

## ORIGINAL ARTICLE

## Obesity Biology and Integrated Physiology

# Impact of starting BMI and degree of weight loss on changes in appetite-regulating hormones during diet-induced weight loss

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## Abstract

**Objective:** The aim of this study was to determine whether the hormone changes following weight loss are proportional to the degree of weight loss and to starting BMI.

**Methods:** A very low-energy diet was used to achieve 15% weight loss. Fasting and postprandial gut hormones and leptin were measured during a meal test at baseline and at 5% (1%), 10% (2%), and 15% (2.5%) weight loss. Linear mixed-effects models were used to analyze hormone changes.

**Results:** From baseline to 5% weight loss, decreases were seen in fasting concentrations of leptin ( $-8.25$  ng/mL;  $p < 0.001$ ), amylin ( $-21.3$  pg/mL;  $p < 0.001$ ), and glucagon-like peptide 1 ( $-59.55$  pg/mL;  $p < 0.001$ ). There was a small further reduction in leptin between 5% and 15% weight loss ( $-1.88$  ng/mL;  $p = 0.019$ ) but not in glucagon-like peptide 1 and amylin. Fasting ghrelin showed a significant increase at 10% weight loss ( $41.64$  pg/mL;  $p = 0.002$ ), with a nonsignificant increase from 10% to 15% loss ( $26.03$  pg/mL;  $p = 0.065$ ). Postprandial changes in hormone levels were variable. There was no correlation between baseline weight and the degree of hormone changes.

**Conclusions:** The majority of changes in fasting gut hormones and leptin occurred in early weight loss, with minor further changes up to 15% weight loss. Starting weight did not affect the degree of hormone change.

## INTRODUCTION

Obesity is a complex, chronic disease, with well-known adverse effects on health. Worldwide, in 2015, a total of 107 million children and 603 million adults had obesity (1). Dietary and lifestyle interventions result in initial weight loss; however, these losses are not well maintained in the longer term (2). Given the relapsing nature of obesity, it is of critical importance to understand the reasons why weight loss is so poorly maintained.

Energy intake and expenditure are tightly regulated by several mechanisms. Chief among these is communication regarding energy

balance between peripheral organs, such as the gut, the pancreas, and adipose tissue, and the brain, mediated by several hormones and neuropeptides (3). Numerous peripheral mediators of appetite have been identified, including leptin, ghrelin, amylin, glucagon-like peptide 1 (GLP-1), cholecystokinin, pancreatic polypeptide, insulin, peptide tyrosine-tyrosine, and gastric inhibitory polypeptide (GIP) (4-10).

Previous research has indicated that weight loss leads to hormonal adaptations, increased hunger, and a decrease in energy expenditure (adaptive thermogenesis) (4,11,12). These changes are long-lasting and they have been hypothesized to be physiological

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drivers of weight regain (11,12). However, what is not known is whether hormone changes occur across a range of excess weights and whether these changes are proportional to the degree of weight loss. The primary objectives of this study were to determine what degree of reduction in body weight is required to bring about these compensatory mechanisms and to investigate whether hormone changes occur equally across a range of BMI values.

## METHODS

### Participants and study oversight

Men and women between the ages of 18 and 65 years, with BMI over 25 kg/m<sup>2</sup> and stable body weight for the past 12 months, were recruited via newspaper and newsletter advertisement. Persons with clinically significant illnesses (such as diabetes, cancer, active thyroid diseases, or serious cardiac, liver, or renal diseases), those taking medications known to be weight-altering, and those with a history of bariatric surgery were excluded. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN: 12614000141640) and approved by the Austin Health Human Research Ethics Committee, and all participants provided written, informed consent.

### Study design

Participants were placed on a very low-energy diet, consisting of two meal-replacement products (Optifast VLCD, Nestle Nutrition Healthcare, Victoria, Australia) per day, plus a meal consisting of 100 to 150 g of protein, with 2 cups of low-carbohydrate vegetables (total of 800-880 kcal [3,360-3,700 kJ] per day). Meal tests were conducted at baseline and after 5% (1%), 10% (2%), and 15% (2.5%) weight loss. This was achieved by instructing participants to monitor their weight at home regularly and to contact one of the investigators (KE) to schedule a visit when within 1 kg of the target weight for that visit. The timing of visits was flexible in order to occur as close as possible to the target weight; however, the maximum duration allowed to achieve the 15% target was 16 weeks.

