



Applied nutritional investigation

Mechanisms of long-term weight regain in patients undergoing sleeve gastrectomy



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ABSTRACT

Objectives: Weight regain after bariatric surgery may be associated with behavioral, metabolic, or mechanical factors alone or in combination. The aim of this study was to investigate which factors are related to weight regain in the long-term after sleeve gastrectomy (SG).

Methods: A retrospective case-control study with 40 patients undergoing SG (32 women, 8 men; age 42.9 ± 10.7 y; preoperative body mass index 35 ± 2.8 kg/m²), was performed. Patients were grouped according percentile $>50\%$ (cases) or $<50\%$ (controls)—of weight regain (%WR cutoff: 25% of weight loss). Weight history, anthropometry, glucose, insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), thyroid-stimulating hormone, resting energy expenditure, body composition, dietary survey, psychological test, and physical activity were recorded. Residual gastric capacity was estimated using a radiologic method.

Results (median [p25–p75]): The evaluation was conducted 38.5 mo (34–41 mo) after SG. Percent weight regain ranged from 2.7% to 129.2% (25.4% [13–37.1]). Patients in the higher %WR group had a greater residual gastric volume (252.7 ± 108.4 versus 148.5 ± 25.3 ; $P < 0.05$) and the estimated volume was significantly correlated with %WR ($r = 0.673$; $P = 0.023$). Significantly higher body mass index ($P = 0.001$), resting energy expenditure ($P = 0.04$), fasting insulin ($P = 0.01$), and HOMA-IR ($P = 0.02$) were observed in the higher %WR group. A higher fat intake and a trend toward higher total energy intake were observed in the group with greater %WR. Clinical or borderline levels of anxiety were more frequently observed in the higher %WR group (70% versus 30%; $P = 0.01$).

Conclusions: Results from the present study demonstrated that the most important factor associated with long-term weight regain after SG was residual gastric volume. Additional prospective studies with larger numbers of patients are necessary to confirm our results.

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data. All authors approved the final version of the manuscript. The authors have no conflict of interest to declare. However, AC has received honorarium as a speaker and member of the advisory board of Genzyme and MSD. MB has received research grants from Covidien.

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Introduction

Obesity has become a worldwide epidemic, and it is associated with an increased risk for chronic diseases such as hypertension, type 2 diabetes, dyslipidemia, and cardiovascular disease [1–3]. The main pillars for obesity treatment are dietary advice, exercise, and pharmacologic treatment; however, these approaches often fail to produce satisfactory results, with 95% of individuals regaining their initial weight within 2 y [4].

It has been demonstrated that bariatric surgery is the most effective therapy for achieving sustained weight loss and managing obesity-related comorbidities [5]. The most commonly used procedure has been the Roux-en-Y gastric bypass (RYGBP), with an average weight loss of 60% to 75% of excess weight [6,7]. However, several studies have reported that 10% to 25% of patients regain a significant amount of the weight lost in the long-term follow-up [8,9]. Several risk factors are predictive for weight regain after RYGBP, including greater severity of obesity, gastric pouch size, lifestyle habits, hormonal status, and mental health [9–11].

In recent years, sleeve gastrectomy (SG) has emerged as an effective and safe surgical alternative, with similar results to RYGBP in the short term, improving comorbidities, and probably inducing fewer complications compared with RYGBP [12–19]. However, it has been reported that in the medium and long term, about 13% to 30% of patients begin to regain weight, as seen after RYGBP [20].

Very few studies have explored the factors that lead some SG patients to regain weight in the long term. A few studies have reported an enlargement of the gastric remnant, with a consequent of greater gastric capacity [21]. Thus, the aim of this study was to evaluate different etiologic factors associated with weight regain in a group of SG patients, at least 2 y after the procedure.

Material and methods

In a cross-sectional, multicentric, retrospective case–control study, 40 patients (32 women and 8 men; mean age 43 ± 11 y; and preoperative body mass index [BMI] 35 ± 2.8 kg/m²) were evaluated at least 2 y after SG. The procedures were performed at Clínica Las Condes, Hospital Dipreca, and University of Chile Clinical Hospital, all in Santiago, Chile, between 2007 and 2009. Sample size was calculated to find a significant difference in the estimated gastric volume among patients undergoing SG with low versus high weight regain. Data of gastric volume estimated 24 to 36 mo after surgery in a Chilean study were used (SD of gastric volume = 85 mL) [22]. With an expected difference in gastric volume of 100 mL, α error 0.05, and statistical power 90%, a sample size of 12 patients per group was calculated. Therefore, 40 patients were recruited.

