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ORIGINAL CONTRIBUTIONS

Correlation Between the Number of Ghrelin-Secreting Cells in the Gastric Fundus and Excess Weight Loss after Sleeve Gastrectomy

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Abstract

Background Weight loss after laparoscopic sleeve gastrectomy (LSG) has been mainly attributed to the restriction of gastric volume; however; other factors may contribute to weight loss after LSG. This study aimed to investigate the correlation between the number of ghrelin-secreting cells in the gastric fundus and excess weight loss (EWL) at 12 months after LSG.

Methods The surface area of the gastric fundus was measured postoperatively in square centimeter. Histopathologic examination of the gastric fundus was made to estimate the number of ghrelin-secreting cells per square centimeter then was multiplied by the surface area of the fundus to calculate the total number of ghrelin-secreting cells in the fundus. The number of ghrelin-secreting cells was correlated with EWL and BMI at 12 months postoperatively.

Results The present study included 39 patients of a mean age of 33.7 years. The mean %EWL at 12 months was 59.7 ± 12.7. The mean total number of ghrelin-producing cells in the gastric fundus was 26,228.4 ± 16,995.3. The total number of ghrelin-secreting cells had a weak positive correlation with BMI at 12 months ($r = 0.2891$, $p = 0.07$), and weak negative correlation with %EWL ($r = -0.1592$, $p = 0.33$).

Conclusion There was a weak correlation between the total number of ghrelin-producing cells in the gastric fundus and plasma ghrelin levels with EWL after LSG.

Keywords Laparoscopic sleeve gastrectomy · Ghrelin-secreting cells · Fundus · Correlation · Weight loss

Introduction

The prevalence of obesity continues to increase worldwide. Morbid obesity is frequently associated with multiple co-morbidities such as diabetes mellitus, hypertension, dyslipidemia, and ischemic heart disease. While lifestyle-altering measures, exercise programs, and diet regimens manage to reduce excess body weight in some patients, bariatric surgery remains the most effective treatment for many patients who fail conservative measures [1].

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Bariatric procedures are initially classified by their presumed mechanism of action into restrictive, malabsorptive, or mixed procedures. Laparoscopic sleeve gastrectomy (LSG) is an example of restrictive bariatric procedures. Though, it started as a first-step operation for the super-obese patients, recent data suggest that SG may be applied as a single-step operation with excellent results in terms of weight loss and improvement in associated comorbidities [2].

The mechanism of weight loss after LSG appears to be multifactorial. Since LSG is a restrictive procedure, it is logical that the main factor responsible for weight loss is minimizing the capacity of the stomach by resection of gastric sleeve as demonstrated in a recent study that correlated preoperative and postoperative gastric volume, measured by CT volumetry, with weight loss after LSG [3]. However, other factors affecting satiety are also involved in weight loss after LSG. These factors include alterations in hormonal levels, impaired gastric motility of the remaining stomach, and elevated pressure within the remaining gastric pouch [4].

The contribution of hormones involved in energy homeostasis and metabolism to the pathogenesis of obesity has been thoroughly investigated [5]. Ghrelin is one of the hormones considered to have the greatest impact on the energy balance. Ghrelin, also known as the appetite hormone, was discovered in 1999 and is a molecule acting on many systems and thought to have an important role in the development of obesity However, the mechanism by which ghrelin hormone affects the development of morbid obesity is still unclear [6].

The role of ghrelin hormone in weight loss after LSG is still controversial. Some investigators [7, 8] noted that plasma ghrelin level tends to decrease after LSG, resulting in decreased appetite and contributing to weight loss. They attributed the decline in plasma ghrelin levels after LSG to the removal of the gastric fundus where the majority of ghrelin-secreting cells are located. However, other researchers [9] found the decrease in ghrelin and leptin concentrations between patients with or without decreased appetite after LSG statistically insignificant, implying no impact of ghrelin hormone on appetite postoperatively.

This study aimed to investigate the correlation between the number of ghrelin-secreting cells detected in the resected gastric fundus and excess weight loss at 12 months after LSG. The type and significance of this correlation may shed light on the actual contribution of ghrelin hormone to weight loss after LSG.

