Sleeve gastrectomy effects on hunger, satiation, and gastrointestinal hormone and motility responses after a liquid meal test

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ABSTRACT

Background: The relation between hunger, satiation, and integrated gastrointestinal motility and hormonal responses in morbidly obese patients after sleeve gastrectomy has not been determined.

Objective: The objective was to assess the effects of sleeve gastrectomy on hunger, satiation, gastric and gallbladder motility, and gastrointestinal hormone response after a liquid meal test.

Design: Three groups were studied: morbidly obese patients (n=16), morbidly obese patients who had had sleeve gastrectomy (n=8), and nonobese patients (n=16). The participants fasted for 10 h and then consumed a 200-mL liquid meal (400 kcal + 1.5 g paracetamol). Fasting and postprandial hunger, satiation, hormone concentrations, and gastric and gallbladder emptying were measured several times over 4 h.

Results: No differences were observed in hunger and satiation curves between morbidly obese and nonobese groups; however, sleeve gastrectomy patients were less hungry and more satiated than the other groups. Antrum area during fasting in morbidly obese patients was statistically significant larger than in the nonobese and sleeve gastrectomy groups. Gastric emptying was accelerated in the sleeve gastrectomy group compared with the other 2 groups (which had very similar results). Gallbladder emptying was similar in the 3 groups. Sleeve gastrectomy patients showed the lowest ghrelin concentrations and higher early postprandial cholecystokinin and glucagon-like peptide 1 peaks than did the other participants. This group also showed an improved insulin resistance pattern compared with morbidly obese patients.

Conclusions: Sleeve gastrectomy seems to be associated with profound changes in gastrointestinal physiology that contribute to reducing hunger and increasing sensations of satiation. These changes include accelerated gastric emptying, enhanced postprandial cholecystokinin and glucagon-like peptide 1 concentrations, and reduced ghrelin release, which together may help patients lose weight and improve their glucose metabolism after surgery. This trial was registered at clinicaltrials.gov as NCT02414893.

INTRODUCTION

Morbid obesity constitutes a major health problem, given the growing prevalence, associated comorbidities, and increased risk of death (1). Bariatric surgery—currently the only effective approach to achieving major, long-term weight loss in morbidly obese individuals—ensures longer survival and resolution or better control of comorbidities (2). A commonly used bariatric procedure is sleeve gastrectomy (SG),7 in which the fundus and a large part of the stomach are excised and stapled into the form of a vertical tube. How exactly this procedure affects hunger, food intake, and satiation is unclear, although it is known to alter hormone responses (3) and gastrointestinal motility.

Subjective hunger sensation needs to be distinguished from food intake capacity, because obese people can ingest large quantities of calories and food yet not feel truly hungry (4). Satiation (5) has been associated with fasting gastric volume, gastric emptying, and upper gastrointestinal motility (6). Although studies have suggested that SG accelerates gastric emptying (7–9), a few studies confirm this (10).

Regarding gastrointestinal hormones, 3 peptides in particular are of interest in morbidly obese (MO) patients before and after surgery: ghrelin, with an orexigenic effect, and cholecystokinin and glucagon-like peptide 1 (GLP-1), with anorexigenic effects. Ghrelin stimulates gastrointestinal motility; mainly produced in the stomach, it plays a major role in long-term weight control and short-term meal initiation (11). In people with normal BMI (in kg/m²), blood concentrations of ghrelin rise and fall before and after eating (12), respectively; however, concentrations tend to remain high in underweight people and low in obese people (11). Cholecystokinin is secreted in the duodenum and proximal jejunum in response to food intake. Cholecystokinin delays gastric emptying, inhibits food intake, and promotes gallbladder contraction and exocrine pancreatic secretion. Bile salts released by the gallbladder in the duodenum inhibit cholecystokinin production as negative feedback (13). GLP-1 is released primarily

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3 Abbreviations used: GLP-1, glucagon-like peptide-1; MO, morbidly obese; SG, sleeve gastrectomy.
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from the distal small bowel (L cells). Its main function is regulation of plasma blood glucose concentrations, referred to as the incretin effect. It also inhibits gastric emptying and gastric and pancreatic secretions and is also thought to mediate the ileal brake (14). Glucose homeostasis is also frequently altered in MO persons, who tend to have high glucose and insulin concentrations mainly due to insulin resistance. The effects of SG on some of these gastrointestinal peptides have been studied in humans (15, 16) but do not address how SG affects gallbladder motility or the integrated relation between postprocedure gastric motility and hormone responses.