Patients taking medications that could affect their weight (antidepressants, corticoids, insulin, etc.), pregnant or lactating women at the time of the evaluation, and those with chronic diseases such as heart, kidney, liver, or lung failure; cancer; immunodeficiency syndrome; or degenerative diseases were excluded. Informed consent was obtained from all patients included in the study. The ethics committees of Clínica Las Condes, Dipreca Hospital, and University of Chile Clinical Hospital approved the study.

Surgical procedure and postoperative management

The SG technique was similar at the three health care centers and consisted of the removal of 80% of the stomach. Gastric tubulization was performed starting 3 to 4 cm from the pylorus by dividing the gastric corpus straight to the His angle. Placing a 34- to 36-F bougie inside the gastric lumen, a gastric tubular pouch with an estimated volume of 80 to 120 mL was left. Clinical protocols of the three centers considered a schedule of postoperative controls according to the national standard for bariatric patients [23], which considers five controls with the dietitian during the postoperative year 1, in addition to evaluations with an internist or specialist in clinical nutrition (four visits) and a surgeon (five visits), and controls with the team of bariatric surgery for the life span from postoperative year 1. In the postoperative dietitian controls, tolerance and adherence to the prescribed food plan, intake of micronutrients in foods and supplements, and feeding technique are observed.

Medical history and medical evaluation

Preoperative BMI, evolution of weight during postoperative year 1, laboratory test results, and minimum postoperative weight were obtained from the database. All individuals were evaluated at the Nutrition Department of Clínica Las Condes. Medical history was obtained and physical examination was performed. Weight (kg)/height (m) was measured according to standardized procedures [24], and current BMI (kg/m²) was calculated.

Evaluation of dietary intake and physical activity

A dietitian conducted a food intake questionnaire by tendency of consumption. Analysis of energy and macronutrients consumed was performed using a Chilean table of food composition [25]. Physical activity in the previous 7 d was evaluated using the Godin Leisure-Time Exercise Questionnaire [26].

Assessment of energy expenditure and body composition

Resting energy expenditure (REE) was measured by indirect calorimetry using a ventilated chamber system (Quark RMR, Cosmed, Italy). Participants were evaluated in the morning, after 12 h of fasting, with at least 30 min of rest in a thermoregulated environment. After a resting period, REE and respiratory quotient were measured for 15 to 20 min, and the last 5 to 10 min were used for calculations. Body composition was measured by bioelectrical impedance measurement (QuadScan 4000 multifrequency Bioelectrical Impedance Analyzer, Bodystat, UK), estimating fat mass and fat-free mass.

Laboratory tests

A fasting blood sample was drawn to determine plasma glucose, insulin, and thyroid-stimulating hormone (TSH) levels. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) index was calculated, and patients with a HOMA-IR index >2.5 were considered insulin resistant [27]. All blood samples were taken and analyzed at Clínica Las Condes.

Psychological evaluation

Standardized questionnaires were used to evaluate binge eating, depression, and anxiety. Binge-eating severity was assessed using the Binge Eating Scale, which indicates absent, moderate (>17 and <27 points), or severe symptoms (≥ 27 points) [28]. Anxiety and depression were evaluated using the Hospital Anxiety and Depression scale self-assessment, which detects states of depression and anxiety in the setting of a medical outpatient clinic [29]. The anxiety and depressive subscales classify the patient as normal, borderline (8–10 points), or with a clinical disturbance (≥ 11 points).

Evaluation of gastric volume

Of the 40 patients, only 11 of those studied agreed to perform the assessment of gastric residual capacity. This test was done on a different day from the rest of the measurements and consisted of esophagus and stomach radiologic imaging after ingestion of 50 mL of diluted barium sulfate and effervescent solution (to distend the stomach). Barium meal test is a well-standardized procedure, and it was done in a single center and analyzed by the same radiologist who was aware of the weight and clinical condition of the patients. There are no radiologic assessments available in the early postoperative stage.

