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ORIGINAL ARTICLE

Clinical Trials and Investigations

Gastrointestinal hormones and appetite ratings after weight loss induced by diet or bariatric surgery

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Abstract

Objective: The aim of this study was to compare changes in gastrointestinal hormones and appetite ratings after a similar weight loss induced by a very low-energy diet alone or in combination with sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).

Methods: Patients with severe obesity scheduled for SG ($n = 15$) and RYGB ($n = 14$) and 15 controls (very low-energy diet alone) were recruited. Body weight/composition, plasma concentrations of ß-hydroxybutyric acid, acylated ghrelin, total glucagon-like peptide-1, total peptide YY, cholecystokinin, and ratings of hunger, fullness, desire to eat, and prospective food consumption were measured pre- and postprandially, before and after 10 weeks of intervention.

Results: Changes in body weight/composition and level of ketosis were similar across groups. In SG and RYGB, basal and postprandial acylated ghrelin declined, and postprandial glucagon-like peptide-1 increased, both significantly more compared with controls. Postprandial peptide YY increased in all groups. Overall, postprandial hunger decreased, and postprandial fullness increased. But ratings of desire to eat and prospective food consumption were more favorable after both surgeries compared with controls.

Conclusions: Weight loss with SG and RYGB leads to more favorable changes in gastrointestinal hormones compared with diet alone, although ratings of appetite were reduced across all groups.

INTRODUCTION

Bariatric surgery is the most effective treatment for obesity, inducing a greater and more sustained weight loss compared with nonsurgical approaches [1]. It is hypothesized that bariatric surgery's success can be partially explained by beneficial changes in the secretion of gastrointestinal (GI) hormones, key regulators of eating behavior and homeostatic appetite control [2].

Patients who have undergone sleeve gastrectomy (SG) report feeling less hungry and more satiated than their nonsurgical counterparts [3], and several studies have shown decreases in appetite also following Roux-en-Y gastric bypass (RYGB) [4, 5]. Plasma concentrations of ghrelin, the only known orexigenic gut-derived signal, have consistently been shown to decline following SG [6, 7]. However, less consensus exists regarding the impact of RYGB on ghrelin plasma concentrations, with some studies showing a decrease [8], while others show no change [9]. The plasma concentrations of glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), collectively known as satiety peptides, have been consistently reported to increase shortly after bariatric surgery and to be sustained for up to 10 years postoperatively [4, 10, 11].

Diet-induced weight loss, on the other hand, has consistently been shown to lead to increased basal ghrelin plasma concentrations and hunger ratings [12, 13]. Moreover, these changes seem to be sustained at 1-year follow-up [13, 14], even with partial weight regain [12]. However, the impact of diet-induced weight loss on the postprandial concentrations of satiety peptides and appetite ratings remains controversial [12–14].

Few studies have compared how weight loss induced by diet versus bariatric surgery impacts the secretion of GI hormones and subjective appetite ratings. RYGB, in combination with a low-calorie diet, was reported to induce a greater weight loss along with decreased motivation to eat and lower basal and postprandial total ghrelin concentrations, as well as greater postprandial concentrations of total GLP-1, PYY_{3-36}, and CCK, compared with dietary restriction alone [15]. However, in another study, a 10-kg weight loss induced by RYGB was reported to decrease total ghrelin plasma concentrations, whereas the same magnitude of weight loss induced by dietary restriction alone had the opposite effect [16]. Moreover, RYGB resulted in more favorable changes in appetite ratings (hunger, satiety, prospective food consumption [PFC], and cravings), despite no changes in total GLP-1 or total PYY concentrations in the postprandial state in either group [16].

Nutritional-induced ketosis has been shown to modulate the concentrations of GI hormones, particularly ghrelin [17, 18], with the increased drive to eat otherwise seen with diet-induced weight loss being attenuated, or even absent, under ketogenic conditions [17, 19, 20]. Interestingly, it has been reported that patients who undergo bariatric surgery develop mild ketosis shortly after surgery [21]. Studies comparing the impact of weight loss induced by diet alone versus bariatric surgery on appetite are limited given that they have not controlled for ketosis, the magnitude of weight loss, or the overall energy deficit and macronutrient composition of the diet. A study controlling for these variables would be useful for elucidating the mechanisms behind the effectiveness of bariatric surgery. Therefore, the aim of this study was to compare how a similar weight loss induced by a very low-energy diet (VLED) alone, or VLED combined with SG or RYGB, impacts GI hormone plasma concentrations and subjective appetite ratings.

Study Importance

What is already known?

- Bariatric surgery leads to substantial and sustained weight loss, concomitant with beneficial changes in gastrointestinal (GI) hormones toward reduced hunger and increased satiety.
- Very low-energy diets (VLED) are effective for weight loss in the short term but are usually followed by an increased drive to eat, and long-term weight loss maintenance is poor.

What does this study add?

- When diet and weight loss are similar, bariatric surgery (both Roux-en-Y gastric bypass and sleeve gastrectomy) leads to a more favorable profile in the concentration of GI hormones, compared with diet-induced weight loss.
- However, an overall reduction in appetite ratings is seen after both diet-induced weight loss and bariatric surgery, likely because participants were under nutritional-induced ketosis.

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

- For patients with severe obesity who cannot, or choose not to, undergo bariatric surgery, VLED seem to be a good alternative, at least in the short term, to induce significant weight loss concomitant with an overall reduction in appetite ratings like what is seen after bariatric surgery.
- Long-term studies are needed to determine whether these initial changes in GI hormones and appetite ratings modulate long-term weight loss outcomes after both diet-induced weight loss and bariatric surgery.

METHODS

Study design

The Effect of DIet-induced weight loss versus Sleeve gastrectomy and Gastric bypass on Appetite (DISGAP) study is a three-arm, nonrandomized controlled trial, comparing how a similar weight loss induced by VLED alone, or VLED in combination with SG or RYGB, impacts different domains of appetite regulation. This paper reports the initial changes in GI hormones and appetite ratings after a similar weight loss achieved across groups. An outline of the study can be seen in Figure 1.