Our aim was to assess the effects of SG on hunger, satiation, gastrointestinal hormone response, and gastric and gallbladder motility as an integrated response after a liquid meal test.

**METHODS**

Three groups were compared: a control group of nonobese persons (with BMI <30), a MO group of patients who fulfilled bariatric surgery criteria (17), and a group of patients who had undergone laparoscopic SG at least 6 months previously. All individuals were recruited at the Hospital de Mataró, Consorci Sanitari del Maresme (Mataró, Barcelona, Spain), and the experiment was performed in our laboratory for 4 h, after which patients were discharged. There was no further follow-up except for the standard procedure for the SG group. The SG technique had been performed laparoscopically by dividing the vascular supply of the greater curvature of the stomach from a point measured at a distance of 5 cm from the pylorus to the left crus of the diaphragm; here the stomach was sectioned close to a 42 French bougie (inserted per orally by the anesthetist) by using a linear stapler. Exclusion criteria were previous cholecystectomy or partial gastrectomy.

Experimental design has been described by our group elsewhere (18). Briefly, after a 10-h overnight fast, participants in all 3 groups were given 200 mL of a standard liquid 400-kcal meal (T-Diet 20/2; Vegenat) containing 20.2 g protein, 15.6 g fat, and 43.4 g carbohydrate. Participants were also administered 1.5 g paracetamol (Laboratorios Gelos) to monitor gastric emptying and 10 g lactulose (Duphalac; Abbot Laboratories). A nurse ensured complete ingestion of the liquid meal in 5 min. Before food intake and at 15, 30, 45, 60, 90, 120, 180, and 240 min after intake, hunger, satiation, and gastric and gallbladder motility were assessed and blood was sampled to determine ghrelin, cholecystokinin, GLP-1, acetaminophen (the absorbed metabolite of paracetamol), glucose, and insulin concentrations.

The study protocol was approved by the institutional review board of the Hospital de Mataró, Consorci Sanitari del Maresme (Mataró, Barcelona, Spain). All participants gave their written informed consent before inclusion.

**Measurements**

Study variables included sociodemographic characteristics; comorbidities; body composition; baseline metabolism, assessed by bioelectrical impedance analysis (Bioimpedance Analyzer Model BIA101; Akern bioresearch Srl); and quality of life, assessed by the Euro-QoL-5D generic quality-of-life questionnaire (www.euroqol.org). Hunger and satiation perceptions were measured by means of a 10-cm visual analog scale, where 0 indicated no hunger/satiation and 10 indicated total hunger/satiation (18). Hormone concentrations were measured by using validated, commercialized, human radioimmunoassay kits as follows: total plasma ghrelin concentrations (Linco Research Inc.), plasma cholecystokinin (26–33) concentrations (Euro-Diagnostica), and active GLP-1 plasma concentrations [GLP-1 (7–36) amide; Millipore]. Plasma insulin concentrations were measured by chemiluminescence (Immulite 2000 DPC; Siemens Medical Solutions Diagnostics) by using sheep and mouse anti-insulin antibodies. Serum glucose was measured with the commercially available Gluco-quant Enzymatic Hexokinase test kit (Roche Diagnostics GmbH). Blood acetaminophen concentrations were determined by using an enzymatic method and colorimetric determinations (Cobas Integra 400 Plus; Roche Diagnostics).

Gallbladder and gastric motility were both measured by using ultrasound (Hitachi EUB-6500 Digital Ultrasound Scanner; Hitachi Medical Co.). Gallbladder volume was calculated by measuring length, width, and height of the gallbladder by using a validated method that considers the gallbladder an ellipsoid cylinder and evaluates gallbladder emptying by sequential volume measurements (18). The gastric antrum area (sagittal image) was measured by positioning the transducer in the epigastric area and using the left lobe of the liver, the superior mesenteric vein, and the aorta as landmarks (19). The first ultrasound measurement was made during fasting, the second was made 5 min after the subject commenced meal ingestion, and further measurements were made at the same time points as for blood samples (15, 30, 45, 60, 90, 120, 180, and 240 min after intake). Antral gastric compliance was defined as the percentage increase in the antral area 5 min after meal ingestion, with increases adjusted to a baseline value of 100 to account for interindividual variability. Gastric emptying was assessed by using the paracetamol absorption test, widely used because the absorption rate for acetaminophen—rapidly absorbed from the small intestine, with no absorption from the stomach—reflects the gastric emptying rate (20). Previous studies (21) have demonstrated a good correlation between gastric emptying half-times for liquids and serum acetaminophen concentrations at 30 and 60 min.

