ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

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ABSTRACT

BACKGROUND

After weight loss, changes in the circulating levels of several peripheral hormones involved in the homeostatic regulation of body weight occur. Whether these changes are transient or persist over time may be important for an understanding of the reasons behind the high rate of weight regain after diet-induced weight loss.

METHODS

We enrolled 50 overweight or obese patients without diabetes in a 10-week weight-loss program for which a very-low-energy diet was prescribed. At baseline (before weight loss), at 10 weeks (after program completion), and at 62 weeks, we examined circulating levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, glucagon-like peptide 1, amylin, pancreatic polypeptide, cholecystokinin, and insulin and subjective ratings of appetite.

RESULTS

Weight loss (mean [±SE], 13.5±0.5 kg) led to significant reductions in levels of leptin, peptide YY, cholecystokinin, insulin ($P<0.001$ for all comparisons), and amylin ($P=0.002$) and to increases in levels of ghrelin ($P<0.001$), gastric inhibitory polypeptide ($P=0.004$), and pancreatic polypeptide ($P=0.008$). There was also a significant increase in subjective appetite ($P<0.001$). One year after the initial weight loss, there were still significant differences from baseline in the mean levels of leptin ($P<0.001$), peptide YY ($P<0.001$), cholecystokinin ($P=0.04$), insulin ($P=0.01$), ghrelin ($P<0.001$), gastric inhibitory polypeptide ($P<0.001$), and pancreatic polypeptide ($P=0.002$), as well as hunger ($P<0.001$).

CONCLUSIONS

One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss. Long-term strategies to counteract this change may be needed to prevent obesity relapse. (Funded by the National Health and Medical Research Council and others; ClinicalTrials.gov number, NCT00870259.)

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N Engl J Med 2011;365:1597-604.

Worldwide, there are more than 1.5 billion overweight adults, including 400 million who are obese.[1] Although dietary restriction often results in initial weight loss, the majority of obese dieters fail to maintain their reduced weight.[2] Understanding the barriers to maintenance of weight loss is crucial for the prevention of relapse.

Body weight is centrally regulated, with peripheral hormonal signals released from the gastrointestinal tract, pancreas, and adipose tissue integrated, primarily in the hypothalamus, to regulate food intake and energy expenditure.[3] The number of identified peripheral modulators of appetite is expanding rapidly and includes leptin, ghrelin, cholecystokinin, peptide YY, insulin, pancreatic polypeptide, and glucagon-like peptide 1 (GLP-1).[4-10]

Caloric restriction results in acute compensatory changes, including profound reductions in energy expenditure[11] and levels of leptin[12] and cholecystokinin[13] and increases in ghrelin[14] and appetite,[15] all of which promote weight regain. It was recently shown that a disproportionate reduction in 24-hour energy expenditure persists in persons who have maintained a reduced body weight for more than 1 year[16]; however, it is not known whether the changes in levels of appetite-regulating hormones that occur during weight reduction are sustained with prolonged maintenance of reduced weight. The present study was designed to address this question, which may be important for understanding the physiological basis of weight regain after weight loss.

Methods

Participants and Study Oversight

We recruited men and postmenopausal women with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) between 27 and 40 by means of newspaper advertisement. Smokers, persons with clinically significant illness, including diabetes, and those taking medications known to affect body weight were excluded. The study was approved by the Austin Health Human Research Ethics Committee, and all participants provided written informed consent.

Study Design

Weight-Loss Phase

For 8 weeks, participants were instructed to replace all three of their daily meals with a very-low-energy dietary formulation (Optifast VLCD, Nestlé) and 2 cups of low-starch vegetables, according to the manufacturer's guidelines, which provided 2.1 to 2.3 MJ (500 to 550 kcal) per day. During weeks 9 and 10, participants who had lost 10% or more of their initial body weight were gradually reintroduced to ordinary foods, and weight was stabilized to avoid the potential confounding effect of active weight loss on hormone profiles. Meal replacements were stopped at the end of week 10.

Weight-Maintenance Phase

At the end of week 10, participants received individual counseling and written advice from a dietician on a dietary intake that would be consistent with their calculated energy expenditure, with the aim of weight maintenance. No specific macronutrient ratios were prescribed, but carbohydrates with a low glycemic index and a reduced intake of fat were recommended. Participants were also encouraged to engage in 30 minutes of moderately intense physical activity on most days of the week. They visited the clinical research unit at Heidelberg Repatriation Hospital every 2 months, and were contacted by telephone between visits for continued dietary counseling.