### Data collection

Participants attended each visit fasting. After collection of anthropometric measurements (weight, height [baseline only], waist and hip circumference, and blood pressure), participants were given a standardized breakfast of a poached egg (60 g), two slices of white toast (Tip Top Sunblest Soft White Sandwich, George Weston Foods Ltd., Enfield, Australia), 10 g of margarine (Flora Original, Unilever, Sydney, Australia), 200 mL of orange juice (Daily Juice, The Daily Drinks Company, Docklands, Australia), two wheat biscuits (Weet-Bix, Sanitarium, Berkeley Vale, Australia), and 120 mL of full-cream

### Study Importance

#### What is already known?

- ▶ Following weight loss, there is a change in hunger- and appetite-controlling hormones that is long-lasting.

#### What does this study add?

- ▶ Hormone changes are already present by the time 5% weight loss occurs.
- ▶ There are only minor changes with further weight loss.
- ▶ Hormone changes occur at all degrees of initial weight.

#### How might these results change the direction of research or the focus of clinical practice?

- ▶ These findings have the potential to change practice, as nearly all guidelines advise 5% weight loss as being realistic; however, there is evidence that greater weight loss has further health benefits. Because our study suggests that 5% weight loss induces a compensatory response, it may not be easier to maintain than 10% or 15% loss; therefore, evidence-based weight-management guidelines should be amended to advise as much weight loss as required for individual needs.

milk. During the meal-test period, participants were seated in a quiet room and were allowed to read or watch television. No food or drink was allowed, except for water, after consumption of the standardized breakfast. Participants also completed ratings of appetite prior to the meal (baseline) and at +30, +60, and +240 minutes, using a validated 100-mm visual analog scale (13).

### Blood sampling

Blood samples were collected at baseline and at 30, 60, and 240 minutes after the breakfast meal. Samples were collected via an intravenous cannula into chilled P800 tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) containing dipotassium EDTA (K<sub>2</sub>EDTA) plus a proprietary protease inhibitor, designed for the collection, storage, and analysis of gut hormones. Tubes were placed on ice immediately after collection and centrifuged within 30 minutes of collection. Plasma was separated into aliquots, which were stored at -80°C until analysis.

### Biochemical assays

Hormone analysis was performed by Cardinal Bioresearch Pty Ltd. (Brisbane, Australia). Fasting and postprandial total amylin

was measured using a Human Metabolic Panel Milliplex kit (Merck Millipore, Darmstadt, Germany). The sensitivity of this assay is 15 pg/mL, and the intra- and inter-assay variation is 9.2% and 13.4%, respectively. Fasting and postprandial total ghrelin, GIP, active GLP-1, and leptin were measured using a Bio-Plex diabetes panel (Bio-Rad, Hercules, California). The sensitivity of the assay is 1.2, 0.8, 5.3, and 3.1 pg/mL for the hormones, as listed previously. The intra- and inter-assay variation is <7% and <15%, respectively. Both assays used are magnetic bead-based multiplex assays, which allow for the simultaneous detection of multiple biomarkers. For each analyte, all samples were tested in duplicate, using the same kit or panel batch number.

## Statistical analyses

All results are reported as mean (SEM). Linear mixed-effects models with random intercepts (participant) and slopes were used to analyze hormone changes. Visit (baseline, 5%, 10%, and 15% weight loss) and postprandial time (0, +30, +60, and +240 minutes) were included as factors to allow for nonlinear change

over time. Interaction terms were included to allow for differences in rate of change of postprandial hormone levels during the different weight-loss phases. Satterthwaite's approximation was used for the degrees of freedom in the calculation of *p* values and confidence intervals (CI). Analyses were conducted in R version 3.3.3, linear mixed-effects models were fitted using the lmer function in the lme4 package (14), and tests and CI for between-visit change used the lmerTest package (R Foundation, Vienna, Austria) (15).