The primary endpoint was the percentage of weight regain (%WR = weight regain [kg]/maximum weight loss [kg] $\times 100$). Patients were classified in two groups: cases (greater weight regain) and controls (less weight regain), depending on whether they were in the >50 th percentile or <50 th percentile for %WR. Weight regain was considered a variable on continuous scale.

Statistical analysis

The variables are expressed as median and percentile distribution (25th–75th percentile), as well as minimum and maximum values. Comparisons between cases and controls were performed using the Mann-Whitney nonparametric test for independent samples. Linear regression analysis or Spearman's rank correlation was used to assess the association between %WR and the variables analyzed. For statistical analysis, the SPSS 11.5 program (SPSS Inc., Chicago, IL, USA) was used and the criterion for significance was set at 5% ($P < 0.05$).

Results

The evaluation was conducted 24 to 55 mo after SG (median [P25–P75]: 38.5 mo [34–41 mo]). Of the 40 patients, weight

regain ranged from 2.7% to 129.2% (median [P25–P75]: 25.4% [13–37.1]). Before surgery 87% of patients had at least one associated disease. Comorbidities were as follow: insulin resistance (n = 21), hypertension (n = 10), dyslipidemia (n = 15), nonalcoholic fatty liver disease (n = 10), glucose intolerance (n = 6), articular pathology (n = 3), and obstructive sleep apnea syndrome (n = 2).

Table 1 shows the comparison between the two groups. No significant difference was found for any variable. The proportion of women was 80% in both groups. The number of visits to the clinical center was not affected by sex. No significant differences were found between groups for preoperative TSH (P = 0.180), fasting plasma glucose (P = 0.962), fasting plasma insulin (P = 0.127), or HOMA index (P = 0.306). Of the patients, 65% showed insulin resistance at the preoperative evaluation (HOMA index >2.5), with no difference in proportions between the two groups.

There was no significant difference in weight regain (%WR, P = 0.795; kg regain, P = 0.529) between patients grouped according to preoperative BMI range (Figs. 1 and 2).

Between-group comparisons of the metabolic, anthropometric, and body composition variables at the final assessment time point are shown in Table 2. REE was significantly higher in the group with greater weight regain, but this difference was not significant after adjusting for fat-free mass (FFM). A linear regression analysis showed that FFM and age explained 69.2% of the variability in REE (r² = 0.692; P < 0.001), and FFM alone explained 66% of the variability in REE (r² = 0.66; P < 0.001). Comparing the regression lines for REE against FFM between cases and controls, no significant difference was found for either the slope or the intercept for absolute values of REE (Fig. 3). Energy and macronutrient intake and Godin's Leisure-Time Exercise Questionnaire scores are compared in Table 3. An absolute higher fat intake and a trend toward higher total energy intake, which disappears when calculating the adequacy of energy intake, were observed in the group with greater %WR. However, the percentage of calories from fat showed no significant

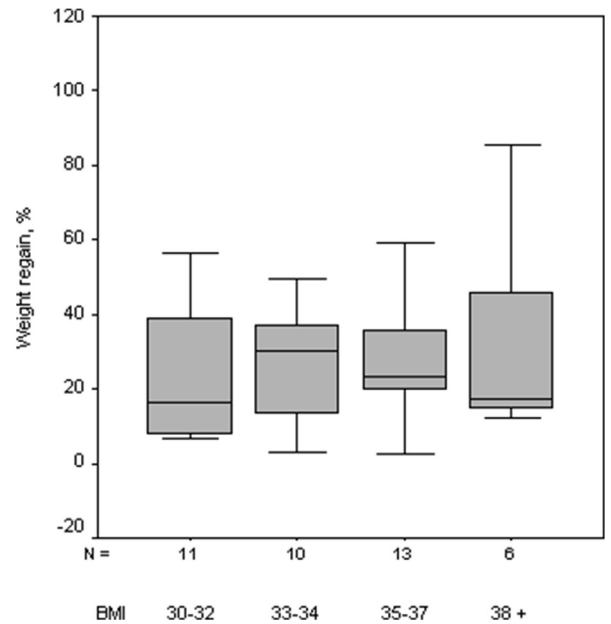


Fig. 1. Percentage of weight regain in the long term after sleeve gastrectomy according to preoperative BMI range. Boxes and whiskers indicate the medians, IQR, and 2.5th and 97.5th percentiles. Difference between groups: P = 0.795. BMI, body mass index; IQR, interquartile range.

difference between groups. Regarding alcohol consumption, no significant differences were detected between both groups.