Data Collection

Testing was performed after an overnight fast at baseline (week 0), week 10, and week 62. Participants wore light clothing and were barefoot when anthropometric measurements were made. Bioelectrical impedance was used to measure body weight and composition, with the use of a body-composition analyzer (TBF-300, Tanita). At each of these visits, the first measurement was made while the patient was fasting (baseline). A standardized breakfast was then provided, which consisted of a boiled egg, toast, margarine, orange juice, cereal biscuits (Weet-Bix, Sanitarium), and whole milk. This meal contained 2.3 MJ (550 kcal), with approximately 51% of the energy from carbohydrate, 33% from fat, and 16% from protein. Blood samples were collected 30, 60, 120, 180, and 240 minutes after the meal. Self-reported ratings of appetite were also recorded at these times with the use of a validated 100-mm visual-analogue scale.[17]

Biochemical Assays

Fasting and postprandial plasma levels of acylated ghrelin, active GLP-1, total gastric inhibitory polypeptide, pancreatic polypeptide, amylin, and peptide YY were measured in the same assay with the

use of the human gut hormone panel (LINCOplex Kit, Millipore). Plasma levels of insulin, leptin, and cholecystokinin were measured with the use of a radioimmunoassay. (Additional details on the assays are available in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STATISTICAL ANALYSIS

Two analyses were conducted. In the intention-to-treat analysis, measures that were missing for participants who discontinued the study were replaced with baseline measures. In the second analysis, the only data included were from participants who completed the study (through the 12-month follow-up period). Since our aim was to examine the nature and duration of the physiological changes that occur as a result of diet-induced weight loss, only the data from participants who completed the study are provided for measures of biochemical values and appetite.

Continuous measures were compared with the use of nonparametric tests (the Wilcoxon signed-rank test for pairwise comparison of changes in measurements between study visits, and the Wilcoxon rank-sum test for comparisons between two independent groups). However for the sake of simplicity, descriptive statistics are reported as means ±SE unless stated otherwise. Exact P values for Wilcoxon tests were computed with the shift algorithm, which also corrected for ties. Comparisons of independent proportions were calculated with Fisher's exact test. Spearman's rank correlations and associated P values were computed with algorithm AS 89.[18]

Analyses of fasting and 4-hour postprandial hormone profiles and ratings on the visual-analogue scale were carried out by fitting linear mixed-effect models to the data. The linear mixed-effect model, a repeated-measures analysis, included fasting and postprandial measurements and both fixed effects (postprandial time, week, and interaction) and random effects (participant characteristics). Linear mixed-effect estimation was carried out with the use of restricted maximum-likelihood methods, and the overall significance of each fixed effect was assessed by means of Wald tests. When no significant interaction could be detected between postprandial time and week (indicating similar postprandial changes relative to fasting values at different weeks), the model was refitted without interaction, and Tukey's test was used for multiple comparisons of means. When interaction was present (suggesting an alteration in the postprandial hormone profile after weight loss), significant differences in linear mixed-effect coefficients at weeks 10 and 62, as compared with those at week 0, were reported for individual postprandial time points, and the linear mixed-effect model was restricted to weeks 10 and 62, for a more direct comparison between these weeks. The analysis of gastrointestinal hormones excluded one participant whose biochemical values were more than 5 SD beyond the mean. At baseline, measures of fasting biochemical data were missing for one participant. Less than 2% of the remaining data were missing. Linear mixed-effect analyses were applied to the raw data with no imputation of missing values. To ensure insensitivity of the results to missing data, analyses were repeated after imputation (see the Supplementary Appendix).

RESULTS

STUDY PARTICIPANTS

Among the 50 participants who began the study, 4 withdrew during the first 8 weeks, while they were on the very-low-energy diet. An additional 7 participants did not lose the required 10% of body weight. During the 12-month follow-up period, 5 participants withdrew. Baseline characteristics of all participants who commenced the study and of those who completed it are shown in Table 1. There were no significant differences in any baseline measurements between those who did and those who did not complete the study, but there was a trend toward a younger age among participants who did not complete the study.

BODY MEASUREMENTS

Changes in body weight (Fig. 1) were significant in both the intention-to-treat analysis and the analysis that included only those participants who completed the study. Although male participants were significantly heavier than female participants throughout the study period (mean [±SD] baseline weight, 105.9±12.6 kg vs. 90.5±11.0 kg; P<0.001), the pattern of weight change was similar for men and women; consequently, the data were combined for the purposes of analysis.

