that weight loss adaptations in leptin, ghrelin and insulin alone do not appear to reliably predict weight regain in free-living individuals, it is clear that a multifactorial approach is necessary in order to adequately make such a prediction.

One aspect of a multifactorial approach may be assessing possible predictors in the postprandial, as well as the fasted, state. In each study reviewed, only the relationship between fasting values of leptin and ghrelin were assessed. These, and other biological factors, are extremely sensitive to acute caloric restriction and intake.[70,71] In addition, obesity seems to not only affect fasting levels but also postprandial changes in both appetite hormones, which are thought to reinforce the obese state.[72,73] Thus, researchers may want to examine whether the dynamic response of such factors to fasting and feeding provides a more reliable means of predicting weight regain. However, the addition of postprandial

assessments does not address the issue that each hormone is but one factor contributing to a complex response.

Sumithran *et al.*[47] suggested that the ability of hormonal adaptations to weight loss to promote weight regain may be a conglomerate effect, rather than resting on the change in one single hormone or peptide.[47] In addition to the commonly assessed leptin, ghrelin or insulin, other important factors such as peptide YY, cholecystokinin, amylin and glucagon-like peptide-1 have significant impacts on appetite[52] and should be considered in assessing conglomerate effects. Assessment of blood glucose homeostasis may also be pertinent, as hypoglycemia following an oral glucose tolerance test has been strongly correlated with weight regain.[74]

As several behaviors and environmental issues have been associated with weight change, it is imperative that a multifactorial approach includes biological and non-biological components. Typically, behavioral researchers have focused on behavioral variables, whereas physiological researchers have examined energy expenditure or hormonal changes. Each is explaining only a small proportion of the variance in weight regain. In order to better understand weight loss maintenance and regain, it is important that future studies assess a broad array of demographic characteristics, such as sex[57] or genetics,[75] behaviors, such as diet composition[76] and physical activity[77] and environmental factors[66,69] as potential predictors, in addition to biological factors known to undergo adaptations to weight loss. Elucidating key biomarkers that can predict an individual's risk based on biology, behavior and environment would be valuable in determining the most effective course of treatment, be it behavioral intervention for diet or exercise, pharmacological or surgical intervention.

Strengths and limitations

Using a thorough literature search, the present study included weight loss trials specifically designed to assess the relationships between weight loss-induced changes in leptin, ghrelin and insulin sensitivity and subsequent weight regain, making it the first comprehensive review of data addressing this question. However, it is important to note that the studies included in this review varied in demographic characteristics, approaches used to produce weight loss, the magnitude of weight loss and change in hormones, duration of follow-up and statistical methods used to analyze the relationship between hormonal changes and weight regain. In particular, the study conducted by Erez *et al.*[40] was perhaps the most well designed to test the hypothesis that changes in leptin with weight predict weight regain in free-living individuals. In this study, multivariate regression models were adjusted for age, sex and other biomarkers that were potential confounders for weight loss.

Summary

Within a comprehensive review of relevant literature, we found no consistent relationship between individual changes in leptin, ghrelin and insulin sensitivity during weight loss and subsequent weight regain in free-living humans. Thus, changes in these hormones in and of themselves are not sufficient to predict weight regain. We further discuss a variety of suggestions aimed to strengthen future research in this area by addressing important limitations highlighted by the present review. Most important is utilizing a multidisciplinary

approach that necessitates collaboration among researchers specializing in physiological, behavioral and environmental contributions to weight regain in order to more effectively predict outcomes regarding weight loss maintenance.

ACKNOWLEDGEMENTS

KS was supported by a T32 Training Fellowship (Training in Behavioral and Preventive Medicine; T32 HL076134).