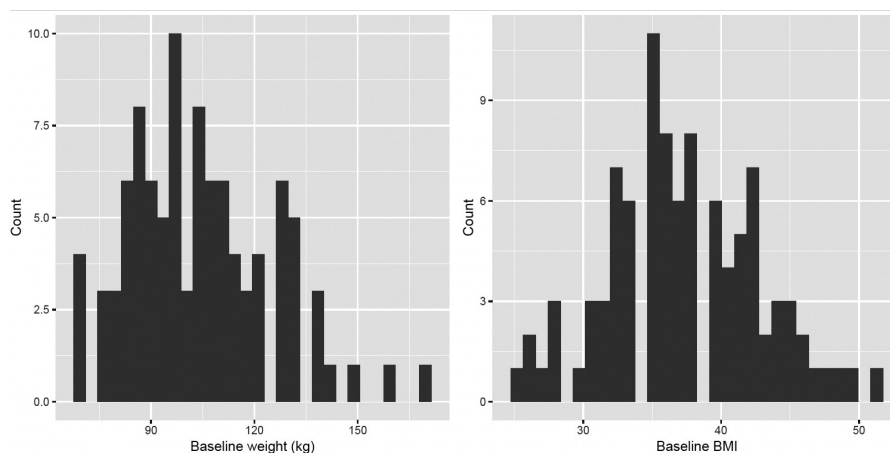
Unpaired *t* tests were used to compare the baseline characteristics of participants who completed the study and participants who withdrew, except for sex, for which the Fisher exact test was used. Appetite ratings on the visual analog scale were analyzed using the Wilcoxon signed rank test. Correlations analyses comparing baseline BMI and weight with the area under the curve of hormone changes were performed using Spearman rank correlation.

Participant data were included in the linear mixed-effects models and correlation analyses only if they achieved the 15% (2.5%) weight-loss target. The *n* value at each visit varied slightly, as participant data were excluded if the participant did not meet or had overshot the target weight for that visit.

**TABLE 1** Baseline characteristics of participants who completed the baseline visit

	Total ( <i>n</i> = 97)	Completers ( <i>n</i> = 49)	Withdrawn ( <i>n</i> = 48)	<i>p</i> value
Sex (male/female; %)	25.8%/74.2%	30.6%/69.4%	20.8%/79.2%	0.35
Age (y)	49.2 ± 11.0	51.1 ± 9.9	47.4 ± 11.8	0.10
Weight (kg)	104.1 ± 20.3	102.4 ± 18.3	105.8 ± 22.0	0.42
BMI (kg/m <sup>2</sup> )	37.3 ± 5.5	36.7 ± 5.1	38.0 ± 5.8	0.25
Systolic blood pressure (mm Hg)	130.2 ± 13.1	133.3 ± 11.2	127.1 ± 14.1	<b>0.02</b>
Diastolic blood pressure (mm Hg)	81.3 ± 7.5	82.0 ± 6.7	80.6 ± 8.1	0.38
Waist circumference (cm)	110.7 ± 14.8	110.1 ± 14.2	111.3 ± 15.3	0.69
Hip circumference (cm)	122.2 ± 11.8	121.3 ± 11.2	123.2 ± 12.2	0.45

Note: Values are presented as mean ± SD; *p* values are for the differences between completers and withdrawals. Values in bold are statistically significant.



**FIGURE 1** Distribution of baseline weight (left panel) and baseline BMI (right panel; *n* = 97)

TABLE 2 Changes in anthropometric measurements

Characteristic	Baseline to 5% weight loss (n = 42)	p value	5% weight loss to 10% weight loss (n = 48)	p value	10% weight loss to 15% weight loss (n = 49)	p value
Weight (kg)	-5.2 (-5.6 to -4.7)	<0.001	-5.1 (-5.6 to -4.5)	<0.001	-5.0 (-5.5 to -4.4)	<0.001
BMI (kg/m <sup>2</sup> )	-1.9 (-2.0 to -1.7)	<0.001	-1.8 (-2.0 to -1.7)	<0.001	-1.8 (-1.9 to -1.6)	<0.001
Systolic blood pressure (mm Hg)	-7.9 (-10.6 to -5.2)	<0.001	-4.0 (-7.0 to -1.0)	0.009	0.5 (-2.7 to 3.7)	0.764
Diastolic blood pressure (mm Hg)	-4.1 (-5.8 to -2.3)	<0.001	-2.3 (-4.2 to -0.4)	0.021	-0.1 (-2.2 to 2.0)	0.892
Waist circumference (cm)	-4.2 (-5.0 to -3.4)	<0.001	-5.0 (-6.0 to -4.1)	<0.001	-4.9 (-5.9 to -3.9)	<0.001
Hip circumference (cm)	-3.0 (-3.7 to -2.2)	<0.001	-4.2 (-5.0 to -3.3)	<0.001	-5.0 (-5.9 to -4.1)	<0.001

Note: Values are presented as mean (95% CI); p values are for the changes in each characteristic within the weight-loss phase. Values in bold are statistically significant.