Psychological tests detected no difference in the frequency of moderate to severe binge-eating disorder between the higher and lower weight regain groups (30% and 20%, respectively; nonsignificant). There was no difference in the frequency of patients with clinical or borderline levels of depression (20% and 5%, in cases and controls, respectively; nonsignificant).

Table 1
Pre- and Postoperative Evolution Parameters: Comparison Between Lower and Higher Weight Regain Groups*

| Parameters | Lower weight regain (n = 20) | | Higher weight regain (n = 20) | | P-value |
|-------------------------------------|------------------------------|-----------------|-------------------------------|-----------------|---------|
| | Median | Range (P25–P75) | Median | Range (P25–P75) | |
| Age (y) | 41.5 | 33.3–58.5 | 39.5 | 37–48 | 0.68 |
| Baseline BMI (kg/m ²) | 35.1 | 32.2–37.4 | 34.9 | 32–36.8 | 0.80 |
| Minimum PO BMI (kg/m ²) | 23.6 | 22.3–26 | 24.4 | 23.1–27.1 | 0.18 |
| Minimum PO weight (kg) | 62 | 57.3–70.5 | 69 | 60–76 | 0.21 |
| Maximum weight loss (kg) | 27.8 | 21.1–36 | 27 | 30.6–23 | 0.94 |
| Weight loss (%) | 28.3 | 23.8–36.9 | 28.3 | 23.6–31.9 | 0.47 |
| Maximum weight loss time (mo) | 8 | 6–12 | 6 | 3.3–11 | 0.09 |
| PO evaluation time (mo) | 39 | 33–42.5 | 36.5 | 34–41 | 0.61 |
| Weight regain time (mo) | 29 | 26.3–35 | 30.5 | 26.3–33 | 0.82 |
| Weight regain (kg) | 3.55 | 1.70–5.75 | 11.05 | 8.75–14.10 | 0.00 |
| BMI regain (kg/m ²) | 1.39 | 0.66–2.19 | 3.85 | 3.21–5.08 | 0.00 |
| First year PO visits (n) | 6 | 4.3–8.8 | 4 | 3–8 | 0.50 |

BMI, body mass index; PO, postoperative
* Lower weight regain: <50th percentile for percent of weight regain; higher weight regain: >50th percentile for percent of weight regain.

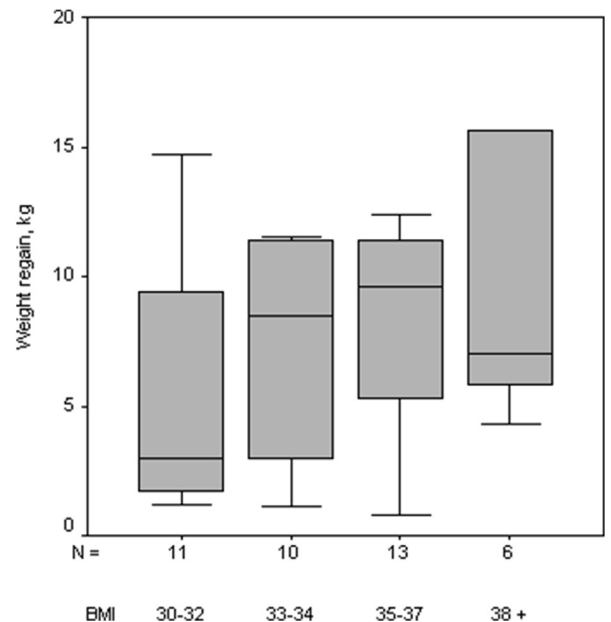


Fig. 2. Weight regain (kg) in the long term after sleeve gastrectomy according to preoperative BMI range. Boxes and whiskers indicate the medians, IQR, and 22.5th and 97.5th percentiles. Difference between groups: P = 0.529. BMI, body mass index; IQR, interquartile range.