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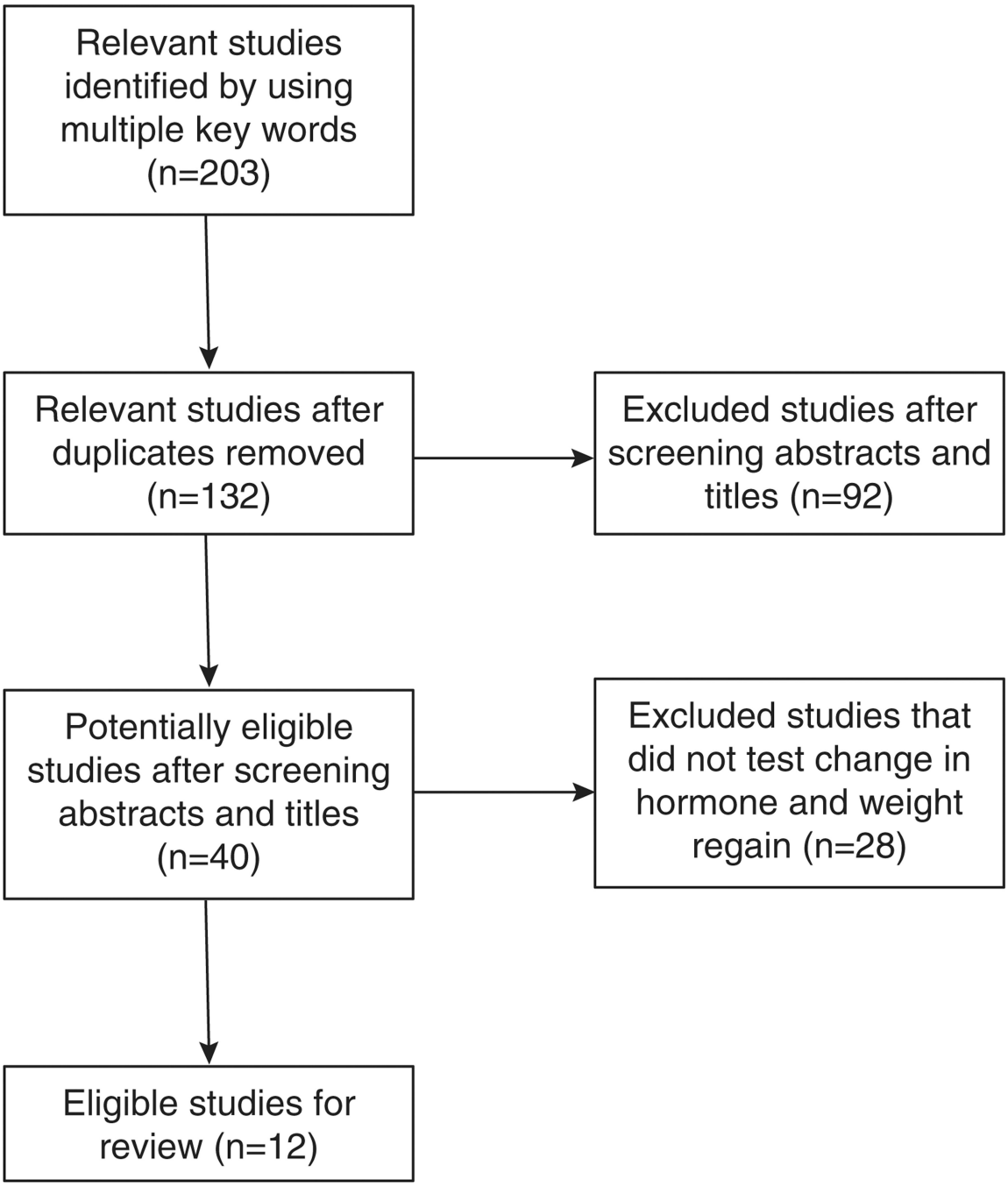

Figure 1.
Study inclusion. This flow chart illustrates the process including relevant studies for the current review.