## RESULTS

### Participants

Of the 97 participants who attended the baseline visit, 70 (72.2%) achieved 5% (1%) weight loss, 64 (66.0%) achieved 10% (2%) weight loss, and 49 (50.5%) achieved 15% (2.5%) weight loss. Withdrawal was attributed to several reasons, the most common being nonadherence to diet or failure to achieve target weight (56.2%) and loss to follow-up (18.8%). Baseline characteristics are shown in Table 1. Participants demonstrated a wide range of weights (67.6-168.0 kg [mean = 104.1 kg, median = 102.2 kg]) and BMI values (25.5-51.6 [mean = 37.3, median = 37]; Figure 1). A comparison of baseline characteristics between participants who completed the study and those who withdrew did not show any significant differences, except for systolic blood pressure, which was significantly lower in the withdrawal group (Table 1).

### Body measurements

Changes in body measurements for participants who completed the weight-loss phase are presented in Table 2. Blood pressure (systolic and diastolic) decreased significantly between baseline and 5% weight loss and 5% to 10% weight loss but it did not change further between 10% and 15% weight loss.

### Hormone changes

#### Fasting hormone levels

Mean fasting ghrelin was largely unaffected with <5% weight loss and it increased between 5% to 10% weight loss (41.64 pg/mL, 95% CI: 16.03 to 67.25,  $p = 0.002$ ). The change in fasting ghrelin between 10% and 15% weight loss tended toward but did not reach statistical significance (26.03 pg/mL, 95% CI: -1.63 to 53.69,  $p = 0.065$ ; Figure 2, Table 3).

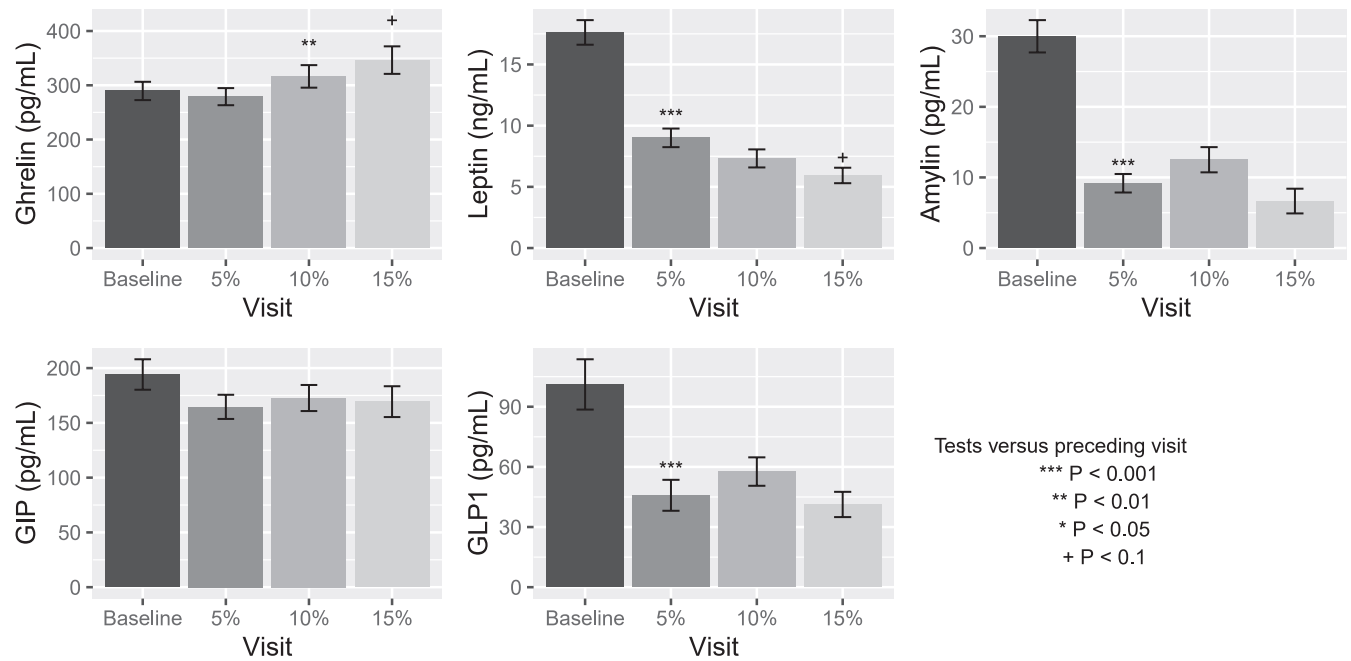
Fasting leptin showed a significant reduction from baseline to 5% weight loss (-8.25 ng/mL, 95% CI: -9.56 to -6.95,  $p < 0.001$ ) and between 5% and 15% weight loss (-1.88 ng/mL, 95% CI: -3.45 to -0.31,  $p = 0.019$ ; Figure 2, Table 3).