Patients and Methods

Study Design and Setting

This was a prospective cohort study on patients with morbid obesity who underwent LSG in the General Surgery Department of Mansoura University Hospitals in the period of June 2016 to June 2017. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of Mansoura Faculty of Medicine.

Eligibility Criteria

Adult patients of both genders with BMI > 40 Kg/m^2 or with BMI > 35 Kg/m^2 with at least one associated major comorbidity were included. We excluded patients with secondary obesity due to metabolic or endocrinal disturbances, patients with psychiatric disorders, and patients unwilling to comply with postoperative dietary regimen and follow-up.

Preoperative Assessment

Careful assessment of patients was done by detailed history taking, thorough physical examination, and investigations. Patients were asked about the onset and duration of morbid obesity and other associated medical comorbidities. Previous attempts for management of morbid obesity were queried. In addition, detailed dietary history was taken from the patients.

Anthropometric measurements including weight and height were recorded and BMI was calculated using the following equation: BMI = weight in kilograms/(height in meters)^2. Subsequently, abdominal examination was done to exclude organomegally, abdominal masses, ascites, and ventral or groin hernias.

Routine preoperative laboratory investigations including complete blood count, liver and kidney function tests, prothrombin time, and random blood glucose were done. Endocrine and metabolic panels including serum lipid profile, thyroid function tests, and fasting and postprandial blood glucose levels were done to exclude secondary causes of obesity. Fasting plasma ghrelin level was measured within 1 week before the procedure.

Abdominal ultrasonography was performed to exclude any associated abdominal pathologies. Cardiac condition was evaluated by electrocardiography and echocardiography in select patients. Pulmonary function tests were done to assess respiratory functions and chest condition.

Procedure

Informed consent for the study was taken from all patients. Preoperative measures against thromboembolism were taken as patients were advised to wear an elastic stocking 24 h before the operation and were administered low molecular weight heparin (enoxaprin, 40 IU) subcutaneously at the night of surgery. Prophylactic antibiotics (cefotaxime, 1 g) were administered intravenously on induction of anesthesia.

All procedures were done under general anesthesia in the supine position. Using a three-port technique, the greater

curvature of the stomach was devascularized using the Harmonic scalpel™ starting at 4 cm away from the pylorus. A 36 French bougie was then inserted transorally, then gastric transection was performed using sequential applications of 60-mm linear staplers beginning at 4 cm proximal to the pylorus. The resected portion of the stomach was extracted through the right upper quadrant trocar then the trocar sites were closed and an intra-abdominal drain was inserted.

Histopathologic Examination

Upon completion of sleeve gastrectomy, the surgical specimen was placed on an examining table and the gastric fundus was measured using points of identification (Fig. 1). The termination of the staple line (point A) represented the junction between the cardia and the fundus, from which a straight line was extended to a corresponding point (point B) on the greater curvature. The fundus was opened along this line and along the greater curvature and the length and width were measured by a ruler. By multiplying the length by the width of the fundus, the surface area was calculated in square centimeter.

Histopathologic examination of the resected gastric sleeve was performed by a staff pathologist. Protocol of pathologic examination included opening of the specimens through the greater curvature, and fixation in 10% formalin for 24 h. After fixation, three biopsied sections taken from three different points of the gastric fundus were embedded in paraffin, cut at 5 mm, and stained with hematoxylin and eosin.

In addition, sections from all blocks were stained with an anti-ghrelin antibody. Ghrelin cells were then counted using a standardized technique with a microscope at × 4000, 10 high-power fields per section (Fig. 2). The count was entered into an Excel spreadsheet where the mean number of cells was calculated.