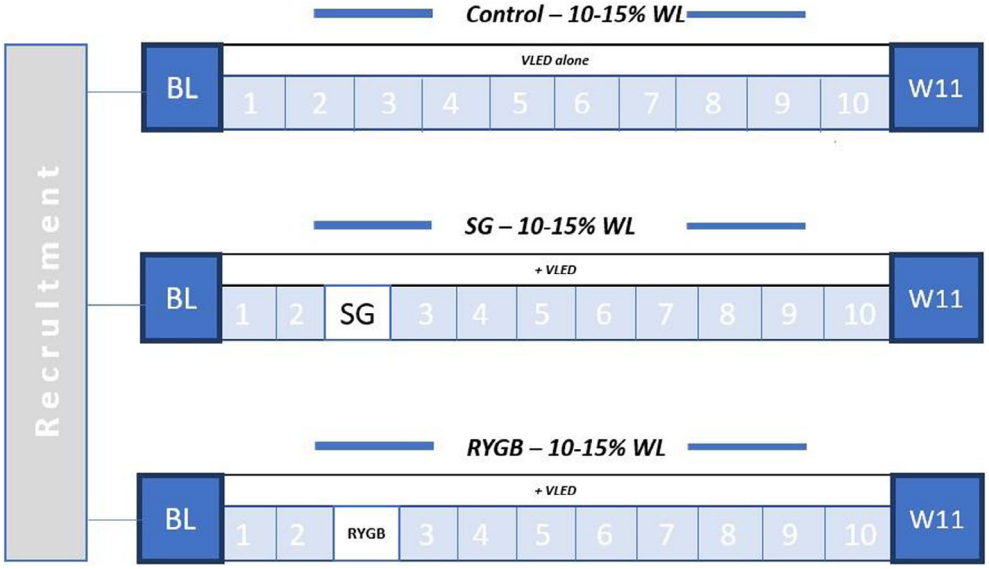

FIGURE 1 Study design. BL, baseline; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VLED, very low-energy diet; W11, week 11; WL, weight loss [Color figure can be viewed at wileyonlinelibrary.com]

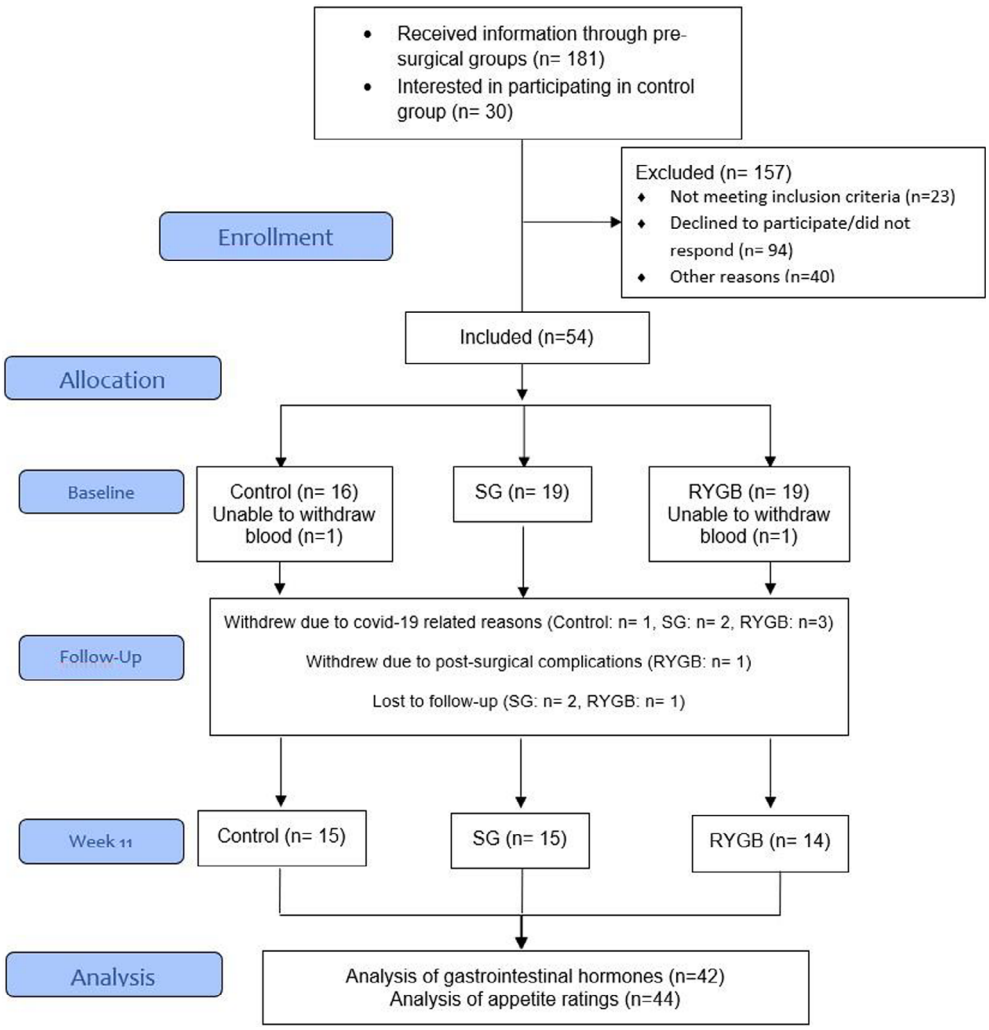

FIGURE 2 Flow diagram of the study. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy [Color figure can be viewed at wileyonlinelibrary.com]

Participants

Adults with severe obesity scheduled for SG or RYGB at two local hospitals in the Central Norway Health Region were recruited for this study. The control group (VLED intervention alone) was composed of patients on a waiting list for bariatric surgery, patients who declined or were not eligible for surgery, as well as individuals with severe obesity from the local community (recruited through advertisements at St. Olav's University Hospital and the Norwegian University of Science and Technology intranet). The control group was recruited aiming to match the preoperative body mass index (BMI), age, and sex of the surgical groups. Recruitment and data collection took place between September 2019 and January 2022. A flow diagram of the study can be seen in Figure 2.

The study was approved by the regional ethics committee (Regional etisk komite [REK], Ref: 2019/252), registered in ClinicalTrials.gov (NCT04051190), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before enrolling in the study. Participants had to be weight stable (self-reported) (< 2-kg body weight change over the last 3 months) and not enrolled in any other obesity treatment or behavioral program. Patients who had previously undergone bariatric surgery, were using medication known to affect metabolism or appetite, or had a current cancer diagnosis, substance abuse, or a psychiatric diagnosis that precluded bariatric surgery (such as eating disorders) were excluded from the study.

Interventions

Surgical procedures

Bariatric surgeries were performed using standard laparoscopic procedures. The SG involved dividing the gastrocolic ligament, initiating the gastrectomy 4 cm proximal to the pylorus along the greater curvature, and creating the sleeve along the lesser curvature using a 36-French bougie. The RYGB procedure involved creating a small (~20–30 mL) proximal gastric pouch and a stapled gastrojejunostomy. A 75– to 150-cm Roux-Y limb was constructed by transecting the jejunum 60 to 100 cm distal to the ligament of Treitz and performing a stapled jejunostomy at this site.