Table 2
Parameters Evaluated ≥ 2 y Postoperatively: Comparison Between Lower and Higher Weight Regain Groups*

| Parameters | Lower weight regain (n = 20) | | Higher weight regain (n = 20) | | P-value |
|----------------------------------|---------------------------------|--------------------|----------------------------------|--------------------|---------|
| | Median | Range (P25–P75) | Median | Range (P25–P75) | |
| REE: measured (kcal/d) | 1465 | 1284–1567.8 | 1575.5 | 1419.3–1656.8 | 0.04 |
| Adjusted for FFM | 1521.2 | 36.3 | 1518 | 36.3 | 0.96 |
| BMI (kg/m ²) | 25.2 | 23.4–27.7 | 29.3 | 27.1–32.2 | 0.00 |
| FFM (kg) | 44.7 | 40.8–51.5 | 49.5 | 45.4–56.4 | 0.04 |
| Body fat (kg) | 23.3 | 19.9–26.7 | 29.1 | 23.5–31.8 | 0.00 |
| Body fat (%) | 33.7 | 30.2–37.5 | 36.1 | 30.9–41.1 | 0.23 |
| TSH (μ U/L) | 1.5 | 1.2–2.5 | 1.7 | 1.3–2.2 | 0.91 |
| Fasting glucose (mg/dL) | 88.5 | 80.5–91 | 85 | 82–92 | 0.88 |
| Fasting insulin (μ U/mL) | 5 | 4–7.8 | 8.5 | 6.3–11.8 | 0.01 |
| HOMA-IR | 1.1 | 0.8–1.6 | 1.8 | 1.2–2.5 | 0.02 |

BMI, body mass index; FFM, fat free mass; HOMA-IR, homeostasis model assessment-estimated insulin resistance; REE, resting energy expenditure; TSH, thyroid stimulating hormone

* Lower weight regain: <50th percentile for percent of weight regain; higher weight regain: >50th percentile for percent of weight regain.

Percentage of patients with clinical or borderline levels of anxiety was significantly greater in the higher %WG (70%) than in the lower %WG group (30%; $P = 0.01$), but anxiety levels were not associated to increased food intake.

To evaluate the association between weight regain and potential predictors, a linear regression analysis was performed in the whole sample, including the following variables: preoperative age, weight, BMI, excess weight, TSH concentration, fasting glucose and fasting insulin concentrations, percent excess weight lost, maximum weight loss, and number of postoperative visits attended. No associations between %WR and the variables analyzed were observed. In a linear regression analysis between %WR and postoperative variables, a significant association was found with current BMI only (r^2 corrected = 0.524). None of the metabolic, psychological, behavioral, and dietary variables was associated with %WR.

In the 11 patients who underwent radiologic estimation of the residual gastric volume (five controls and six cases), a median volume of 174 mL was found, with a range between 123 and 434 mL. Those in the higher %WR group (cases) had a

greater gastric volume (252.7 ± 108.4 versus 148.5 ± 25.3 ; $P < 0.05$). Estimated gastric volume was significantly correlated with %WR (Spearman's $r = 0.673$; $P = 0.023$), as shown in Figure 4.

Discussion

The underlying mechanisms contributing to weight regain in the long term after SG have been poorly explored. Most of the previous published studies focused on the size and enlargement of the gastric remnant. One study reported that 11 of 53 patients undergoing SG required an additional malabsorptive procedure at a later stage because of weight regain [18]. In another series of 201 patients undergoing SG, 5.4% of patients showed a weight regain after 6 to 57 mo of postoperative follow-up; a dilation of the antrum and gastric fundus was present in all the patients [30].

It has been reported that a removed gastric volume <500 mL seems to be a predictor of failure in treatment or early weight regain after SG [21]. When the volume of gastric remnant was assessed with computed tomography scans, one study found an increased risk for weight regain for volumes >255 mL [31].

In agreement with these previous studies, the present study found that patients with greater weight regain had a higher residual gastric volume compared with those with less weight regain. We did not perform a direct measure of gastric volume, although estimation with a barium meal has demonstrated a good correlation with volume measured by computed tomography scan [22].