Mean fasting amylin and GLP-1 decreased significantly between baseline and 5% weight loss (both  $p < 0.001$ ). There were no further significant changes in fasting concentrations of these hormones between 5% and 10% weight loss or between 10% and 15% weight loss (Figure 2).

There were no significant changes in mean fasting GIP during weight loss.

#### Impact of gender on hormone changes

Overall levels of leptin and ghrelin were different between men and women when gender was included as a covariate in the linear



**FIGURE 2** Fasting hormone levels at baseline, 5%, 10%, and 15% weight loss. *P* values for the changes vs. the preceding visit (linear mixed-effects modeling). *P* values not shown for the test of 5% weight loss vs. 15% weight loss; ghrelin,  $p < 0.001$ ; leptin,  $p = 0.019$ ; amylin,  $p = 0.566$ ; GIP,  $p = 0.999$ ; and GLP-1,  $p = 0.909$  ( $n = 49$ ). GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1

mixed-effects model analysis (Supporting Information Table S1). However, separate analysis for women (Supporting Information Table S2) or men (Supporting Information Table S3) showed no major differences in the response of hormones to weight loss, with the exception of GLP-1, in which women had significant changes at 5% weight loss and men did not.

### Postprandial hormone levels

Unlike the fasting hormone levels, the postprandial changes after weight loss were variable between the different hormones (Figure 3).

At baseline, and at all degrees of weight loss, ghrelin levels fell for the first 60 minutes post meal and then rose back to baseline. Postprandial changes were significantly different between visits (time  $\times$  visit interaction:  $p < 0.001$ ), largely because of a greater increase in ghrelin between 60 and 240 minutes at baseline, than after weight loss (Figure 3).

The postprandial rise in amylin levels was not proportional to the degree of weight loss but was highest at baseline and lowest at 15% weight loss (Figure 3). Postprandial GLP-1 changes were also not proportional to weight loss, but the postmeal increase in GLP-1 was lowest at 15% weight loss.

Postprandial GIP levels were significantly elevated following 5% weight loss (328.2 pg/mL, 95% CI: 241.9 to 414.5,  $p < 0.001$ ), with no further significant increases after 10% and 15% weight loss (all  $p > 0.5$ ).

As expected, leptin levels did not change postprandially.

### Correlation analyses and appetite ratings

No significant correlations were found between changes in area under the curve for hormone levels after 5%, 10%, or 15% weight loss and baseline BMI or baseline weight. Data are presented in Tables 4 and 5. No significant changes were found in fasting or postprandial ratings of appetite (data not shown).

## DISCUSSION

Long-term weight-loss maintenance is hampered by vigorous physiological defenses, which favor weight regain. Energy expenditure declines following weight loss below that expected at the new lower weight. Little research has examined whether physiological hormonal adaptations are affected by starting weight or amount of weight lost. Here, we report that significant changes occur in levels of leptin, amylin, and GLP-1 by 5% weight loss and in ghrelin from 10% weight loss. Further changes in these fasting hormone levels are minimal with progressive weight loss. There were no changes in fasting GIP levels with weight loss. Postprandially, changes in ghrelin, GLP-1, and amylin are greater at 15% weight loss compared with 5% or 10% weight loss, although these changes are not clearly progressive with weight loss. We also found no correlations between hormone changes and baseline BMI or weight.

The finding, that the largest changes in fasting and/or postprandial circulating levels of the appetite-regulating hormones examined were detected when participants had lost 5% of their starting weight,