Diet

All participants followed a formula-based VLED, using commercial food packs (Lighter Life, Harlow), for 10 weeks under the guidance of a registered dietitian. The average daily macronutrient composition of the VLED was 750 kcal, and percent energy (E%) was 26 E% fat, 36 E% carbohydrates, 5 E% fiber, and 33 E% protein. The products consisted of shakes, soups, textured meals, porridge, and bars with approximately 150 kcal/product. Participants could choose any combination of five products per day. They were encouraged to consume a maximum of 100 g of low-starch vegetables and 2.5 L of water daily. Alcohol consumption was not allowed during the 10-week intervention. Noncaloric beverages were allowed, in addition to a maximum of 500 mL of low-energy drinks (< 3 kcal/100 mL).

Patients scheduled for SG and RYGB initiated the VLED 2 weeks prior to surgery and continued for another 8 weeks afterward. The surgical groups were instructed to consume only fluid food packs the first weeks postoperatively, gradually increasing the texture of the food. All participants were asked to fill out a self-reported food diary. At weekly scheduled follow-ups, food diaries were discussed, side effects recorded, body weight monitored, and acetoacetate (a ketone body) measured in urine with ketostix (Bayer Ketostix 2880 Urine Reagent Test Strip, Ascensia Diabetes Care), as a measure of dietary compliance.

Physical activity

Participants were asked to maintain their physical activity (PA) levels during the 10-week intervention. Compliance with this recommendation was assessed by asking participants to wear SenseWear armbands (BodyMedia) for 7 days prior to baseline (BL) and on the last week of the study (W10). Data were considered valid if participants wore the device for ≥ 4 days, including at least 1 weekend day, on more than 95% (22.8 h/d) of the time [22]. Average steps per day, PA levels, metabolic equivalents, and total PA duration were included in the analysis.

Outcome variables

After an overnight fast (at least 10 hours), participants came to the obesity outpatient clinic at St. Olav's University Hospital on two occasions: before start of the dietary intervention (BL) and after 10 weeks (W11), to measure body weight and composition, plasma concentrations of GI hormones, and appetite ratings.

Air-displacement plethysmography (BodPod, COSMED) was used to measure body weight, fat mass (FM), and fat free mass (FFM).

Blood samples were collected in 4-mL EDTA-coated tubes and drawn at fasting, every 15 minutes for the first hour after a standardized breakfast, and then at 30-minute intervals until 150 minutes. The breakfast consisted of a 200-mL commercial low-glycemic drink (Diben Drink, Fresenius Kabi Norge AS) (300 kcal, 42 E% fat, 35 E% carbohydrates, 3 E% fiber, and 20 E% protein), and participants were asked to drink it slowly over a 15-minute period, to avoid dumping syndrome.

For acylated ghrelin (AG) and total PYY, 1 mL of whole blood was transferred into a microtube and a 20-μL mixture of inhibitor (10 μL of Pefabloc [Roche Diagnostic] + 10 μL of dipeptidyl-peptidase IV inhibitor [Merck Millipore]) was added. For CCK and total GLP-1, 500 KIU of aprotinin (DSM, Coatech AB) per milliliter of whole blood was added to the EDTA tubes. Samples were then centrifuged at 2106 relative centrifugal force (RCF) for 10 minutes

at 18 °C and the plasma frozen at −80 °C until further analysis. Plasma samples were analyzed for AG and total PYY using a Human Metabolic Hormone Magnetic Bead Panel (HMHEMAG-34 K, Merck KGaA). Cross-reactivity between antibodies and any of the other analytes in this panel is nondetectable or negligible. CCK and total GLP-1 were analyzed using "in-house" radioimmunoassay (RIA) methods [23, 24]. Intra- and inter-assay coefficients of variation were < 10% and < 20% for AG and total PYY; and < 5% and < 15% for total GLP-1 and CCK, respectively. All the samples from the same participant were analyzed in the same plate. The analyses of AG and total PYY were performed by the same technician at NTNU's lab. CCK and total GLP-1 were both analyzed at the University of Copenhagen, Denmark. A ketone body assay kit (MAK134, Sigma-Aldrich) was used to measure ß-hydroxybutyric acid (ßHB) plasma concentrations.

Appetite ratings (hunger, fullness, desire to eat [DTE], and PFC) were assessed using a 10-cm visual analog scale [25] at fasting, immediately after the standardized breakfast, and every 30 minutes for a period of 2.5 hours.

Sample size calculation

Given that RYGB has been shown to induce a larger increase in GLP-1 area under the curve (AUC) compared with SG [6] and dietary restriction alone [15], for this exploratory study, we hypothesized that bariatric surgery would induce a two (SG) and three (RYGB) times larger increase in total GLP-1 postprandial concentrations (AUC) compared with diet-induced weight loss alone (∼600 pmoL/mL × min) [13]. For a power of 80%, a significance level of 0.05, and assuming a standard deviation of 1000 min × pmol/L, and a within-group variance of 640,000 min × pmol/L, 45 participants would be required (15 in each group).

Statistical analysis

The statistical analysis was carried out using SPSS Statistics, version 27 (IBM Corp.). Residuals were checked for normality using the Shapiro–Wilk test and visual inspection of QQ plots and histograms and they did not deviate significantly from normality. Data are presented as means ± standard errors of the mean (SEM), unless otherwise stated. All data (anthropometrics, GI hormones, appetite ratings, and ßHB) were analyzed using a linear mixed-effects model with restricted maximum likelihood estimation, including fixed effects for time, group, and their interaction. Bonferroni correction was used for post hoc pairwise group comparisons. We were unable to collect blood samples from two participants at BL (one control, one RYGB), and these were therefore excluded from the analysis of GI hormones. Total and incremental (or decremental) area under the curve (*t*AUC, *i*AUC, and *d*AUC, respectively) for GI hormone concentrations and appetite ratings was calculated using the trapezoid rule.