Changes in anthropometric measurements for the participants who completed the study are shown in Table 2. The mean weight loss at the end of week 10 was 13.5±0.5 kg (14.0% of initial weight). All anthropometric measurements de-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Total (N=50)	Completed Study (N=34)	Did Not Complete Study (N=16)	P Value
Age (yr)	54.4±10.9	56.0±10.6	51.0±11.2	0.05
Female sex (%)	68	68	69	1.00
Weight (kg)	95.4±13.5	96.3±13.7	93.6±13.5	0.47
BMI	34.7±3.2	34.7±3.7	34.5±2.0	0.86
Waist circumference (cm)	103.1±10.0	103.6±10.9	102.1±8.1	0.75
Hip circumference (cm)	120.8±8.0	120.6±8.2	121.2±7.8	0.84
Blood pressure (mm Hg)				
Systolic	135.5±20.2	137.9±20.2	130.3±19.7	0.17
Diastolic	83.1±10.8	82.8±11.8	83.8±8.7	0.71
Heart rate (beats/min)	74.6±8.5	74.9±7.3	74.0±10.8	0.86
Fat (%)	52.1±9.3	51.6±8.5	53.3±11.0	0.68

* Plus–minus values are means ±SD. BMI denotes body-mass index, calculated as the weight in kilograms divided by the square of the height in meters.

creased significantly between weeks 0 and 10 and remained significantly below baseline values at week 62. Only data from the 34 patients who completed the study are included in the analyses that follow.

HORMONAL REGULATORS OF APPETITE

Leptin

During the weight-loss period, mean fasting plasma levels of leptin decreased by 64.5±3.4% (P<0.001). Levels rose between weeks 10 and 62, but at week 62, they remained 35.5±4.7% below baseline levels (P<0.001). Reductions in leptin levels from baseline at weeks 10 and 62 remained significant when adjusted for fat mass, and the ratio of leptin to fat mass was significantly lower at week 10 than at week 62 (Table 1 in the Supplementary Appendix). Percentage reductions in leptin and weight correlated strongly at week 10 (r=0.78, P<0.001) and week 62 (r=0.78, P<0.001). There was a strong linear relationship between the log-transformed percentage of leptin regained and weight regained, indicating that leptin levels and body weight rose concurrently.

Gastrointestinal Hormones

Mean fasting and postprandial levels of ghrelin, peptide YY, amylin, and cholecystokinin are shown in Figure 2. (Fig. 1 in the Supplementary Appendix provides these data for the remaining hormones studied, and Table 1 in the Supplementary Appendix provides information on the area under the curve and the median percentage changes in biochemical values from baseline.)

The linear mixed-effect analysis of hormone levels according to postprandial period and study week revealed that postprandial changes were highly significant for each hormone studied (P<0.001 for all comparisons). The interaction between the postprandial period and study week was not significant for ghrelin, peptide YY, GLP-1, cholecystokinin, or pancreatic polypeptide, suggesting that there were similar patterns of postprandial hormone suppression or secretion at baseline and at weeks 10 and 62. For each of these hormones, however, each week was highly significant (P≤0.001 for ghrelin, peptide YY, pancreatic polypeptide, and cholecystokinin; P=0.008 for GLP-1), indicating differences in absolute hormone levels at each study week.

Mean levels of ghrelin rose significantly with weight loss (P<0.001 for the change from baseline to week 10). Although ghrelin levels fell between week 10 and week 62 (P<0.001), the mean level remained significantly higher at 62 weeks than at baseline (P<0.001). For peptide YY, mean levels were significantly lower at weeks 10 and 62 than at baseline (P<0.001 for both comparisons), with levels that were significantly lower at week 62 than those at week 10 (P=0.004). For amylin, the interaction between postprandial period and study week was close to being significant (P=0.05). Fast-

ing levels of amylin declined significantly with weight loss (P=0.008 for the change from baseline to week 10; P=0.05 for the change from baseline to week 62). The reduction from baseline in amylin secretion within the first 30 minutes after eating was significant at week 10 (P=0.002) and approached significance at week 62 (P=0.08). The mean level of cholecystokinin was significantly lower at weeks 10 and 62 than at baseline (P<0.001 and P=0.04, respectively), with no significant difference in levels between weeks 10 and 62.