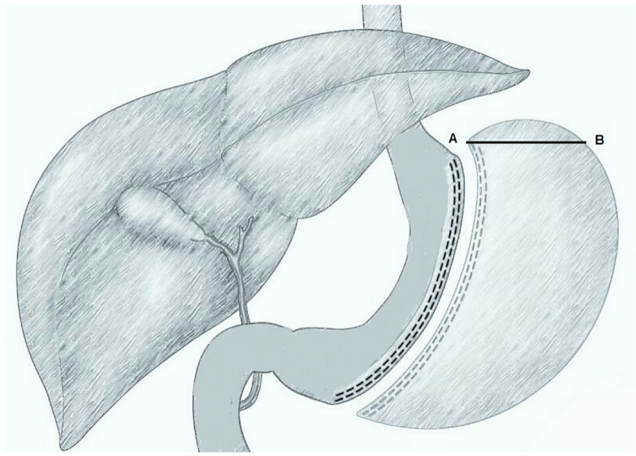

Fig. 1 Diagram demonstrating the line demarcating the gastric fundus from the body of the stomach used for calculation of the surface area of the fundus

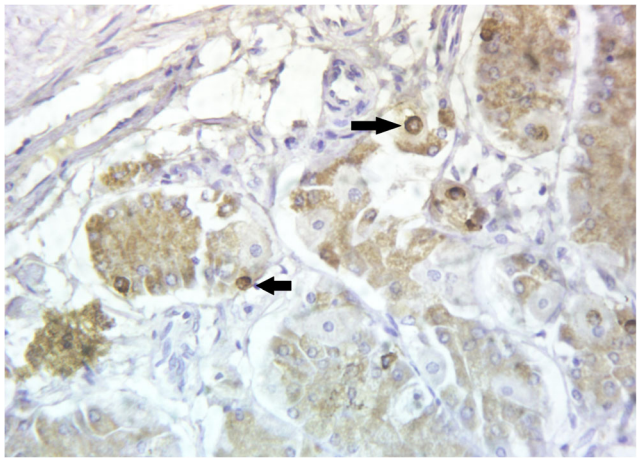

Fig. 2 Gastric mucosa with positive reaction to ghrelin immunohistochemistry with a microscope at × 400 high-power

After histopathologic examination of the specimen, the histologic landmarks of the fundus such as numerous gastric pits, small lumen of gastric glands, cord of cells appearance of the glands, and thin circular muscle layer were confirmed.

The number of ghrelin cells per square centimeter was multiplied by the surface area of the resected gastric fundus in square centimeter to calculate the total number of ghrelin-producing cells in the gastric fundus which was defined as "Ghrelin Index".

Follow-up

Patients were instructed to visit the outpatient clinic at 1 and 2 weeks after LSG for assessment of general condition, wound status, and for removal of stitches, then every month for 12 months. At 6 and 12 months after the procedure, body weight was recorded and the amount and percentage of weight loss was calculated. The improvement in associated comorbidities was recorded at 12 months after LSG. Fasting plasma ghrelin was measured at 12 months after LSG.

Sample Size Calculation

The sample size was calculated based on the population size which was estimated according to the annual admission rate of patients with morbid obesity that undergo LSG in the general surgery departments of Mansoura University Hospitals (40–50 patients per year). Setting the confidence level at 95% and the margin of error at 5%, a minimum of 37 patients were required to be a representative sample. In order to compensate for loss to follow-up or drop-outs, a total of 39 patients were considered appropriate for the study.

Statistical Analysis

Data were analyzed by SPSS version 23 (IBM Corp., Bristol, UK). Continuous Data were expressed in the form of mean ± standard deviation (SD), or median and normal range. Categorical data were expressed as number and proportion. Paired student's *t* test was used for analysis of quantitative data. Fisher's exact test or chi-square test was used to analyze categorical data. The correlation between the number of ghrelin-secreting cells in the gastric fundus and excess weight loss was assessed by Pearson's correlation coefficient test. Correlation coefficients were classified as strong (− 1.0 to − 0.5 or 0.5 to 1.0), moderate (− 0.5 to − 0.3 or 0.3 to 0.5), and weak (− 0.3 to − 0.1 or 0.1 to 0.3). *p* values less than 0.05 were considered significant.

Results

Patients' Characteristics

The present study included 39 patients with morbid obesity who underwent LSG. Patients were 36 (92.3%) females and three (7.7%) males. The mean age of patients was 33.7 ± 7.7 years, ranging from 21 to 47 years. Twenty (51.3%) patients aged above 40 years.