TABLE 3 Changes in fasting hormone levels

Hormone	Baseline to 5% weight loss (n = 49)	p value	5% weight loss to 10% weight loss (n = 42)	p value	10% weight loss to 15% weight loss (n = 48)	p value	5% weight loss to 15% weight loss (n = 49)	p value
Ghrelin (pg/mL)	-18.6 (-41.9 to 4.8)	0.122	41.64 (16.03 to 67.25)	<b>0.002</b>	26.03 (-1.63 to 53.69)	0.065	67.67 (39.74 to 95.6)	<b>0.001</b>
Leptin (ng/mL)	-8.25 (-9.56 to 6.95)	< <b>0.001</b>	-0.53 (-1.97 to 0.908)	0.467	-1.34 (-2.90 to 0.217)	0.091	-1.88 (-3.45 to -0.31)	<b>0.019</b>
Amylin (pg/mL)	-21.83 (-29.73 to -13.91)	< <b>0.001</b>	3.00 (-5.77 to 11.76)	0.502	-5.78 (-15.36 to 3.81)	0.237	-2.78 (12.29 to 6.73)	0.566
GLP-1 (pg/mL)	-59.55 (-88.43 to -34.60)	< <b>0.001</b>	16.82 (-10.80 to 44.43)	0.232	-18.57 (-48.74 to 11.60)	0.227	-1.76 (-31.95 to 28.44)	0.909
GIP (pg/mL)	-32.44 (-115.93 to 51.07)	0.449	7.90 (-84.15 to 99.95)	0.866	-7.83 (-108.02 to 92.37)	0.878	0.07 (-100.57 to 100.72)	0.999

Note: Values are presented as mean (95% CI); p values are for the changes in each hormone within the time period. Values in bold are statistically significant.

Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

is most consistent with a "threshold" model (16) for this component of the adaptive response to weight loss. Rosenbaum and Leibel have demonstrated that the disproportionate decrease in resting energy expenditure is best explained by a threshold model (at 10% weight loss), whereas the decline in non-resting energy expenditure appears to progress with continued weight loss (16).

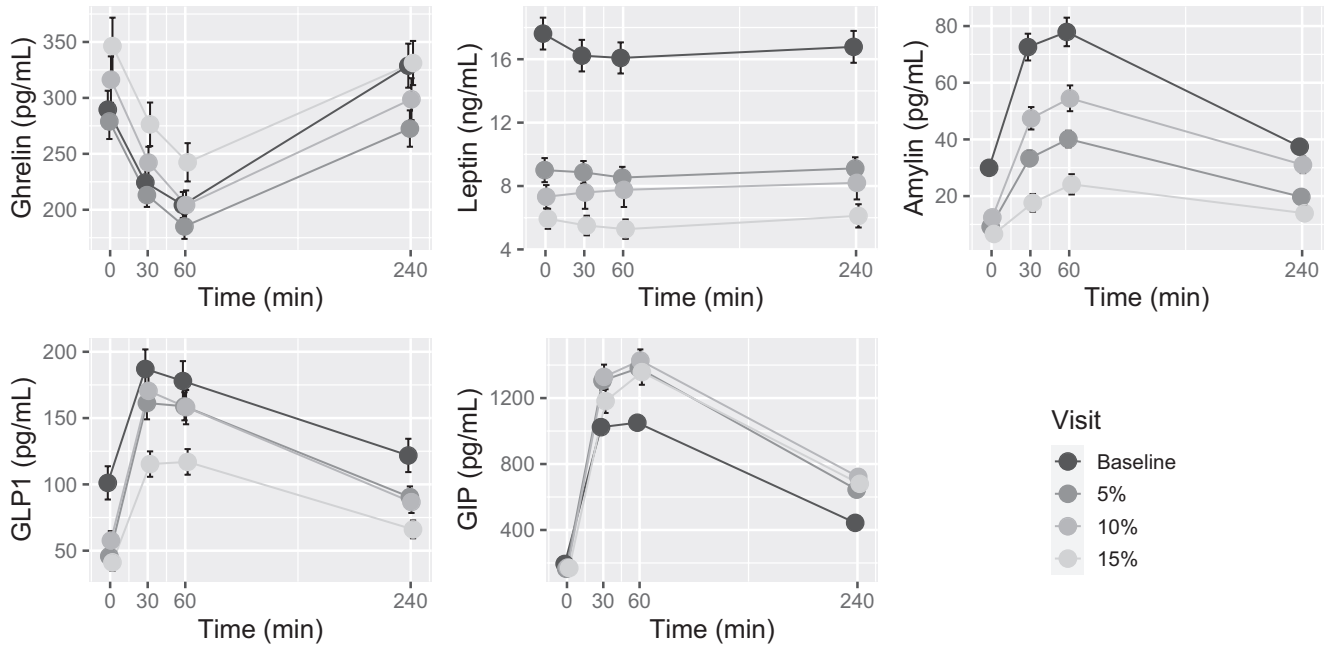
It is well-established that, during weight loss, elements of the counterregulatory response are variably influenced by negative energy balance and reduction in fat stores. For example, reductions in circulating levels of leptin and biologically active thyroid hormones are more pronounced during weight loss than after a period of maintenance of the reduced weight (17). Whether the pattern of changes in gut hormones differs between active weight-loss and weight-maintenance phases was not examined in the present study, but we have previously reported a greater reduction in circulating amylin during weight loss than after weight stabilization (18) and a persistence of changes in several gut hormones for at least 1 year after a period of negative energy balance (11).