For gastric inhibitory polypeptide, the interaction between postprandial period and study week was significant (P=0.02), owing to the greater secretion of this hormone in the first 60 minutes after meals at weeks 10 and 62 than at baseline (P=0.004 and P<0.001, respectively). Mean levels of gastric inhibitory polypeptide did not differ significantly between weeks 10 and 62. Mean levels of GLP-1 did not change significantly between baseline and week 10; the levels at week 62 were slightly but significantly lower than baseline levels (P=0.005).

Decreases in insulin levels after weight loss were evident, and the interaction between postprandial period and study week was significant (P<0.001), with significant reductions in meal-stimulated insulin release 30 and 60 minutes after eating, both from baseline to week 10 (P<0.001 for the two postprandial comparisons) and from baseline to week 62 (P<0.001 for the comparison at 30 minutes; P=0.01 for the comparison at 60 minutes). Mean levels of pancreatic polypeptide were significantly higher at week 10 and week 62 than at baseline (P=0.008 and P=0.002, respectively), with no significant difference between levels at weeks 10 and 62.

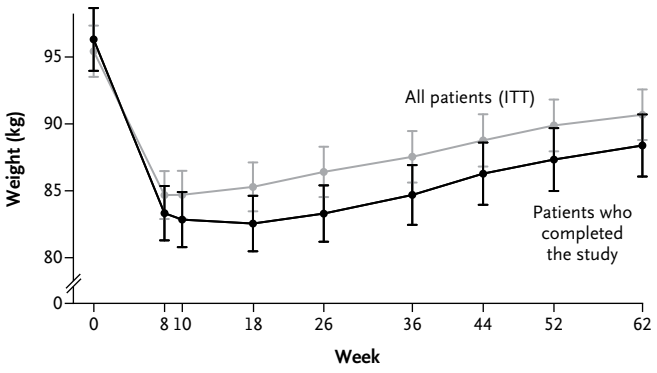

Figure 1. Mean (±SE) Changes in Weight from Baseline to Week 62.
The weight-loss program was started at week 0 and completed at week 10. ITT denotes intention to treat.

APPETITE

Figure 3 shows mean ratings, on a visual-analogue scale, of fasting and postprandial hunger and desire to eat at baseline and at weeks 10 and 62. (Additional ratings are available in Fig. 2 and Table 2 in the Supplementary Appendix.) The linear mixed-effect analysis revealed that mean ratings of hunger, desire and urge to eat, and prospective consumption were significantly higher at weeks 10 and

Table 2. Changes in Body Measurements.*

Variable	Baseline to Wk 10	P Value	Wk 10 to Wk 62	P Value	Baseline to Wk 62	P Value
Weight (kg)	−13.5±0.5	<0.001	5.5±1.0	<0.001	−7.9±1.1	<0.001
Percent change in weight	−14.0±0.4	<0.001	4.4±0.7	<0.001	−8.2±1.1	<0.001
BMI	−4.8±0.1	<0.001	2.0±0.3	<0.001	−2.8±0.4	<0.001
Waist circumference (cm)	−11.1±0.5	<0.001	4.1±0.9	<0.001	−7.0±1.1	<0.001
Hip circumference (cm)	−9.0±0.4	<0.001	2.5±0.8	0.002	−6.5±0.8	<0.001
Blood pressure (mm Hg)						
Systolic	−13.5±2.7	<0.001	5.9±3.1	0.05	−7.7±3.2	0.03
Diastolic	−8.8±1.7	<0.001	4.9±1.7	0.009	−4.0±1.4	0.01
Heart rate (beats/min)	−4.7±1.6	0.005	1.9±1.8	0.30	−2.8±1.8	0.04
Fat (%)	−9.8±0.7	<0.001	4.5±0.8	<0.001	−5.3±0.9	<0.001

* Plus–minus values are means ±SE. P values are for the changes in body measurements within each time period.