RESULTS

Participants

Table 1 shows mean characteristics of the groups at baseline and week 11. A total of 44 participants completed BL and W11 assessments ($n = 15$ VLED, $n = 15$ SG, and $n = 14$ RYGB). A main effect of time was seen for all anthropometric variables ($p < 0.001$, for all). Post hoc analysis showed no differences in any anthropometric variables between groups at BL or W11 or in changes over time. Participants lost on average 18.3 ± 0.6 kg (16%), and BMI was reduced by 6.3 ± 0.8 kg/m^2, FM decreased by 13.5 ± 0.5 kg (24%), and FFM decreased by 4.8 ± 0.3 kg (8%) ($p < 0.001$, for all). All participants were in nutritional-induced ketosis at W11, with no significant differences in ßHB plasma concentrations between groups. No changes over time or differences between groups were seen for any of the PA variables assessed (data not shown).

Gastrointestinal hormones

Mean basal and postprandial plasma concentrations of GI hormones at BL and W11 can be seen in Table 2, and the postprandial curves over time can be seen in Figure 3A–D.

An overall reduction in basal and postprandial ghrelin concentrations was seen

A main effect of time, group, and time × group interaction was seen for basal AG concentrations ($p < 0.001$, for all). Post hoc analysis showed that SG and RYGB experienced a decrease in basal AG concentrations ($p < 0.001$ and $p = 0.13$, respectively), whereas controls showed no change over time and had higher basal concentrations compared with SG and RYGB at W11 ($p < 0.001$, for both). A main effect of time ($p < 0.001$, for both) and group ($p = 0.002$, and $p = 0.003$, respectively) was also seen for AG *t*AUC and *d*AUC. Controls had significantly greater postprandial concentrations (tAUC and iAUC) at W11 compared with SG ($p = 0.003$, for both) and RYGB ($p = 0.013$ and $p = 0.014$).

There was an overall reduction in basal and postprandial concentrations of total GLP-1

A main effect of time was seen for basal GLP-1 ($p = 0.002$) and a main effect of time, group, and time × group interaction for GLP-1 *t*AUC and *i*AUC ($p < 0.001$, for all). Post hoc analysis showed no differences between groups in postprandial GLP-1 concentrations at BL. An increase was seen for GLP-1 (*t*AUC and *i*AUC) after both surgical procedures (SG: $p = 0.02$, for both, RYGB: $p < 0.001$, for both), whereas no changes were seen for controls. At W11, postprandial GLP-1 (*t*AUC and *i*AUC) had increased significantly more after both bariatric

TABLE 1 Demographic and anthropometric variables by group at baseline and week 11

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
n	15	15	14	15	15	14			
Age (y)	45.5 ± 2.6	39.6 ± 2.4	46.7 ± 2.5					NS	
Females, %	69	79	61					NS	
Body weight (kg)	115.4 ± 3.9[a]	117.6 ± 3.6[b]	120.4 ± 3.7[c]	98.1 ± 3.9[a]	98.6 ± 3.6[b]	101.6 ± 3.7[c]	$p < 0.001$	NS	NS
Weight loss (kg)				−17.3 ± 1.0	−19.0 ± 1.0	−18.8 ± 1.0			
BMI (kg/m^2)	39.7 ± 0.9[a]	40.2 ± 0.7[b]	41.6 ± 1.1[c]	33.7 ± 0.9[a]	34.1 ± 0.8[b]	35.0 ± 1.3[c]	$p < 0.001$	NS	NS
FM (%)	46.6 ± 1.5[a]	47.9 ± 1.4[b]	47.0 ± 1.4[c]	41.0 ± 1.5[a]	43.0 ± 1.4[b]	42.7 ± 1.4[c]	$p < 0.001$	NS	NS
FM (kg)	53.7 ± 2.6[a]	56.5 ± 2.4[b]	56.5 ± 2.4[c]	40.4 ± 2.6[a]	42.4 ± 2.4[b]	43.6 ± 2.4[c]	$p < 0.001$	NS	NS
FFM (%)	53.0 ± 1.5[a]	52.1 ± 1.4[b]	53.0 ± 1.4[c]	59.1 ± 1.5[a]	57.0 ± 1.4[b]	57.3 ± 1.4[c]	$p < 0.001$	NS	NS
FFM (kg)	61.7 ± 2.6	61.1 ± 2.4[b]	63.8 ± 2.4[c]	57.8 ± 2.5[a]	56.2 ± 2.4[b]	58.1 ± 2.4[c]	$p < 0.001$	NS	NS
βHB (mM)	0.1 ± 0.2[a]	0.1 ± 0.2[b]	0.0 ± 0.2[c]	0.7 ± 0.2[a]	1.1 ± 0.2[b]	0.5 ± 0.2[c]	$p < 0.001$	NS	NS

Note: Data presented as estimated marginal means ± SEM. Means sharing the same superscript letter denote significant changes over time ($p < 0.001$ for all).
Abbreviations: βHB, beta-hydroxybutyric acid; FFM, fat free mass; FM, fat mass; NS, not significant; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

procedures compared with controls, and concentrations were greater in RYGB compared with both SG and controls ($p < 0.001$, for all).

All groups experienced an increase in total PYY in the postprandial state

No main effects were seen for basal PYY concentrations. A main effect of time and time × group interaction was seen for PYY *t*AUC ($p = 0.005$, and $p = 0.034$, respectively), and a main effect of time was seen for PYY *i*AUC ($p < 0.005$). Post hoc analysis showed that all groups experienced an increase in PYY *t*AUC and *i*AUC over time ($p = 0.008$ and $p = 0.005$ for all). At W11, RYGB had greater PYY *t*AUC compared with SG ($p = 0.034$).

An overall reduction in basal CCK was seen

A main effect of time and group was seen for basal CCK plasma concentrations ($p < 0.001$, for both). Post hoc analysis showed that controls had higher basal CCK concentrations compared with SG ($p < 0.001$) and RYGB ($p = 0.003$) at BL. Basal CCK concentrations declined overall ($p < 0.001$), and at W11, no differences between groups were seen. No main effects were seen for postprandial CCK concentrations.

Appetite ratings

Mean scores for appetite ratings, fasting and postprandially, at BL and W11 can be seen in Table 3. Postprandial curves over time can be seen in Figure 4A–D.

An overall reduction in postprandial hunger and an increase in postprandial fullness ratings were seen across WL modalities

No main effects were seen for fasting hunger ratings. A main effect of time was seen for postprandial (*t*AUC and *d*AUC) hunger ratings ($p = 0.001$ and $p = 0.032$, respectively), with no differences between groups.

An overall increase in postprandial fullness ratings was seen at W11, with a main effect of time for postprandial (*t*AUC) fullness ($p = 0.011$).