The mean preoperative weight was 137.8 ± 7.8 Kg (range, 112–180). The mean preoperative height was 163.5 ± 1.4 cm (range, 148–178). The mean preoperative BMI was 52.5 ± 3.3 Kg/m^2 (range, 38.8–63.9). Twenty-one (53.9%) patients had BMI > 50 and 18 (46.1%) had BMI < 50.

Twenty-eight (71.8%) patients had obesity-related comorbidities: eight patients had type II DM, six had arterial hypertension, 11 had dyslipidemia, and three had joint pain. In addition, 12 patients had fatty liver in abdominal ultrasonography.

Technical Details

The mean operation time was 63.4 ± 4.2 min (range, 30–90). The mean hospital stay was 2.28 ± 1.4 days (range, 2–4). There was no conversion to open surgery in any patient.

Weight Loss and Improvement in Comorbidities after LSG

At 6 months postoperatively, significant weight loss was noted as the mean preoperative body weight dropped from 137.8 ± 7.8 to 107.5 ± 4.9 Kg ($p < 0.0001$). At 12 months, the mean body weight also showed significant decrease from 107.5 ± 4.9 to 94 ± 0.7 ($p < 0.0001$).

The preoperative BMI decreased from 52.5 ± 3.3 to 40.46 ± 2.2 Kg/m^2 ($p < 0.0001$) at 6 months and then to 35.4 ± 0.28 ($p < 0.0001$) at 12 months. The mean percentage of excess weight loss (%EWL) at 12 months was 59.7 ± 12.7 (range, 50–78.7). Patients with baseline BMI < 50 had significantly lower postoperative BMI and significantly higher %EWL at 12 months after LSG compared to patients with baseline BMI > 50 (Table 1).

At 12 months of follow-up, six (75%) of eight patients with diabetes, four (66.6%) of six patients with hypertension, and two (66.6%) of three patients with joint pain showed improvement in their preoperative comorbidities.

Number of Ghrelin-Secreting Cells in the Gastric Fundus and Changes in Plasma Ghrelin Levels

The mean number of ghrelin-producing cells per square centimeter in the gastric fundus was 604.6 ± 200.2. The mean surface area of the gastric fundus was 41.2 ± 1.6 cm^2. The mean total number of ghrelin-producing cells in the gastric fundus (Ghrelin Index) was 26,228.4 ± 16,995.3. The preoperative plasma ghrelin level was 549.3 ± 36.1 pg/mL which

Table 1 Comparison between patients with BMI less or more than 50 regarding number of ghrelin-secreting cells in the fundus, surface area of the fundus, and weight loss

Variable	Preoperative BMI < 50 Kg/m^2	Preoperative BMI > 50 Kg/m^2	*p* value
Number	18	21	–
Mean preoperative BMI (Kg/m^2)	44.5 ± 12.1	57.1 ± 12.8	0.003
Number of ghrelin-secreting cells per square centimeter in the fundus	568 ± 178.4	657.3 ± 208.3	0.16
Total number of ghrelin-secreting cells in the fundus	19,611.9 ± 16,124.7	29,108.2 ± 11,049.6	0.03
Surface area of the fundus in square centimeter	39.5 ± 1.06	42.2 ± 1.34	< 0.0001
Mean preoperative plasma ghrelin level	546.2 ± 11.7	559 ± 19.3	0.01
BMI at 12 months postoperatively (Kg/m^2)	31.8 ± 2.2	37.9 ± 4.3	< 0.0001
Percentage of EWL at 12 months	63.16 ± 7	57.2 ± 5.9	0.006

BMI body mass index, *EWL* excess weight loss

decreased significantly ($p < 0.0001$) to 449.2 ± 8.5 pg/mL at 12 months postoperatively.

On subgroup analysis, the surface area of gastric fundus was significantly smaller, the total number of ghrelin-secreting cells in the fundus was significantly less, and the preoperative plasma ghrelin level was significantly lower in patients with BMI < 50 than patients with BMI > 50. There was no significant difference in the number of ghrelin-secreting cells per square centimeter of the gastric fundus between both groups (Table 1).