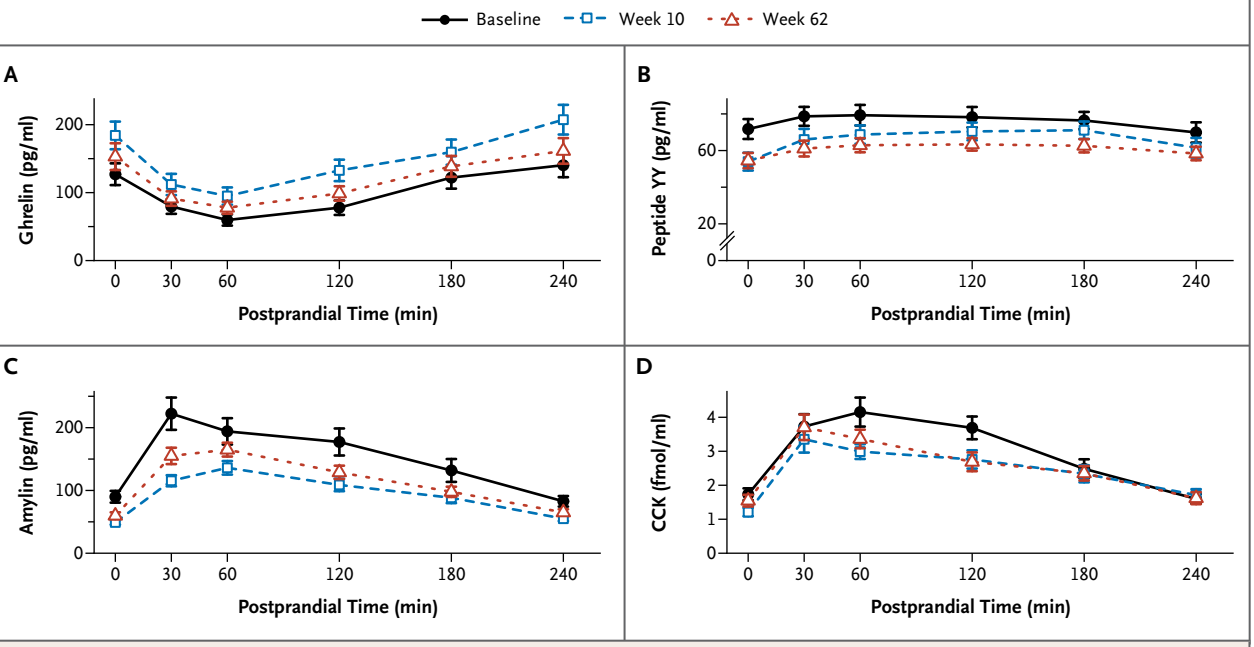

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

62 than at baseline (P<0.001 for all comparisons), with no significant differences between mean ratings at weeks 10 and 62 and no significant interactions between postprandial period and study week. Ratings for preoccupation with thoughts of food, as compared with baseline ratings, tended to increase at week 10 (P=0.09) and were significantly increased at week 62 (P=0.008). Mean ratings for fullness did not change significantly from baseline to week 10 or week 62 but were significantly lower at week 62 than at week 10 (P=0.03).

DISCUSSION

Although short-term weight loss is readily achieved through dietary restriction, only a small minority of obese people maintain diet-induced weight loss in the long term.[19] A multitude of hormones, peptides, and nutrients are involved in the homeostatic regulation of body weight, many of which are perturbed after weight loss. Whether these changes represent a transient compensatory response to an energy deficit is unknown, but an important finding of this study is that many of these alterations persist for 12 months after weight loss, even after the onset of weight regain, suggesting that the high rate of relapse among obese people who have lost weight has a strong physiological basis and is not simply the result of the voluntary resumption of old habits.

Leptin, an adipocyte hormone, is an indicator of energy stores[20] and acts in the hypothalamus to reduce food intake and increase energy expenditure.[21,22] Ghrelin, peptide YY, gastric inhibitory polypeptide, GLP-1, cholecystokinin, pancreatic polypeptide, and amylin are released from the gastrointestinal tract and pancreas in response to nutrient intake; all but two inhibit intake.[8,10,23-25] The exceptions are ghrelin, which stimulates hunger,[7] and gastric inhibitory polypeptide, which may promote energy storage.[26,27]

Caloric restriction results in a rapid, profound reduction in circulating levels of leptin[28,29] and energy expenditure[30] and an increase in appetite.[15] Other effects of diet-induced weight loss include increased levels of ghrelin[14] and reduced levels of peptide YY[31] and cholecystokinin.[13] Our study shows that after diet-induced weight loss, there are alterations in the postprandial release of amylin and pancreatic polypeptide and, more important, that changes in levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, pancreatic polypeptide, amylin, and cholecystokinin, as well as changes in appetite, persist for 12 months. In ad-

dition, these changes would be expected to facilitate regain of lost weight, with the exception of the change in the level of pancreatic polypeptide, which reduces food intake.[10] However, our findings are consistent with a study of obese children in which levels of pancreatic polypeptide increased after diet-induced weight loss.[32]