To our knowledge, no other risk factors for weight regain after SG have been reported. However, studies evaluating weight regain after RYGBP have shown multiple conditions associated with this adverse result, including dietary noncompliance, frequency of follow-up visits to a dietitian, physical inactivity, mental health disturbances, and hormonal and metabolic factors [8,9,11,32–38]. Poor diet quality, characterized by excessive intake of calories, snacks, sweet, and fatty foods, and higher intake of high glycemic index carbohydrates, was reported in patients who regained weight after RYGBP [33,36].

In the present study, patients with weight regain tended to have a higher caloric intake and a significantly higher consumption of fat compared with the control group. However, the contribution of fat to total caloric intake did not differ between groups, and it was higher than recommended in both case and control patients (~42% and ~37%, respectively). No differences in alcohol consumption or sweet foods or sugar intake were found between the groups. These results could be explained by the small size of the sample or by the low reliability of food intake records. It is well known that obese patients tend to underreport their food intake by up to 30%, and this may occur in patients with weight regain after the SG. Another suggested factor for weight regain after RYGBP is physical inactivity [33]; however, we observed only a trend toward a lower level of physical activity in the group with higher %WR.

Another reported factor leading to weight regain after RYGBP are psychological disturbances. One study reported that binge eaters tend to regain more weight after RYGBP compared with nonbinge eaters [37]. Depression, alcohol, food urges, and the presence of binge eating were reported to be predictors of weight regain after RYGBP [10,37], and a recent review suggested that the development of binge eating and loss of control over eating is associated with less weight loss, more weight regain after the bariatric surgery, or both [38]. In the present study, patients with higher weight regain exhibited a significantly

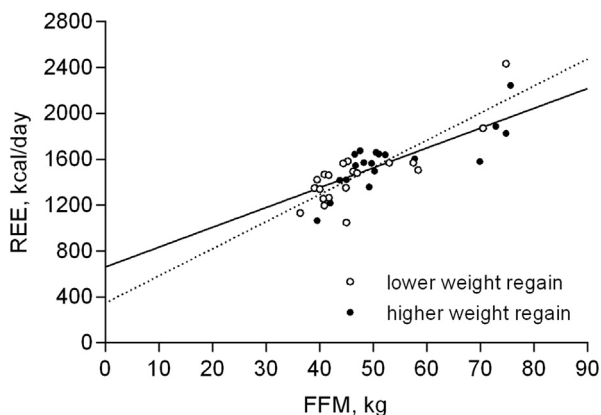


Fig. 3. Regression analysis for REE and FFM in higher and lower weight regain groups. FFM, fat-free mass; REE, resting energy expenditure.

Table 3
Dietary Intake and Physical Activity Evaluated ≥ 2 y Postoperatively: Comparison Between Lower and Higher Weight Regain Groups*

| Parameters | Lower weight regain (n = 20) | | Higher weight regain (n = 20) | | P-value |
|--|------------------------------|-----------------|-------------------------------|-----------------|---------|
| | Median | Range (P25–P75) | Median | Range (P25–P75) | |
| Energy intake (kcal/d) | 1608.1 | 1274.6–2010.7 | 1947 | 1535.6–2385 | 0.09 |
| (kcal/kg/d) | 22.9 | 18.9–31 | 23.4 | 17.7–29.9 | 0.89 |
| Adequacy of energy intake [†] (%) | 88.8 | 112.3–70.9 | 90.7 | 76.5–127.1 | 0.42 |
| Protein intake (g/d) | 78.5 | 94.8–58.9 | 85 | 70–115.2 | 0.25 |
| (% Energy) | 19.3 | 16.4–22.9 | 18.6 | 14.5–20.4 | 0.47 |
| Carbohydrate intake (g/d) | 149.5 | 120.9–198.2 | 189.5 | 140.9–218 | 0.21 |
| (% Energy) | 41.3 | 34.9–45.6 | 38.7 | 33.2–42.9 | 0.26 |
| Fat intake (g/d) | 64.3 | 51.1–94.7 | 88.6 | 68.5–105.3 | 0.04 |
| (% Energy) | 37.4 | 33.4–44.3 | 41.7 | 37.2–44.5 | 0.28 |
| Sweet foods (times/wk) | 5 | 2–7 | 4 | 2–7 | 0.80 |
| Sugar intake (g/wk) | 13.3 | 3.7–28.1 | 5.8 | 0–19.2 | 0.22 |
| Alcohol consumption (g/d) | 3.05 | 0.10–10.4 | 3.30 | 0.13–19.4 | 0.81 |
| Godin questionnaire score | 13.9 | 0.3–25.7 | 7.0 | 0–23.6 | 0.49 |

* Lower weight regain: <50th percentile for percent of weight regain; higher weight regain: >50th percentile for percent of weight regain.