Correlation Between the Number of Ghrelin-Secreting Cells in the Gastric Fundus and Preoperative Plasma Ghrelin Level

The preoperative plasma ghrelin level had a strong positive correlation with the number of ghrelin-producing cells per square centimeter in the gastric fundus ($r = 0.9548$, $p < 0.00001$) and also a strong positive correlation with the total number of ghrelin-producing cells in the gastric fundus ($r = 0.8557$, $p < 0.00001$) (Fig. 3).

Correlation Between the Number of Ghrelin-Secreting Cells in the Gastric Fundus and Weight Loss after LSG

The number of ghrelin-producing cells per square centimeter in the gastric fundus had a weak positive correlation with BMI at 6 months after LSG ($r = 0.319$, $p = 0.047$), weak positive correlation with BMI at 12 months after LSG ($r = 0.267$, $p = 0.099$), and weak negative correlation with %EWL at 12 months ($r = -0.1837$, $p = 0.26$).

The total number of ghrelin-producing cells in the gastric fundus (Ghrelin Index) had a moderate positive correlation with BMI at 6 months after LSG ($r = 0.4215$, $p = 0.007$), weak positive correlation with BMI at 12 months after LSG ($r = 0.2891$, $p = 0.07$), and weak negative correlation with %EWL at 12 months after LSG ($r = -0.1592$, $p = 0.33$) (Fig. 4**).**

Postoperative plasma ghrelin level had a weak positive correlation with %EWL at 12 months postoperatively ($r = 0.18$, $p = 0.27$). Summary of the correlations between ghrelin-secreting cells, plasma ghrelin level, and weight loss is illustrated in Table 2**.**

Discussion

Although LSG is classified as pure restrictive bariatric procedure, some investigators assumed that weight loss after LSG may be attributed to factors other than mechanical restriction of the gastric capacity. It has been shown that LSG results in alterations in gut hormones that may contribute to weight loss postoperatively. Plasma levels of ghrelin, amylin, and adipocytokine leptin showed marked decrease after LSG and in contrast, plasma levels of pancreatic polypeptide (PP), peptide-YY (PYY), and glucagon-like peptide-1 (GLP-1) showed remarkable increase after the procedure [10].

We conducted this prospective study to determine the correlation between the number of ghrelin-secreting cells detected in the resected gastric fundus and weight loss after LSG and to clarify the type and significance of this correlation in order to elucidate the role of ghrelin hormone in weight loss after LSG.

In a previous study by our unit, Sabry et al. [11] recorded a significant decrease in plasma ghrelin levels after LSG which was associated with significant weight loss. Furthermore, the authors found that ghrelin-secreting cells were mainly located

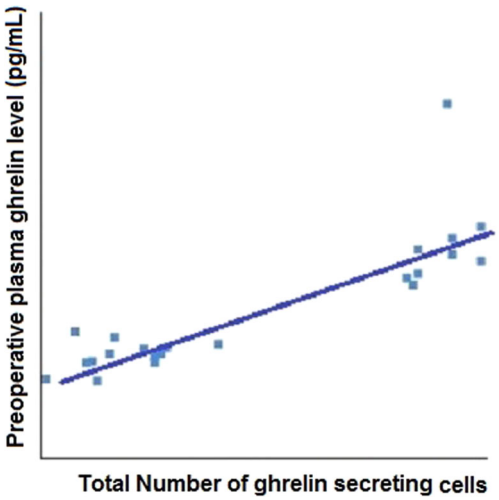

Fig. 3 Dispersion diagram displaying the correlation between the total number of ghrelin-secreting cells in the gastric fundus and preoperative plasma ghrelin level in picograms per milliliter