Overall decreases in DTE in the fasting and postprandial state were seen

A main effect of time ($p = 0.005$) was seen for fasting DTE, whereas a main effect of time and group ($p = 0.017$ and $p = 0.006$, respectively) was observed for DTE *t*AUC and a time × group interaction ($p = 0.035$) for DTE *d*AUC. Post hoc analysis showed that DTE ratings

TABLE 2 Plasma concentration of gastrointestinal hormones at baseline and week 11 by group

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
Basal AG (pmol/L)	40.1 ± 4.6	27.6 ± 4.3^{b}	26.1 ± 4.7^{c}	45.1 ± 4.7 $^{*\& \Omega ¤}$	6.6 ± 4.4^{b} $^{*\Omega}$	16.1 ± 4.8^{c} $^{\& ¤}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
AG *t*AUC (pmol/mL *min)	521.9 ± 83.1	237.8 ± 78.0	331.0 ± 85.9	432.1 ± 85.5 $^{*\&}$	21.5 ± 82.1 *	70.5 ± 88.6$^{\&}$	$p < 0.001$	$p = 0.002$	NS
AG *d*AUC (pmol/mL *min)	515.9 ± 82.6	233.6 ± 77.6	327.1 ± 85.5	425.4 ± 84.5 $^{*\&}$	20.5 ± 81.7 *	68.2 ± 88.1$^{\&}$	$p < 0.001$	$p = 0.003$	NS
Basal GLP-1^{total} (pmol/L)	6.4 ± 1.2	8.6 ± 1.1	7.8 ± 1.3	3.0 ± 1.2	4.5 ± 1.2	6.8 ± 1.3	$p = 0.002$	NS	NS
GLP-1 *t*AUC (pmol/mL *min)	58.6 ± 46.7	43.3 ± 42.3^{b}	66.2 ± 48.4^{c}	52.3 ± 48.4$^{\& \Omega ¤}$	189.4 ± 44.7^{b} $^{\# \Omega}$	548.0 ± 48.4^{c} $^{\& \# ¤}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
GLP-1 *i*AUC (pmol/mL *min)	57.6 ± 46.2	42.0 ± 41.9^{b}	65.0 ± 48.0^{c}	51.9 ± 46.2$^{\&}$	188.7 ± 44.6^{b} $^{\#}$	547.0 ± 47.9^{c} $^{\& \#}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Basal PYY^{total} (pmol/L)	19.1 ± 3.0	14.6 ± 2.8	11.6 ± 3.1	17.1 ± 3.1	11.8 ± 2.9	16.6 ± 3.2	NS	NS	NS
PYY *t*AUC (pmol/mL *min)	292.6 ± 164.7^{a}	154.3 ± 156.4^{b}	691.3 ± 169.3^{c}	725.6 ± 167.4^{a}	587.3 ± 156.4^{b} $^{\#}$	1124.3 ± 172.2^{c} $^{\#}$	$p = 0.005$	NS	$p = 0.034$
PYY *i*AUC (pmol/mL *min)	275.5 ± 166.5	176.7 ± 158.9	674.8 ± 171.2	739.4 ± 169.3	640.6 ± 164.1	1138.7 ± 174.1	$p = 0.005$	NS	NS
Basal CCK (pmol/L)	2.4 ± 0.3 $^{*\&}$	0.8 ± 0.3 *	1.1 ± 0.3$^{\&}$	1.3 ± 0.3	0.5 ± 0.3	0.4 ± 0.3	$p < 0.001$	$p < 0.001$	NS
CCK *t*AUC (pmol/mL *min)	11.7 ± 1.8	6.1 ± 1.7	7.1 ± 1.9	7.5 ± 1.8	5.6 ± 1.8	6.4 ± 1.9	NS	NS	NS
CCK *i*AUC (pmol/mL *min)	11.3 ± 1.8	6.0 ± 1.6	6.9 ± 1.9	7.3 ± 1.8	5.6 ± 1.7	6.3 ± 1.9	NS	NS	NS

Note: Data are presented as estimated marginal means ± SEM. Conversion from metric to SI units has been applied as follows: ghrelin pg/mL × 0.3 = pmol/L, PYY pg/mL × 0.25 = pmol/L. Post hoc pairwise comparisons corrected with Bonferroni adjustment. Averages sharing the same superscript letter denote a significant change over time ($p < 0.05$). Averages sharing the same superscript symbol denote significant differences between groups ($^{*\&\#}$, $p < 0.05$) or significant differences in the changes over time between groups at week 11 ($^{\Omega ¤}$, $p < 0.05$).

Abbreviations: AG, acylated ghrelin; CCK, cholecystokinin; *d*AUC, decremental area under the curve; GLP-1, glucagon-like peptide-1; *i*AUC, incremental area under the curve; NS, not significant; PYY, peptide YY; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy; *t*AUC, total area under the curve.