Table 1

Studies of leptin changes during weight loss and weight regain

Author group and year of publication (citation)	Sample description	Intervention	Initial weight loss and follow-up status	Do decreases in leptin predict regain	Does low baseline leptin predict regain	Does low end point leptin predict regain
Wing *et al.*[45]	Subjects 52 Women Age (years) 41.6 ± 8.0 BMI (kg/m^2) 31.1 ± 3.7	Approach Behavioral intervention with restricted diet (1000–1500 kcal per day) Weight loss-phase 4 months Maintenance phase 6 months	Initial − 8.1 ± 3.6 kg Follow-up − 7.2 ± 6.3 kg	No Declines in fasting leptin during weight loss not associated with weight regain (r = 0.19, P>0.05). (Analysis controlled for change in body weight during weight loss)	No Baseline leptin was not associated with weight regain (P>0.05)	NT
Torgerson *et al.*[42]	Subjects 69 (65% Women) Age (years) M: 44.0 ± 11.9 W: 44.1 ± 11.2 BMI (kg/m^2) M: 39.1 ± 4.5 W: 37.8 ± 3.3	Approach Very low-calorie diet (450 kcal per day) Weight-loss phase 16 weeks Maintenance phase 32 weeks	Initial M: − 20.3 ± 6.7% W: − 15.6 ± 6.9% Follow-up M: − 14.4 ± 7.5% W: − 11.8 ± 8.4%	No Smaller declines in leptin were associated with weight regain (T-ratio = 6.56, P<0.001)	No High baseline leptin associated with weight regain (T-ratio = 4.70, P<0.001)	NT
Mavri *et al.*[44]	Subjects 30 Women Age (years) 40 BMI (kg/m^2) 30.6 ± 5.0	Approach Hypocaloric diet (800–1200 kcal per day Weight–loss phase 3 months Maintenance phase 5 months	Initial − 16 ± 6% body weight Follow-up 12 regained[a], 18 maintained[b]	No Declines in fasting leptin during weight loss larger (− 60%, P<0.01) in those who subsequently maintained weight loss compared with those who regained (− 22%, P = 0.07)	Yes Lower baseline leptin found in those who subsequently regained compared with those who maintained weight loss (P = 0.04)	NT
Vogels and Westerterp-Plantenga[46]	Subjects 103 Age (years) 48 ± 9.5 BMI (kg/m^2) 31.1 ± 3.7	Approach Very low-calorie diet (500 kcal per day) Weight-loss phase 6 weeks Maintenance phase 22.5 months	Initial − 7.2 ± 3.1 kg Follow-up 90 regained[c], 13 maintained[d]	No Declines in fasting leptin during weight loss similar between regainers (− 68%) and maintainers (− 57%) (not tested statistically)	No Baseline leptin not different between maintainers and regainers (P>0.05)	NT
Crujeiras *et al.*[43]	Subjects 104 (47% Women) Age (years) 35 ± 6 BMI (kg/m^2) 31.1 ± 2.9	Approach Hypocaloric diet (30% kcal restriction) Weight-loss phase 8 weeks Maintenance phase 6 months	Initial − 5.0 ± 2.2% body weight Follow-up − 5.68% body weight	No Smaller declines in leptin during weight loss associated with weight regain (r = 0.30, P = 0.005; OR = 0.141, P = 0.001) (Analysis controlled for change in body weight during weight loss)	No High baseline leptin associated with weight regain (r = 0.25, P = 0.021)	NO High post-weight loss leptin associated with weight regain (r = 0.26, P = 0.014)
Erez *et al.*[40]	Subjects 272 (14% Women) Age (years) 51.2 ± 6.4 BMI (kg/m^2) 30.9 ± 3.6	Approach Restricted low-fat or Mediterranean diets (1500–1800 kcal per day) or non-restricted low carbohydrate	Initial − 6.1 ± 5.4% body weight Follow-up − 4.7 ± 5.7% body weight	Yes Larger declines in fasting leptin during weight loss predicts weight regain (β = − 0.131, P = 0.013) (analysis controlled for change in body weight during weight loss)	NT	NT

Int J Obes (Lond). Author manuscript; available in PMC 2017 March 20.

Author group and year of publication (citation)	Sample description	Intervention	Initial weight loss and follow-up status	Do decreases in leptin predict regain	Does low baseline leptin predict regain	Does low end point leptin predict regain
		Weight-loss phase 6 months Maintenance phase 18 months				
Soni *et al.*[41]	Subjects 200 Women Age (years) 57.1 ± 2.9 years BMI (kg/m^2) 30.3 ± 3.7	Approach Lifestyle intervention with restricted low-fat diet (1300–1500 kcal per day) Weight-loss phase 18 months Maintenance phase 12 months	Initial − 10.5 lbs (range: + 18 to − 77.5 lbs) Follow-up[e] 1st (n = 47): + 9.2 to 22 lbs 2nd (n = 47): + 4.7 to 9.2 lbs 3rd (n = 46): + 0.0 to 4.7 lbs 4th (n = 48): − 0.0 to 30 lbs	Yes Larger declines in fasting leptin during weight loss associated with weight regain (P = 0.008) Change in fasting leptin during weight loss not associated with weight regain when limiting analysis to subjects losing >l0 lbs DNS	No Baseline leptin not associated with weight regain (DNS)	NT
Sumithran *et al.*[47]	Subjects 34 (69% Women) Age (years) 56.0 ± 10.6 BMI (kg/m^2) 34.7 ± 3.7	Approach Very low-calorie diet (500–550 kcal per day Weight-loss phase 8 weeks Maintenance phase 12 months	Initial − 13.5 ± 0.5 kg Follow-up − 7.9 ± 1.1 kg	No Declines in fasting leptin during weight loss not associated with weight regain (DNS)	NT	NO Post-weight loss leptin not associated with weight regain (DNS)
Wang *et al.*[48]	Subjects 96 Women Age (years) 29–49 BMI (kg/m^2) Maintainers 34.5 ± 4.8 Regainers 33.3 ± 4.3	Approach Low-calorie diet (790 kcal per day) Weight-loss phase 8 weeks Maintenance phase 6 months	Initial Maintainers − 11.2 kg Regainers − 9.5 kg Follow-up Maintainers − 14.5 Regainers − 5.6 kg	No Declines in fasting leptin during weight loss was not predictive of weight regain (odd ratio exp(B) = 0.55, P = 0.60)[f] (Analysis controlled for change in weight)	No Baseline leptin not associated with weight regain (odd ratio exp(B) = 0.56, P = 0.70)[f]	NO Post-weight loss leptin not associated with weight regain (odd ratio exp(B) = 0.56, P = 0.95)[f]