[†] Adequacy of energy intake was calculated as the percentage of total energy requirements (measured resting energy expenditure \times 1.3 as physical activity factor).

higher prevalence of anxiety compared with the lower weight regain group. We can hypothesize that anxiety could predispose individuals to a pattern of unhealthy eating; however, no differences in the prevalence of binge-eating disorder was found between groups, and no association was found between anxiety levels and food intake or %WR.

Regarding preoperative and first postoperative year factors, no significant differences were detected in the present study. At the time of the final evaluation, patients with greater weight regain had higher insulin resistance compared with the control group, which could be explained by the higher BMI and body fat in that group. In this evaluation, no significant difference in resting metabolic expenditure between patient groups was found, probably because of the lack of difference in the FFM between the two groups. Previous studies reported a significantly lower resting metabolic rate in patients who regained weight compared with those who maintained their body weight after RYGB [34].

The lower preoperative BMI of the patients studied (30–41 kg/m²) in comparison with other published studies that have investigated on subsequent weight regain after SG makes it difficult to extrapolate our findings to the clinical practice in bariatric surgery of other countries. However, the growing number of bariatric surgeries in patients with a BMI <40 or <35 kg/m² [39] forces us to investigate the long-term outcomes with this surgical technique.

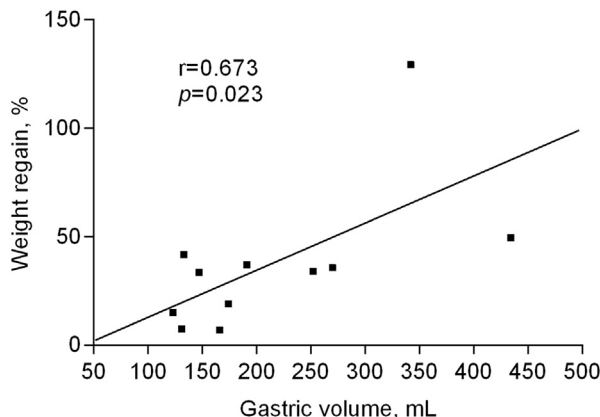


Fig. 4. Correlation between weight regain and radiologic gastric capacity in 11 patients ≥ 2 y after sleeve gastrectomy.

Conclusion

The present study detected a significant association between gastric volume and long-term weight regain after SG. However, additional studies with greater numbers of patients are required to confirm these results. Moreover, similar to patients undergoing gastric bypass, it is possible that weight regain after SG could be multifactorial, and it likely involves a complex interplay between psychosocial conditions, nutritional habits, hormonal status, and a complex genetic and anatomic milieu affecting many regulatory pathways that modulate food intake behavior and energy metabolism. Therefore, it is critical to identify key modifiable causes for weight regain and target them early and effectively. It is important to investigate the mechanisms of weight regain related to an increase in gastric remnant volume. In addition to a higher capacity for food intake, increased serum concentrations of ghrelin could be involved. It should be important to include its measurement in the future.

Finally, at present there is no agreement on how to define a significant weight regain and some studies have used arbitrary criteria such as: %WR >15% [10], %WR >20% [40], or %WR >50% of the lost weight [8]. In the present study, %WR >25% emerged from the statistical analysis searching for the median of the variable, but it seems reasonable to consider it a good cutoff from the point of view of clinical relevance of weight recovered. In patients undergoing bariatric surgery it can be expected that 20% to 25% of the lost weight will be regained over a period of 10 y [41].

Long-term and prospective analyses are needed to quantify the real prevalence of weight regain after SG. For this purpose, it will be important to establish a worldwide definition of weight regain after bariatric surgery to allow for comparisons between different studies.

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