In contrast to our findings, Magkos et al. showed a progressive decrease in leptin levels with 5%, 11%, and 16% weight loss (19). However, our results for leptin are consistent with other studies that have shown that the predominant fall in leptin occurs early after the onset of energy restriction (20,21).

In our study, hormone changes prior to 5% weight loss were not investigated. However, other studies have reported conflicting findings. Varady et al. found that, in women with obesity, there was no significant change in leptin in those who lost <5% weight (22), whereas Keim et al. found a 57% reduction in circulating leptin after 1 week of energy restriction, when only 0.5% weight loss had occurred (22). Levels of leptin and ghrelin were different between men and women when gender was included as a covariate in the linear mixed-effects model analysis (Supporting Information Table S1). In addition, with the exception of GLP-1, separate analysis for women (Supporting Information Table S2) or men (Supporting Information Table S3) showed no major differences in the response of hormones to weight loss.

In the present study, there were no significant changes detected in subjective appetite ratings. This differs from previous studies that have shown changes in appetite and neural activation in brain areas involved in cognitive control of food intake after weight loss (11,23,24). It is not clear why findings in the current study were different, but it has been noted previously that subjective appetite is difficult to measure accurately with visual analog scales and may not reliably predict energy intake (25).

Current clinical guidelines advise a weight loss of 5% to 10% for health benefits (26,27). Although the health benefits of a modest weight loss are undisputed, many studies have demonstrated that greater losses produce greater health benefits (19,28,29). For example, the Look AHEAD (Action for Health in Diabetes) study showed that cardiovascular disease risk was significantly improved with 5% to <10% weight loss, but further weight loss demonstrated further benefits (30). A study by Madsen et al. found that a weight loss of >10% was required to improve adiponectin levels



**FIGURE 3** Fasting and postprandial hormone levels, at baseline, 5%, 10%, and 15% weight loss ( $n = 49$ )

**TABLE 4** Correlation between weight at baseline and hormone level change (area under the curve)

Hormone	<i>r</i> value, 5% weight loss ( $n = 42$ )	<i>p</i> value	<i>r</i> value, 10% weight loss ( $n = 48$ )	<i>p</i> value	<i>r</i> value, 15% weight loss ( $n = 49$ )	<i>p</i> value
Ghrelin	-0.17	0.21	-0.18	0.19	-0.18	0.25
Leptin	-0.19	0.15	-0.15	0.26	-0.21	0.19
Amylin	0.15	0.27	0.15	0.29	0.19	0.26
GLP-1	-0.14	0.30	-0.23	0.10	-0.01	0.96
GIP	-0.10	0.47	-0.12	0.40	0.07	0.68

Note: *r* value = Spearman rank correlation.

Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

**TABLE 5** Correlation between BMI at baseline and hormone level change (area under the curve)

Hormone	<i>r</i> value, 5% weight loss ( $n = 42$ )	<i>p</i> value	<i>r</i> value, 10% weight loss ( $n = 48$ )	<i>p</i> value	<i>r</i> value, 15% weight loss ( $n = 49$ )	<i>p</i> value
Ghrelin	-0.14	0.30	-0.13	0.36	-0.21	0.19
Leptin	-0.02	0.89	-0.07	0.62	0.05	0.76
Amylin	-0.03	0.82	-0.11	0.45	-0.01	0.97
GLP-1	-0.20	0.14	-0.24	0.08	0.07	0.69
GIP	-0.10	0.45	-0.22	0.10	0.09	0.57

Note: *r* value = Spearman rank correlation.

Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

and inflammatory markers (31). In a study of patients with obesity and nonalcoholic fatty liver disease, Vilar-Gomez et al. found that, whereas a modest weight loss of 7% to 10% produced a significant improvement in disease parameters, a weight loss of >10% was required to produce a resolution in steatohepatitis (32). Magkos et al. concluded that 5% weight loss has benefits to cardiovascular

disease risk factors and multiorgan insulin sensitivity, and further weight loss led to more improvements in insulin sensitivity and  $\beta$ -cell function (16). The Diabetes Remission Clinical Trial (DiRECT) study showed that diabetes remission varied with the degree of weight loss, with 7% of those who lost 0 to 5 kg achieving remission compared with 34% of those who lost 5 to 10 kg and 86% of

those who lost more than 15 kg (33). These studies demonstrate that additional weight loss beyond the recommended 5% or 10% is more beneficial to health.