Abbreviations: BMI, body mass index; β, linear regression beta coefficient; DNS, data not shown; NT, not tested; OR, odds ratio; r, Pearson correlation coefficient. These studies are provided in chronological order, followed by alphabetical order.

[a] Regainers = regained >40% of lost weight.

[b] Maintainers = regained none.

[c] Regainers = regained >10% of their weight.

[d] Maintainers = regained none or <10% of their weight.

[e] Quartiles of weight change.

[f] Estimate from Volcano plot.

Table 2

Studies of ghrelin changes during weight loss and regain

Author group and year of publication (citation)	Sample description	Intervention	Initial weight loss and follow-up status	Do increases in ghrelin predict regain	Does high baseline ghrelin predict regain	Does high end point ghrelin predict regain
Garcia *et al.*[49]	Subjects 48 Mexican women Age (years) 43.6 ± 7.9 BMI (kg/m^2) 37.7 ± 7.9	Approach Behavioral intervention with calorie restriction (− 500 kcal per day) + Orlistat Weight-loss phase 6 months Maintenance phase 6 months	Initial − 3.3 BMI units Follow-up − 3.8 BMI units	No Weight loss-induced increases in fasting ghrelin return to baseline values with sustained weight loss maintenance (not statistically tested)	NT	No Low post-weight loss ghrelin associated with weight regain (r = − 0.46, P<0.01)
Crujeiras *et al.*[43]	Subjects 104 (47% Women) Age (years) 35 ± 6 BMI (kg/m^2) 31.1 ± 2.9	Approach Hypocaloric diet (30% kcal restriction) Weight-loss phase 8 weeks Maintenance phase 6 months	Initial − 5.0 ± 2.2% body weight Follow-up − 5.68% body weight	No Decreases in fasting ghrelin during weight loss associated with weight regain (OR = 3.109, P = 0.008)	No Low baseline ghrelin associated with weight regain (r = − 0.25, P = 0.012)	No Low end point ghrelin associated with weight regain (r = − 0.26, P = 0.007)
Soni *et al.*[41]	Subjects 200 Women Age (years) 57.1 ± 2.9 BMI (kg/m^2) 30.3 ± 3.7	Approach Lifestyle intervention with low-fat diet (1300–1500 kcal per day) Weight-loss phase 18 months Maintenance phase 12 months	Initial − 10.5 lbs (range: + 18 to − 77.5 lbs) Follow-up[a] 1st (n = 47): + 9.2 to 22 lbs 2nd (n = 47): + 4.7 to 9.2 lbs 3rd (n = 46): + 0.0 to 4.7 lbs 4th (n = 48): − 0.0 to 30 lbs	No Change in fasting ghrelin during weight loss not associated with weight regain (P = 0.10)	No Baseline ghrelin not associated with weight regain (DNS)	NT
Sumithran *et al.*[47]	Subjects 34 (69% Women) Age (years) 56.0 ± 10.6 BMI (kg/m^2) 34.7 ± 3.7	Approach Very low-calorie diet (500–550 kcal per day) Weight-loss phase 8 weeks Maintenance phase 12 months	Initial − 13.5 ± 0.5 kg Follow-up − 7.9 ± 1.1 kg	No Change in fasting ghrelin during weight loss not associated with weight regain (DNS)	NT	No Post-weight loss ghrelin not associated with weight regain (DNS)

Abbreviations: BMI, body mass index; DNS, data not shown; NT, not tested; OR, odds ratio; r, Pearson correlation coefficient. These studies are provided in chronological order, followed by alphabetical order.

[a]Quartiles of weight change.