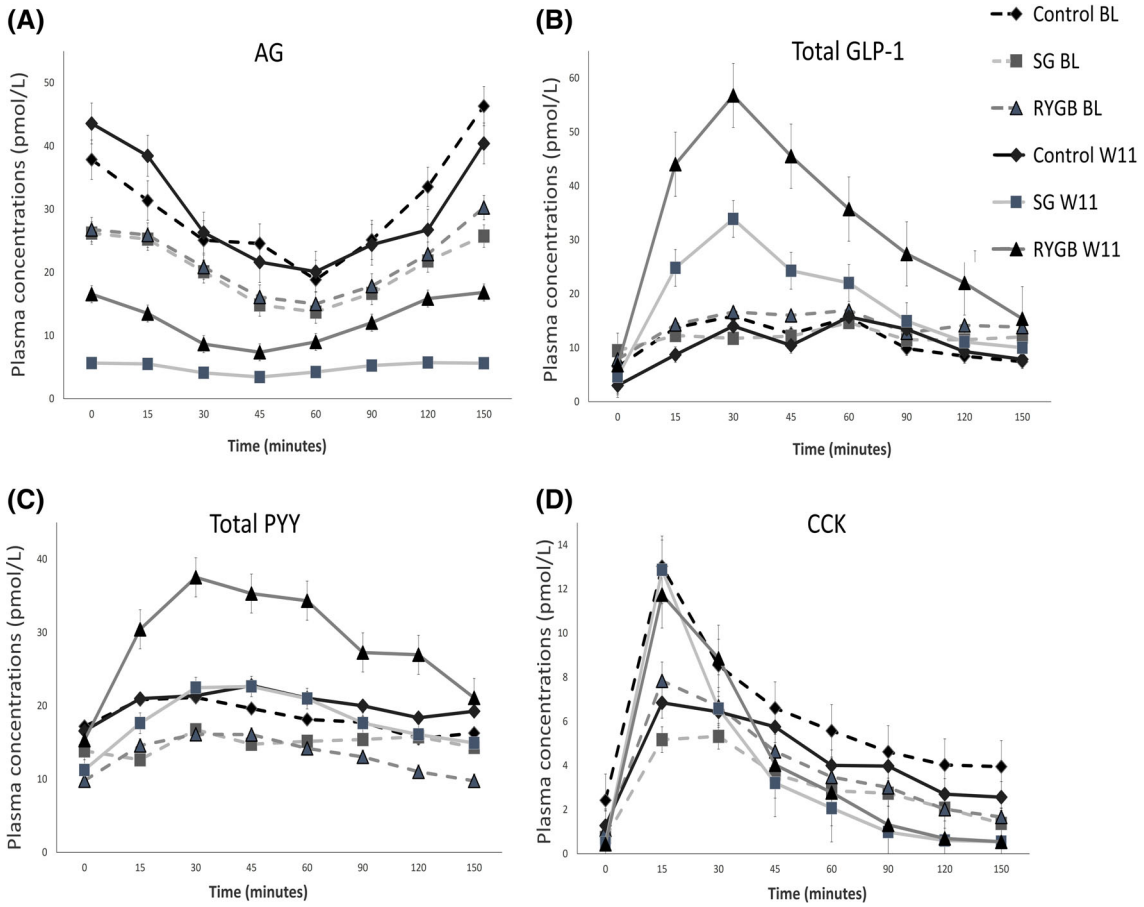

FIGURE 3 Mean postprandial concentrations of gastrointestinal hormones at baseline (BL) and week 11 (W11). Dotted lines indicate baseline concentrations, and solid lines indicate week 11 concentrations. AG, acylated ghrelin; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy [Color figure can be viewed at wileyonlinelibrary.com]

at W11 were lower in SG compared with controls ($p = 0.029$), and postprandial ratings (*t*AUC) were lower in RYGB compared with controls ($p = 0.019$).

An overall decrease in ratings of PFC, both fasting and postprandially, was seen

A main effect of time and time × group interaction was seen for PFC in the fasting state ($p < 0.001$, for both), and a main effect of time ($p < 0.001$) and group ($p = 0.028$) was seen for PFC tAUC. Post hoc analysis showed that RYGB presented with greater PFC ratings in fasting at BL compared with controls ($p = 0.017$). At W11, SG and RYGB had lower fasting (for both) and *t*AUC (RYGB) PFC ratings, compared with controls ($p < 0.001$ for both and $p = 0.015$, respectively).

DISCUSSION

This study aimed to compare changes in GI hormone concentrations and subjective appetite ratings in individuals with severe obesity achieving a similar weight loss with VLED alone or in combination with SG or RYGB. It represents the first attempt to perform such comparisons when changes in body weight and composition, as well as magnitude of nutritional-induced ketosis, are similar across groups. SG and RYGB groups experienced a decrease in both basal and postprandial AG concentrations and an increase in postprandial total GLP-1 concentrations. All groups experienced an increase in postprandial concentrations of total PYY. At W11, RYGB obtained the greatest postprandial concentrations of both total GLP-1 and total PYY. Postprandial CCK concentrations remained unchanged over time for all groups. Overall, postprandial hunger decreased, and postprandial fullness increased. Moreover, larger decreases in fasting and postprandial DTE and PFC were seen after both bariatric procedures, and at W11, ratings tended to be overall lower in SG and RYGB compared with controls.

It is generally accepted that individuals with obesity present with lower basal and postprandial ghrelin concentrations compared with individuals without obesity [26–28], and that diet-induced weight loss leads to an increase in ghrelin concentrations [13, 15, 16]. In the present study, controls showed no changes in AG concentrations, despite substantial weight loss. Ketosis was shown to prevent the increase in ghrelin plasma concentrations otherwise seen following diet-induced

TABLE 3 Subjective appetite ratings at baseline and week 11 by group

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
Hunger in fasting (cm)	3.2 ± 0.8	2.7 ± 0.7	3.9 ± 0.7	3.7 ± 0.8	2.9 ± 0.8	3.1 ± 0.8	NS	NS	NS
Hunger *t*AUC (cm × min)	524.3 ± 72.1	415.9 ± 66.2	404.2 ± 68.0	311.9 ± 74.5	320.1 ± 74.5	118.4 ± 77.1	$p = 0.001$	NS	NS
Hunger *d*AUC (cm × min)	2.1 ± 118.2	−2.0 ± 108.5	−83.5 ± 114.7	−248.1 ± 122.1	−129.9 ± 122.1	−340.2 ± 126.4	$p = 0.032$	NS	NS
Fullness in fasting (cm)	1.7 ± 0.6	1.0 ±. 0.5	1.4 ± 0.6	2.4 ± 0.6	1.7 ± 0.6	2.5 ± 0.6	NS	NS	NS
Fullness *t*AUC (cm × min)	577.3 ± 85.8	610.5 ± 78.8	584.7 ± 80.9	841.4 ± 88.1	641.9 ± 86.6	705.2 ± 89.5	$p = 0.011$	NS	NS
Fullness *i*AUC (cm × min)	269.4 ± 102.8	445.6 ± 94.3	396.6 ± 99.7	491.3 ± 106.2	360.1 ± 106.2	357.9 ± 109.9	NS	NS	NS
DTE in fasting (cm)	4.8 ± 0.8	4.0 ± 0.7	4.0 ± 0.8	4.2 ± 0.8*	1.1 ± 0.8 *	2.9 ± 0.8	$p = 0.005$	NS	NS
DTE *t*AUC (cm × min)	399.7 ± 55.5.	289.3 ± 50.9	241.5 ± 52.3	330.5 ± 57.3[&]	175.2 ± 57.3	99.7 ± 59.3[&]	$p = 0.017$	$p = 0.006$	NS
DTE *d*AUC (cm × min)	−314.2 ± 107.1	−375.4 ± 98.2	−215.7 ± 103.7	−289.5 ± 110.4	13.9 ± 110.0	−318.1 ± 113.8	NS	NS	$p = 0.035$
PFC in fasting (cm)	2.7 ± 0.7[&]	4.6 ± 0.6	5.3 ± 0.6[&]	2.9 ± 0.7[# ¤]	1.3 ± 0.6.8[#]	1.4 ± 0.7[¤]	$p < 0.001$	NS	$p < 0.001$
PFC *t*AUC (cm × min)	422.7 ± 59.4	358.5.4 ± 54.5	325.2 ± 56.0	327.8 ± 61.3[&]	135.2 ± 61.1	74.9 ± 63.2[&]	$p < 0.001$	$p = 0.028$	NS
PFC *d*AUC (cm × min)	−70.8 ± 108.8	−289.3 ± 99.8	−401.5 ± 105.5	−118.3 ± 112.3	−63.1 ± 112.3	−142.3 ± 125.6	NS	NS	NS