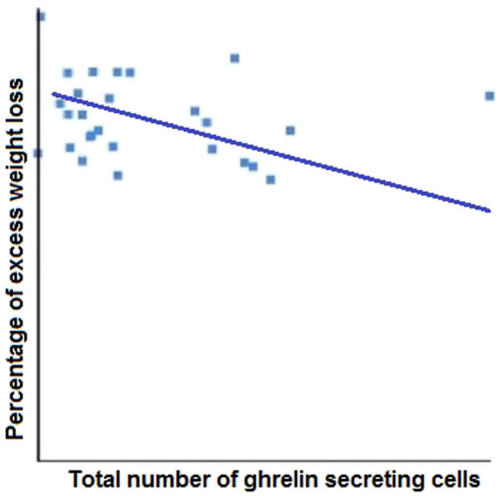

Fig. 4 Dispersion diagram displaying the correlation between the total number of ghrelin-secreting cells in the gastric fundus and percentage of excess weight loss at 12 months after sleeve gastrectomy

Table 2 Correlation between plasma ghrelin level, number of ghrelin-secreting cells in the fundus, and weight loss after sleeve gastrectomy

Correlation	Correlation coefficient	*p* value
Preoperative plasma ghrelin level in picograms per milliliter with number of ghrelin-producing cells per square centimeter	0.9548	< 0.0001
Preoperative plasma ghrelin level in picograms per milliliter with the total number of ghrelin-producing cells	0.8557	< 0.0001
Number of ghrelin-producing cells per square centimeter with BMI at 6 months after LSG	0.319	0.047
Number of ghrelin-producing cells per square centimeter with BMI at 12 months after LSG	0.267	0.099
Number of ghrelin-producing cells per square centimeter with %EWL at 12 months	− 0.1837	0.26
Total number of ghrelin-producing cells with BMI at 6 months after LSG	0.4215	0.007
Total number of ghrelin-producing cells with BMI at 12 months after LSG	0.2891	0.07
Total number of ghrelin-producing cells with %EWL at 12 month	− 0.1592	0.33

BMI body mass index, *EWL* excess weight loss

in the gastric fundus, thus the idea of the present study was derived from this important observation. We assumed that since the main source of ghrelin hormone is located in the fundus, then a relation between the number of ghrelin-secreting cells in the fundus and EWL postoperatively may exist and needs to be further investigated.

We studied 39 patients with morbid obesity who underwent LSG in this prospective observational study. Almost all patients were female reflecting the female predominance of obesity as documented in the literature. The majority of patients were of middle age with approximately half of the patients aging between 30 and 40 years in concordance with the average age of patients undergoing bariatric surgery for morbid obesity [12, 13].

As previously reported in the literature [2], we recorded significant EWL after 6 and 12 months of LSG with significant reduction in BMI. The average percentage of EWL at 12 months was within the range of EWL reported in the literature (58–68%). Similarly, an improvement in the associated comorbidities including DM, hypertension, and joint pain was observed. It was notable that patients with BMI less than 50 achieved better results in terms of reduction in BMI and EWL compared to patients with BMI > 50 which we have reported in a previous study [14].

We opt to correlate weight loss after LSG with the total number of ghrelin-secreting cells in the fundus rather than the number of ghrelin-secreting cells per square centimeter. We thought that the total number of cells (defined as Ghrelin Index) is a better parameter than the number of cells per square centimeter which does not take in account the variation in the total surface area of the gastric fundus which can be considerable among obese individuals according to preoperative BMI.

Braghetto et al. [15] found that the mean width of the gastric fundus was 5.8 cm in patients with BMI less than 50 and 6.8 cm in patients with BMI more than 50, hence the total surface area of the gastric fundus is different in each group, and so will be the total number of ghrelin-producing cells. In concordance with these findings, we found the total surface area of the gastric fundus in patients with BMI less than 50 significantly less than patients with BMI more than 50. Equally, the total number of ghrelin-secreting cells and preoperative plasma ghrelin levels were significantly lower in patients with BMI < 50.

The present study is the first study to investigate the relation between weight loss after LSG and the total number of ghrelin-secreting cells in the gastric fundus as revealed after thorough literature search. We studied the correlation between the total number of ghrelin-secreting cells and the number of cells per square centimeter individually with postoperative BMI and EWL at 12 months after the procedure.