Table 3

Studies of insulin sensitivity changes during weight loss and regain

Author group and year of publication (citation)	Sample description	Intervention	Initial weight loss and follow-up status	Do increases in insulin sensitivity predict regain	Does baseline insulin sensitivity predict regain	Does end point insulin sensitivity predict regain
Yost *et al.*[51]	Subjects 10 Women Age (years) 36 ± 2 BMI (kg/m^2) 34.9 ± 1.1	Approach Low-calorie liquid diet (900 kcal per day) Weight-loss phase 3 months+ 3 months isocaloric maintenance Maintenance phase 18 months	Initial − 11.4 ± 2.2 kg Follow-up 1.1 kg	Yes Increases in insulin sensitivity during weight loss associated with weight regain (r^2=0.78, P = 0.013)	NT	NT
Wing Study 1[52]	Subjects 125 subjects Age (years) 38.7 ± 5.0 BMI (kg/m^2) 30.9 ± 2.2	Approach Behavioral weight loss program with kcal restriction (1000–1500 kcal per day) Weight-loss phase 6 months Maintenance phase 24 months	Initial Study 1: − 9.8 ± 5.5 kg Follow-up Study 1: − 2 kg	No Change in insulin sensitivity during weight loss not associated with weight regain (r = 0.00 for fasting insulin, r = − 0.08 for post glucose-load insulin)	No Baseline insulin sensitivity not associated with weight regain (r = 0.08 for fasting insulin, r = − 0.01 for post glucose-load insulin)	No Post-weight loss insulin sensitivity not associated with weight regain (r = 0.01 for fasting insulin, r = − 0.08 for post glucose-load insulin)
Wing Study 2[52]	Subjects 33 T2D subjects Age (years) 55.8 ± 9.2 BMI (kg/m^2) 36.5 ± 4.8	Approach Behavior modification plus very low-calorie diet (400–500 kcal per day) or balanced low-calorie diet (1000–1200 kcal per day) Weight-loss phase 6 months Maintenance phase 18 months	Initial − 18 kg Follow-up − 8 kg	No Change in insulin sensitivity during weight loss not associated with weight regain (r = 0.20)	No Baseline insulin sensitivity not associated with weight regain (r = − 0.05)	No Post-weight loss insulin sensitivity not associated with weight regain (r = 0.17)
Crujeiras *et al.*[43]	Subjects 104 (47% Women) Age (years) 35 ± 6 BMI (kg/m^2) 31.1 ± 2.9	Approach Hypocaloric diet (30% kcal restriction) Weight-loss phase 8 weeks Maintenance phase 6 months	Initial − 5.0 ± 2.2% body weight Follow-up − 5.68% body weight 49 subjects regained at least 10% of lost weight 55 subjects maintained	No Change in fasting insulin during weight loss not associated with weight regain (OR = 0.541, P = 0.153)	No Baseline insulin not associated with weight regain (r = 0.013)	No Post-weight loss insulin not associated with weight regain (r = 0.047)
Soni *et al.*[41]	Subjects 200 Women Age (years) 57.1 ± 2.9 BMI (kg/m^2) 30.3 ± 3.7	Approach Lifestyle intervention with restricted low-fat diet (1300–1500 kcal per day) Weight-loss phase 18 months Maintenance phase 12 months	Initial − 10.5 lbs (range: + 18 to − 77.5 lbs) Follow-up[a] 1st (n = 47): + 9.2 to 22 lbs 2nd (n = 47): + 4.7 to 9.2 lbs 3rd (n = 46): + 0.0 to 4.7 lbs 4th (n = 48): − 0.0 to –30 lbs	No Change in fasting insulin during weight loss not associated with weight regain (P = 0.30)	No Baseline insulin not associated with weight regain (DNS)	NT
Sumithran *et al.*[47]	Subjects 34 (69% Women)	Approach	Initial − 13.5 ± 0.5 kg	No Change in fasting insulin	NT	No Post-weight loss

Author group and year of publication (citation)	Sample description	Intervention	Initial weight loss and follow-up status	Do increases in insulin sensitivity predict regain	Does baseline insulin sensitivity predict regain	Does end point insulin sensitivity predict regain
	Age (years) 56.0 ± 10.6 BMI (kg/m^2) 34.7 ± 3.7	Very low-calorie diet (500–550 kcal per day) Weight-loss phase 8 weeks Maintenance phase 12 months	Follow-up − 7.9 ± 1.1 kg	not associated with weight regain (DNS)		insulin not associated with weight regain (DNS)

Abbreviations: BMI, body mass index; DNS, data not show; NT, not tested; OR, odds ratio; *r*, Pearson correlation coefficient; T2D, type 2 diabetes. These studies are provided in chronological order, followed by alphabetical order.

[a]Quartiles of weight change.