Note: Data are presented as estimated marginal means ± SEM. Conversion from metric to SI units has been applied as follows: ghrelin pg/mL × 0.3 = pmol/L, PYY pg/mL × 0.25 = pmol/L. Post hoc pairwise comparisons corrected with Bonferroni adjustment. Averages sharing the same superscript letter denote a significant change over time ($p < 0.05$). Averages sharing the same superscript symbol denote significant differences between groups (*&#, $p < 0.05$) or significant differences in the changes over time between groups at week 11 (¤¤, $p < 0.05$).

Abbreviations: CCK, cholecystokinin; *d*AUC, decremental area under the curve; DTE, desire to eat; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curve; NS, not significant. PFC, prospective food consumption; PYY, peptide YY; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy; *t*AUC, total area under the curve.

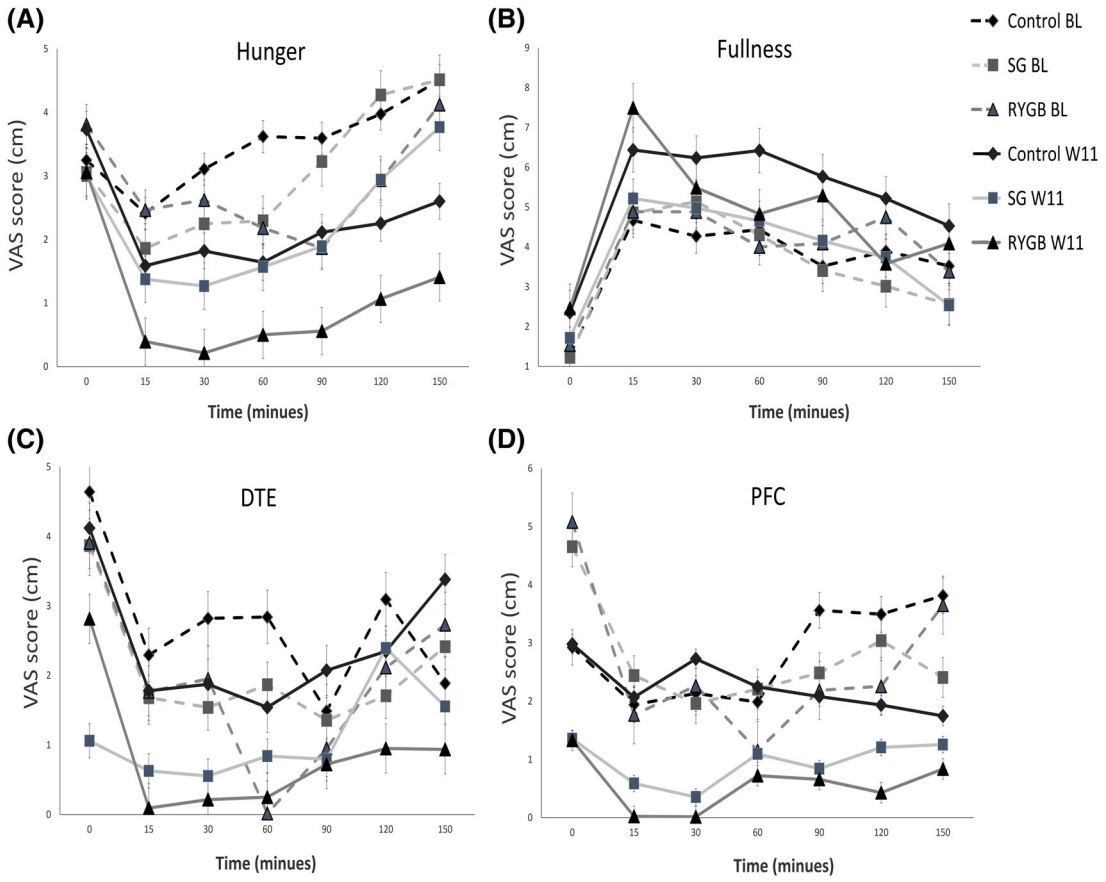

FIGURE 4 Mean postprandial ratings of appetite at baseline (BL) and week 11 (W11). Dotted lines indicate baseline ratings, and solid lines indicate week 11 ratings. DTE, desire to eat; PFC, prospective food consumption; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VAS, visual analog scale [Color figure can be viewed at wileyonlinelibrary.com]

weight loss [17, 18, 20], which might explain these findings. The main production site of ghrelin is the fundus of the stomach, which is removed during the SG procedure. It is therefore not surprising that the present, as well as several other studies [6, 7, 10], report a reduction in AG concentrations post SG. The present study also confirmed previous findings that ghrelin decreases post RYGB [10, 15, 16, 29], and that concentrations are lower when compared with dietary restriction alone [15, 16]. However, not all are in agreement [4, 28], and an increase in both total ghrelin and AG concentrations has also been reported post RYGB [27]. These conflicting findings likely result from differences in the surgical technique, namely the size of the remaining pouch.

The impact of diet-induced weight loss on postprandial concentrations of the satiety peptides GLP-1 and PYY remains controversial [12–14]. Based on previous literature, we hypothesized that WL with SG and RYGB would induce a two- and threefold larger increase in GLP-1 AUC compared with VLED alone [13]. The present study showed no changes in postprandial total GLP-1 concentrations after weight loss induced by VLED alone, whereas the magnitude of increase seen after SG and RYGB was larger than hypothesized. Although increased postprandial total PYY concentrations were seen across all groups, the increases were larger following RYGB. Several other studies report increased postprandial concentrations of both GLP-1 and PYY following both surgical procedures and also demonstrate that RYGB results in larger postprandial concentrations of these gut hormones compared with SG (as well as controls) [6–8, 10, 11, 15, 28, 30]. Alterations in the plasma concentrations of these satiety peptides post bariatric surgery may be due to accelerated gastric emptying, caused by the surgical alterations of the stomach, leading to an exaggerated secretion of satiety hormones after SG [6], and possibly by faster nutrient contact with the distal gut due to anatomical shortcuts following RYGB [31]. In addition, the anatomical rearrangement that follows bariatric surgery, especially RYGB, seems to lead to the proliferation of GI hormone-secreting cells [32]. Postprandial GLP-1 concentrations at 1-year follow-up have been associated with greater weight loss post RYGB [33], and increased postprandial responses of both GLP-1 and PYY were shown to be sustained for up to 10 years post bariatric surgery [4, 10, 11]. As a result, GLP-1 analogs have become increasingly popular in the management of obesity by increasing satiety and reducing food intake and body weight [34]. Interestingly, with the second-generation GLP-1 receptor agonists, it is possible to obtain weight losses approaching those observed after bariatric surgery [35].