Therefore, the improvement in diabetes seems to be proportional to the degree of weight loss. In contrast, the changes in hunger-altering hormones are not linear. So why does the body defend even modest degrees of weight loss vigorously? This is probably a survival mechanism. When we were hunter-gatherers, it would take a substantial amount of time to find food; therefore, the signal to “go to find food” had to occur early after weight loss to be effective.

There are some limitations to this study. First, these results may not be readily generalizable to all populations, given that our sample consisted of mostly women of middle age. As some participants were premenopausal and some were postmenopausal, this may also affect the interpretation of results. In addition, we specifically studied hormonal changes at the points of 5%, 10%, and 15% weight loss; therefore, we cannot be certain that the hormonal adaptations to different or larger weight losses would be the same. As with many weight-loss studies, the rate of attrition was high. Statistical analyses only included those participants who achieved the weight-loss targets; therefore, there is a possibility that there was a difference in hormone levels in those participants who did not achieve the weight-loss targets, although analysis of baseline characteristics between completers and drop-outs showed no difference (except in systolic blood pressure, which, although statistically significant, is unlikely to be of relevance here). In addition, we did not examine the effect of the changes seen on weight-loss maintenance or weight regain. We also did not measure circulating levels of thyroxine (T4), triiodothyronine (T3), and reverse triiodothyronine (rT3) and levels of Agouti-related peptide (AgRP). Although the circulating level of AgRP is of dubious physiological relevance, the changes in T3 to rT3 conversion with different degrees of weight loss may be relevant and should be studied.

In summary, the present study indicates that the majority of fasting hormonal adaptations to weight loss appear at 5% weight loss and persist up to 15% weight loss, with little change in magnitude with progressive weight loss. These results indicate that higher degrees of weight loss do not invoke progressively stronger physiological defenses against weight loss. This suggests that there may be reason to aim for greater weight-loss targets than are currently recommended in many clinical guidelines, particularly for people with severe obesity and weight-related complications or risk factors that are not well-controlled after 10% weight loss.

## CONCLUSION

Long-term weight-loss maintenance appears to be very difficult, with both observational studies and clinical trials showing that many people who intentionally lose weight using lifestyle interventions alone will regain this weight within 1 to 5 years (2,27-29). Therefore, support is required to assist weight-reduced people in maintaining weight loss in the long term.○

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

JP was chair of the medical advisory board for Saxenda (Novo Nordisk A/S) in Australia. He is a member of the medical advisory board for the introduction of Semaglutide in Australia for Novo Nordisk. He has given lectures on the management of obesity for iNova Pharmaceuticals marketers of phentermine (Duromine) and naltrexone/bupropion (Contrave) and for Novo Nordisk marketers of liraglutide (Saxenda) in Australia. He is on the Australian Medical Advisory Board for Contrave. PS has participated in advisory boards and a lecture for Novo Nordisk A/S unrelated to this work. The other authors declared no conflict of interest. The study was not commercially sponsored, and there were no agreements regarding confidentiality of the data between the sponsor and the authors or their institutions.

## AUTHOR CONTRIBUTIONS

Joseph Proietto and Priya Sumithran conceived the idea for the study, and Joseph Proietto, Priya Sumithran, and Kira-Ann L. Edwards designed the study. Data were collected by Kira-Ann L. Edwards and Stefanie Kalfas and analyzed by Luke A. Prendergast, Kira-Ann L. Edwards, and Joseph Proietto, who vouch for the data and analysis. Kira-Ann L. Edwards, Priya Sumithran, Joseph Proietto, and Luke A. Prendergast wrote the paper (first draft written by Kira-Ann L. Edwards). All authors reviewed and revised the manuscript, vouch for the data and analysis, and agree with the decision to publish the paper.

## CLINICAL TRIAL REGISTRATION

Australian New Zealand Clinical Trials Registry (ACTRN: 12614000141640).

## DATA AVAILABILITY STATEMENT

Individual participant data collected during the trial, after deidentification, will be made available to researchers whose proposed use of the data has been approved by a research ethics committee to achieve aims in the approved proposal. Data will be made available immediately following publication for 5 years (until December 31, 2026) by contacting the corresponding author ([j.proietto@unimelb.edu.au](mailto:j.proietto@unimelb.edu.au)).

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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