**Statistical analyses**

For statistical analysis purpose, 3 main periods—fasting, early postprandial (0–60 min), and late postprandial (60–240 min)—were established. AUC for the 2 postprandial periods was calculated for all study variables (with respect to zero for hunger and satiation scores). Incremental areas under or over the baseline value were calculated for hormone and motility responses (18). Gastric emptying (paracetamol absorption test) was evaluated by measuring concentration increases at 30 min and AUC at 60 min. Absolute and relative percentage values were used for ultrasound measurements of the gastric antrum (18). To explore the cholecystokinin release feedback loop, gallbladder contractors were defined as individuals with a postprandial gallbladder volume below 50% of fasting volume in the first 60 min after food intake (22). Accepting a risk of 0.05 and a β risk of 0.2 in a one-sided test, 13 subjects were necessary in any group to recognize a difference ≥1 unit as...
RESULTS

Participant clinical characteristics

Forty persons were recruited: 16 to the nonobese group, 16 to the MO group, and 8 to the SG group. Main characteristics and comorbidities for each group are summarized in Table 1. The SG group was older on average than the nonobese group, fat-free mass percentage and muscle mass percentage were higher in the nonobese group than in the MO group, and C-reactive protein was higher in the MO group than in the other 2 groups.

<p>| TABLE 1 | Main characteristics of the study groups |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>NOb (n = 16)</th>
<th>MO (n = 16)</th>
<th>SG (n = 8)</th>
<th>NOb vs. MO</th>
<th>MO vs. SG</th>
<th>NOb vs. SG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.6 ± 10.5</td>
<td>46.8 ± 9.4</td>
<td>54.5 ± 7.9</td>
<td>0.090</td>
<td>0.086</td>
<td>0.005</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>62.5</td>
<td>62.5</td>
<td>62.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.6 ± 2.3</td>
<td>46.9 ± 5.7</td>
<td>34.9 ± 4.3</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Time after SG, mo</td>
<td>12.8 ± 3.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.20 ± 0.20</td>
<td>0.69 ± 0.39</td>
<td>0.30 ± 0.18</td>
<td>0.001</td>
<td>0.015</td>
<td>0.047</td>
</tr>
<tr>
<td>Fat-free mass, %</td>
<td>72.8 ± 11.2</td>
<td>57 ± 7.9</td>
<td>67.5 ± 14.9</td>
<td>0.001</td>
<td>0.071</td>
<td>0.245</td>
</tr>
<tr>
<td>Muscle mass, %</td>
<td>50.9 ± 7.4</td>
<td>38.3 ± 7.0</td>
<td>41.8 ± 14.5</td>
<td>0.001</td>
<td>0.903</td>
<td>0.033</td>
</tr>
<tr>
<td>Metabolic rhythm</td>
<td>1558 ± 221</td>
<td>1910 ± 398</td>
<td>1691 ± 328</td>
<td>0.004</td>
<td>0.058</td>
<td>0.854</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM type 2</td>
<td>0 (0)</td>
<td>3 (18.8)</td>
<td>3 (37.5)</td>
<td>0.226</td>
<td>0.362</td>
<td>0.028</td>
</tr>
<tr>
<td>GERD</td>
<td>1 (6.3)</td>
<td>3 (18.8)</td>
<td>4 (50)</td>
<td>0.600</td>
<td>0.167</td>
<td>0.028</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazol</td>
<td>2 (12.5)</td>
<td>8 (50.0)</td>
<td>6 (75.0)</td>
<td>0.054</td>
<td>0.388</td>
<td>0.005</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0 (0)</td>
<td>5 (31.3)</td>
<td>1 (12.5)</td>
<td>0.043</td>
<td>0.621</td>
<td>0.330</td>
</tr>
</tbody>
</table>

1 Mann-Whitney U test was used to compare medians between 2 groups. \(\chi^2\) or Fisher exact test was used to compare proportions between groups. DM, diabetes mellitus; GERD, gastroesophageal reflux disease; MO, morbidly obese; NOb, nonobese; NSAID, nonsteroidal anti-inflammatory drug; SG, sleeve gastrectomy.