We identified a weak positive correlation between the number of ghrelin-producing cells per square centimeter in the gastric fundus and BMI at 6 months and 12 months after LSG and a weak negative correlation with %EWL at 12 months. On the other hand, the total number of ghrelin-producing cells in the gastric fundus had a stronger correlation with BMI at 6 months and at 12 months after LSG and a weak negative correlation with %EWL at 12 months postoperatively. Similarly, the postoperative plasma ghrelin level had a weak correlation with %EWL after LSG.

The weak correlations between the number of ghrelin-producing cells and plasma ghrelin levels on one hand with %EWL on the other hand may imply that the change in ghrelin hormone postoperatively may not be an influential factor in weight loss after LSG. In line with our findings, other investigators assessed the changes in fasting and prandial gut hormones, including ghrelin hormone, after LSG and RYGB and found that although ghrelin levels decreased after LSG and increased after RYGB, ghrelin did not have a tangible effect on weight loss after bariatric surgery [16]. Furthermore, Goeiten et al. [17] reported that there was no distinct correlation between total plasma ghrelin levels and weight loss at 3 months after LSG, although both parameters showed a significant decrease. The authors explained this that ghrelin is only one of the myriad of factors contributing to the success of LSG.

Although we found a weak correlation between ghrelin hormone and weight loss after LSG, it is important to note that ghrelin has a documented role in the pathogenesis of obesity as Fabiana et al. [18] found the density of ghrelin-producing cells in the oxyntic mucosa and plasma ghrelin levels higher in morbidly obese patients than non-obese patients. In line with this observation, we also noted higher preoperative plasma ghrelin level in patients with BMI > 50 compared to patients with BMI < 50.

Ghrelin is a potent orexigenic peptide that helps in gaining weight by stimulating food intake, stimulating gastric contraction and enhancing gastric emptying, inducing hunger sensation, and by stimulating secretion of growth hormone, ACTH, and cortisol causing an increase in non-fat body mass [19]. Moreover, Asakawa et al. [20] have shown that plasma ghrelin levels were elevated in the fasting state and returned to basal levels after feeding.

We also found a strong positive correlation between the total number of ghrelin-secreting cells in the fundus and plasma ghrelin levels before LSG which is logical since the gastric fundus is the main source of plasma ghrelin as reported in the literature [11]. Plasma ghrelin levels showed significant decrease after LSG which is also logical since around 75% of the stomach volume, including the fundus, are resected in LSG [21]. The present study may conclude that the changes in plasma ghrelin level after LSG are a consequence of the procedure, yet may not play a tangible role in weight loss postoperatively.

Limitations of the current study include the small number of patients included, short follow-up, and not estimating the number of ghrelin-producing cells in the body and antrum of the stomach. The correlation between the weight and volume of the resected stomach and weight loss after LSG was not made in the present study; however, previous investigators [22] have reported this correlation. Furthermore, we only explored the role of ghrelin hormone in weight loss after LSG; however, the role of other gut hormones such as leptin as potential contributor to weight loss after LSG needs to be further studied.

Conclusion

There was a weak correlation between the total number of ghrelin-producing cells in the gastric fundus and plasma ghrelin levels with EWL after LSG. Patients with BMI > 50 had larger surface area of the gastric fundus, larger total number of ghrelin-secreting cells in the fundus, and higher preoperative plasma ghrelin level than patients with BMI < 50. This observation may be indicative of differences in pathology at baseline between super-obese and obese patients which may explain the difference in EWL after LSG between the two groups.

Author Contributions *Hossam Elbanna and Abdulaziz Itlaybah* designed the study and contributed to data collection and analysis and writing of the manuscript. *Sameh Emile, Ahmed AbdelMawla,* and *Waleed Thabet* contributed in data collection and analysis and writing of the manuscript. *Wagdi Elkashef* performed histopathologic examination of the gastric fundus for ghrelin-secreting cells and contributed to data collection and analysis. *Haitham Elkaffas* contributed to data analysis, drafting, and revision of the manuscript. *Noha Abdelsalam* contributed to follow-up of patients, providing nutritional support after surgery, data collection, and drafting of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights This study was conducted in accordance with the declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of Mansoura Faculty of Medicine.

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