A greater-than-predicted decline in 24-hour energy expenditure after weight loss also persists for 1 year or more after the loss in weight has been maintained.[16] In obese rats with diet-induced weight loss, normalization of enhanced metabolic efficiency lags behind weight regain.[33]

Taken together, these findings indicate that in obese persons who have lost weight, multiple compensatory mechanisms encouraging weight gain, which persist for at least 1 year, must be overcome in order to maintain weight loss. These mechanisms would be advantageous for a lean person in an environment where food was scarce, but in an environment in which energy-dense food is abundant and physical activity is largely unnecessary, the high rate of relapse after weight loss is not surprising. Furthermore, the activation of this coordinated response in people who remain obese after weight loss supports the view that there is an elevated body-weight set point in obese persons and that efforts to reduce weight below this point are vigorously resisted. In keeping with this theory, studies have shown that after adjustment for body composition, people whose weight is normal and those who are obese have similar energy requirements for weight maintenance[11] and equivalent reductions in energy expenditure[30] after weight loss. If this is the case, successful management of obesity will require the development of safe, effective, long-term treatments to counteract these compensatory mechanisms and reduce appetite. Given the number of alterations in appetite-regulating mechanisms that have been described so far, a combination of medications will probably be required. Several such combinations are undergoing evaluation,[34,35] but none have been approved by the Food and Drug Administration. Bariatric surgery has well-documented favorable effects on appetite-mediating hormones, hunger, body weight, hypertension, dyslipidemia, type 2 diabetes, and mortality.[36-38] However, because of the attendant costs and long waiting periods, bariatric surgery is not readily accessible to most people.

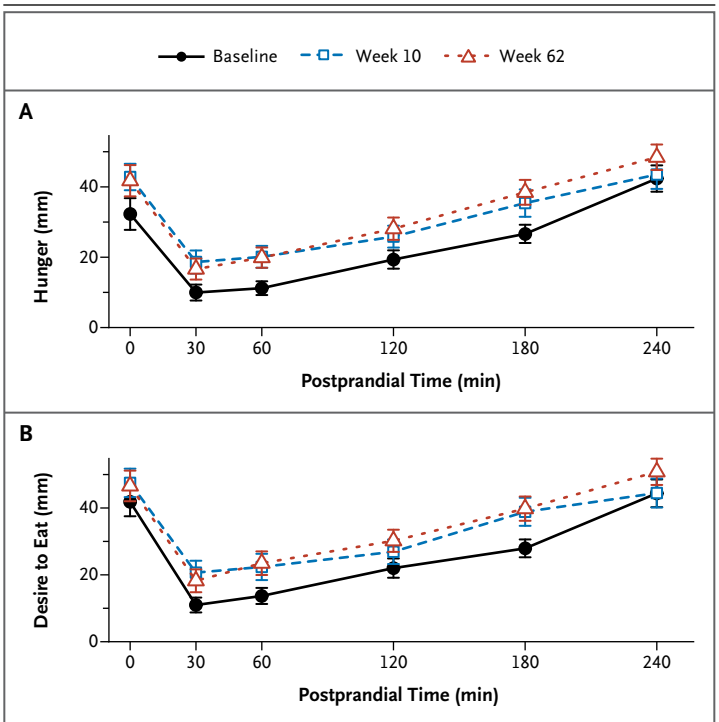

Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

There are several limitations of this study. First, the attrition rate was high, as it typically is in studies of long-term weight loss.[19] The analyses included only those participants who completed the study, since our intention was to assess the duration of physiological responses to substantial weight loss. However, the possibility that changes in hormone levels and appetite differed in patients who discontinued the study cannot be ruled out. Second, the use of a multiplex assay inevitably results in measurements of individual hormones that are less accurate and precise than those obtained with an optimized assay. However, these factors are likely to minimize the detection of changes occurring after weight loss. Finally, the possibility that weight loss may alter central sensitivity to circulating hormones was not examined.

In conclusion, we found that the compensatory changes in circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to baseline values within 12 months after the initial weight reduction.

Supported by a project grant from the National Health and Medical Research Council (508920), a scholarship from the Endocrine Society of Australia, a Shields Research Scholarship from the Royal Australasian College of Physicians (to Dr. Sumithran), and funding from the Sir Edward Dunlop Medical Research Foundation (to Dr. Proietto).

Disclosure forms provided by the authors are available at NEJM.org.

We thank Celestine Bouniou, John Cardinal, Sherrell Cardinal, Christian Rantzau, Rebecca Sgambellone, Sherley Visinoni, and Mildred Yim for providing technical assistance.

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