2 Mean ± SD (all such values).

Hunger and satiation

Visual analog scale results for the 3 study groups, before and after liquid food intake (fasting and postprandial periods, respectively), are shown in Figure 1. SG patients showed less hunger and more satiation than persons in the nonobese group (general linear model, \(P = 0.003\) and \(P = 0.011\), respectively) and more satiation than the MO group during fast (\(P = 0.008\)) and the first 90 min after intake. Hunger was similar for MO and nonobese participants throughout the study.

Gastric and gallbladder motility

Antral compliance 5 min after intake was similar for all 3 groups (209.9% ± 108.9%, 181.2% ± 92.4%, and 164.2% ± 43.5% for the nonobese, MO, and SG groups, respectively), whereas antrum area during fasting was greatest in the MO group. No gastric emptying differences were observed between the MO and nonobese groups, whereas the SG group showed accelerated gastric emptying compared with the other groups (AUC\(_{0-60}\); \(P = 0.002\) and \(P = 0.005\), respectively). Gallbladder emptying curves were similar for the 3 groups, as shown in Figure 2. All 3 groups had fairly similar contractor rates (75%, 87.5%, and 100% for the nonobese, MO, and SG groups, respectively). Fasting gallbladder volume was lowest in the nonobese group and highest in the SG group (32.5 ± 8.6 mL, 59.9 ± 20.1 mL, and 76.8 ± 39.5 mL for the nonobese, MO, and SG groups, respectively). These differences between SG and nonobese groups and between MO and nonobese groups were significant (\(P < 0.017\)). Fasting gallbladder volume in the MO group was similar to that in the SG group (\(P = 0.548\)). The SG group was fastest in reducing gallbladder volume to the minimum (27.9 ± 10.3 min, 43.1 ± 19.6 min, and 60.0 ± 28.5 min for the SG, nonobese, and MO groups, respectively), with significant differences between the SG and the MO groups (\(P = 0.005\)).
Gastrointestinal peptides

Ghrelin, cholecystokinin, and GLP-1 curves for the 3 study groups are shown in Figure 4. Compared with the nonobese group, the MO group had significantly lower fasting ghrelin ($P = 0.003$) but showed no significant differences in fasting cholecystokinin ($P = 0.04$) and GLP-1 ($P = 0.123$) concentrations ($P < 0.017$ was significant). The drop in ghrelin observed in the nonobese group after food intake was not observed in the other 2 groups. The SG group had lower fasting ghrelin ($P = 0.003$) concentrations compared with the nonobese group and higher fasting GLP-1 concentrations than did the MO ($P = 0.001$) group. In the postprandial period, the SG group had the lowest
ghrelin (general linear model, $P < 0.017$) and highest cholecystokinin and GLP-1 peaks ($\text{AUC}_{0–60}; P < 0.017$) compared with the other 2 groups.

Glucose homeostasis

For the entire meal test period, glucose and insulin concentrations were higher for the MO and SG groups compared with the nonobese group, as shown in Figure 5. Fasting glucose for the SG group was similar to that for the nonobese group ($P = 0.903$), whereas fasting insulin in the SG group was still higher than that for the nonobese group ($P = 0.003$). In the early postprandial period, glucose and insulin concentrations were also higher in the SG ($\text{AUC}_{0–60}; P = 0.008$ and $P < 0.001$, respectively) and MO ($\text{AUC}_{0–60}; P < 0.001$ and $P < 0.001$, respectively) groups compared with the nonobese group. Insulin concentrations in the SG group normalized at 120 min after food intake ($P > 0.017$), whereas they remained high in the MO group, even in the late postprandial period.