Diet-induced weight loss has previously been shown to decrease postprandial CCK concentrations in individuals with obesity but not when participants are ketotic [36]. This is in line with the present

findings showing no changes over time in postprandial CCK concentrations across groups under nutritional-induced ketosis. With RYGB, the duodenum is excluded from contact with nutrients, which could explain why an increased CCK response was not seen after this bariatric procedure. However, previous literature on this issue is inconsistent. Peterli et al. [10] reported an increase in postprandial CCK response following SG but not RYGB. On the other hand, Schmidt et al. [15] reported a marked increase in postprandial CCK, along with GLP-1 and PYY response, post RYGB.

Despite supposedly less beneficial alterations in GI hormonal concentrations with weight loss induced by diet alone, an overall reduction in ratings of postprandial hunger, as well as an overall increase in postprandial fullness, was seen in the present study. It has previously been demonstrated that the expected increase in hunger that follows weight loss is prevented and postprandial fullness sometimes increased when participants are ketotic [20, 36]. Even though ketosis has been associated with a greater weight loss 1 year post SG [37], the impact of ketosis on appetite in the context of bariatric surgery is underinvestigated [21, 37]. Moreover, SG reduced ratings of DTE in the fasting state at W11, and both fasting and postprandial DTE ratings were lower in SG and RYGB groups, respectively, compared with controls. In addition, fasting and postprandial PFC ratings decreased more so after bariatric surgery, and ratings were significantly lower compared with controls at W11. Even though the association between plasma concentrations of GI hormones and subjective appetite ratings is complex [38], the lower drive to eat seen across groups in the present study is not unexpected, given that participants experienced no changes (or even a decrease) in ghrelin concentrations as well as increases in postprandial PYY and/or GLP-1 concentrations.

Several aspects may help explain the lack of alignment between the plasma concentrations of GI hormones and appetite feelings seen in the present study. Subjective appetite ratings are likely to reflect individual factors, such as learned behaviors throughout the life-span [39]. Also, dumping syndrome is a common side effect of bariatric surgery, especially post RYGB, that is suggested to alter the pleasantness of foods, specifically foods rich in carbohydrates and fats [40]. The nature of the dietary regime and the test meal used might also play a role. Although the test meal was standardized for all participants on both assessment days, the meal contained twice the number of calories compared with each of the food packs participants consumed during the 10-week intervention period. Moreover, it is debatable to what degree subjective hunger ratings can reflect actual physiological needs. For example, although hunger ratings in the fasting state are most likely a reflection of energy depletion, hunger ratings in the fed state may also be impacted by the hedonic properties of food [41]. In light of this, our group recently showed, in these same participants, an overall reduction in hedonic hunger (measured postprandially) after both diet-induced weight loss and bariatric surgery [42]. Emerging evidence also has shown that GI hormones also act in mesolimbic pathways [43], and as such, GI hormones might play a role both in homeostatic and hedonic appetite control. In our previous analysis and compared with controls, additional favorable changes in food reward (measured both pre- and postprandially) were seen both after SG and RYGB [42], and this might reflect the present findings of favorable DTE and PFC ratings post bariatric surgery.

This study has several strengths. First, weight loss, diet composition, and ketosis level were similar across groups, allowing for the identification of the impact of SG and RYGB alone on the outcome variables. Second, sex distribution, age, baseline anthropometric variables, and PA levels were similar in all groups and therefore unlikely to have affected the variables of interest. Finally, the significance level was adjusted for multicomparisons, using Bonferroni adjustment. However, this study also suffers from some limitations. First, with this study design, we cannot establish a cause–effect relationship. Second, we could not ensure that pre- and postintervention measurements were taken in the same phase of menstrual cycle, as the intervention period was 10 weeks. This is important, as phase of menstrual cycle is known to impact on appetite [44]. However, the distribution was likely to occur at random, so there is no strong indication that this constitutes a major issue in our analysis. Third, although this study obtained enough power to detect significant differences among groups for the main outcome variable (GLP-1 AUC), we cannot rule out the possibility that the study was underpowered to detect true differences in the other variables. Fourth, even though the standardization of the diet and test meal is a strength, we cannot rule out that some of the differences found among groups, especially bariatric groups versus controls, is due to transitory changes in postoperative physiology, including fluid shifts and changes in absorption and metabolism. Also, because of the low-glycemic-index nature of the test meal, its macronutrient composition was not in line with nutritional guidelines. Fifth, a Milliplex kit was used to analyze AG and total PYY, which is expected to result in less accurate measures than specific assays for each hormone. Last, but not least, stress is a potential mediator of appetite and eating behavior [45]. Given that this study was carried out under unusual circumstances (COVID-19 pandemic), stress could have had some influence on both GI hormone concentrations and subjective appetite measures.

CONCLUSION

Changes in GI hormones, which are involved in homeostatic appetite regulation, following RYGB and SG seem to be more favorable compared with when weight loss is induced by dietary restriction alone. However, weight loss, independently of modality, seems to be associated with an overall appetite reduction. This might reflect the fact that the magnitude of weight loss and the level of nutritional-induced ketosis, as well as the dietary intervention, were similar across groups. Larger studies with a longer duration are needed to determine whether these initial changes in GI hormone concentration and subjective appetite ratings modulate long-term weight loss outcomes after both diet and bariatric surgery.O

AUTHOR CONTRIBUTIONS

Catia Martins and Marthe Isaksen Aukan formulated the research questions and designed the study. Marthe Isaksen Aukan, Silje

Skårvold, and Ingrid Øfsti Brandsæter carried out the study. Jens Frederik Rehfeld and Jens Juul Holst measured CCK and GLP-1 concentrations, respectively. Marthe Isaksen Aukan analyzed the data. All authors were involved in the writing of the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

CLINICAL TRIALS REGISTRATION

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DATA AVAILABILITY STATEMENT

Data described in the manuscript will be made available upon request pending.

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