DISCUSSION

The main results of the study are that MO patients had similar hunger and satiation sensations and similar gastric emptying and gallbladder motility but lower fasting and postprandial ghrelin concentrations than did nonobese individuals and that SG was associated with reduced hunger and increased satiation, with faster gastric emptying, higher early postprandial peak concentrations of cholecystokinin and GLP-1, and reduced ghrelin concentrations. These different motility and hormone results for SG patients suggest that SG surgery may cause weight loss through several changes in gastrointestinal physiology that diminish hunger and enhance satiation. Our study suggests these different motility and hormonal responses interact after SG, therefore controlling hunger and satiation in these patients. This topic has not been fully addressed in humans and rarely in animals (23).
Hunger and satiation are very subjective perceptions that are understood and interpreted in different ways by different people. Hunger can even be “taught,” as when overweight patients are trained to correlate “true” hunger with low blood glucose concentrations, demonstrated by Ciampolini et al. (4). Previous studies have described obese people to be hungrier than non-obese individuals (24, 25). Regarding satiation, Delgado-Aros et al. (26) reported that greater BMI and greater fasting gastric volumes were both independently associated with delayed satiation after a nutrient liquid test that intended to achieve maximum satiation. Surprisingly, the results in this study show that MO patients were no hungrier or no less satiated than nonobese persons and that SG patients had less hunger than MO and nonobese patients and felt more satiated than nonobese patients. This finding corroborates some studies (27) but not others (28). These differences could be explained by the fact that this study tried to assess the effect of morbid obesity and SG on hunger and satiation after a standard liquid meal test, with just enough caloric intake to inhibit hunger and induce satiation, and did not try to assess maximal intake capacity.

The paracetamol absorption test was used to assess gastric emptying because it has been reported to correlate well with scintigraphy—considered the gold standard—for liquid meal tests (21). Similar gastric emptying rates were observed for MO and nonobese individuals but a highly accelerated rate for SG patients; this result agrees with some studies (8, 9, 29) but contradicts others (30, 31), which suggested that antrum size after SG could influence gastric emptying. Some authors have hypothesized that higher intragastric pressure (32) with less peristalsis of the sleeve and faster propagation of antral propulsion waves (33) may play a role in this accelerated emptying. The larger fasting gallbladder in MO and SG patients compared with nonobese individuals described in this study is also corroborated by other authors (34). No differences in overall gallbladder emptying were found. This finding disagrees with previous studies that demonstrate that gallbladder contraction is impaired in obese patients (34, 35).

Baseline and postprandial hormonal concentrations were also significantly modified in SG patients. Postprandial ghrelin concentrations were lowest in SG patients, agreeing with findings by other authors (16, 36). Ghrelin differences between nonobese and MO individuals could be attributable to their different BMIs (37). Differences between MO and SG may be a consequence of the excision of the gastric body and fundus where most ghrelin is released. As generally accepted, fasting ghrelin concentrations were lower and postprandial suppression was decreased in MO compared with nonobese individuals (37, 38).

The higher cholecystokinin peak observed in SG patients during the initial postprandial period may be explained by accelerated gastric emptying and the sudden arrival of nutrients to the duodenum (23) and might also contribute to greater satiation. The fact that gallbladder motility was not impaired explains the normal cholecystokinin drop after the peak, indicating a preserved bile salt feedback regulation. These results were similar to those of the few studies that have addressed this topic (39, 40), and these high concentrations could be associated with the higher satiation scores reported for SG patients (23). Camilleri and Grudell (5) suggested that cholecystokinin tended to relax the fundus and inhibit the antrum, and MO patients have been reported to be less sensitive to both cholecystokinin and GLP-1 (41). This sensitivity might be enhanced after bariatric surgery (42).

The finding that MO patients showed lower fasting and postprandial concentrations of GLP-1 corroborates those of previous studies (42–44). Likewise, the finding that higher concentrations of GLP-1 at 15 min for the SG group coincided with peak satiation corroborates the finding reported by Näsllund et al. (44) that the intravenous GLP-1 infusion caused a reduced
gastrectomy and GI physiologic changes

REFERENCES

The authors’ responsibilities were as follows—EM, MS-P, EP, and PC: designed the research; EM, MS-P, and XS: conducted the research; MS-P and EP: analyzed data; EM, MS-P, and PC: wrote the manuscript and had primary responsibility for the final content; and all authors: read and approved the final manuscript. The authors declared no conflicts of interest.


