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REVIEW

Morbid Obesity and Sleeve Gastrectomy: How Does It Work?

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Abstract Laparoscopic sleeve gastrectomy is known to be a safe and effective procedure for treating morbid obesity and is performed with increasing frequency both in Europe and the USA. Despite its broad use, many questions about the remaining gastric tube diameter, its long-term efficacy, its effects on gastric emptying, and the hormones involved still remain to be answered. In order to use such a relatively new surgical procedure wisely, it is essential for every surgeon and physician to understand how sleeve gastrectomy acts in obesity and what its potential benefits on the patients' metabolism are. This review focuses on the most important pathophysiologic questions referred to sleeve gastrectomy on the literature so far, in an attempt to evaluate the different issues still pending on the subject.

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Introduction

Laparoscopic sleeve gastrectomy (LSG) has been conquering its position among laparoscopic adjustable gastric banding (LAGB), laparoscopic Roux-en-Y gastric bypass (LRYGBP), and bilio-pancreatic diversion with duodenal switch (BPD-DS) in the surgical field of bariatric patients' management for the last decade. LSG belongs to the purely restrictive operations [1] and has been initially performed as part of a staged surgical approach for high-risk morbidly obese patients [2] and more recently as a sole weight loss operation for patients with lower body mass index (BMI). Studies report a weight loss after LSG ranging from 35% to 72% excess body weight loss (EBWL) and 51–83% at 12 months [3–6]. Comorbidities like diabetes, hyperlipidemia, hypertension, and sleep apnea demonstrated resolution rates at least comparable to other restrictive procedures, 12–24 months after LSG [6]. Furthermore, LSG's complication rates are similar to those of LAGB, but are significantly lower compared to LRYGBP and BPD-DS (7.4% for LSG, 22.8% for LRYGBP, and 48.2% for BPD-DS as reported by Lee et al. [4], which is the only study comparing all three procedures simultaneously). Various studies refer complication rates that vary from 0% to 24% with an overall mortality rate of 0.39% [7]. LSG has been proved to exhibit multiple advantages compared to other bariatric procedures. The lack of a foreign body, preservation of the pylorus and the antral mill mechanism, avoidance of the dumping syndrome, non-altering the absorption of orally administered drugs, short postoperative hospitalization, and relatively easy laparoscopic perfor-

mance are only a few of them. The most important advantage of the procedure though is the ability to be performed in super-super obese patients (BMI>60 kg/m^2), in an attempt to "stage" the bariatric operation minimizing the surgical risk so that the definitive procedure could be performed after an initial weight loss, diminishing that way both morbidity and mortality of these patients. Furthermore, it can be used in patients contraindicated for intestinal bypass like those with ulcer history, chronic anemia, Crohn's disease, or renal failure.

However, numerous questions remain to be answered before LSG takes its definitive place in bariatric surgery, such as whether its performance should only be limited in bridging towards LRYGBP or BPD-DS, what should the BMI threshold for its performance be, and mainly, whether the EBWL achieved after LSG is satisfactory in the long run. In order to understand the potential benefits of this relatively new surgical procedure, it is essential for every surgeon to scratch under the surface and understand the mechanism of action of LSG and its potential benefits on the patients' metabolism. Gastric volume restriction, decrease of dilatation, alterations in gastric tube's gradient and pressure, hormone influence, and gastric motility change are the major issues that will be further discussed in this review.

Does Size Matter?

LSG philosophy was based on reduction of the gastric volume and limitation of food intake. As such, it is more than logical to assume that the size of the remaining stomach is crucial to the success of the operation. In order to achieve this, a bougie is passed into the stomach to assist in calibrating the size of the sleeve. The stomach is transected from the greater curvature towards the lesser one, until it reaches the bougie and then continues cephalad in parallel to it until the angle of His [8]. However, the size of the bougie that should be used in LSG and its impact on the maximal EBWL is still in debate [3, 4, 9, 10]. In most studies, bougie size varies from 32 to 60 Fr.

To begin with, one should consider what the difference in the bougie size actually means. Taking under consideration that 1 Fr equals 0.3 mm, a bougie of 36 Fr has 1.2 cm diameter and contains 26 cm^3 volume, does not vary significantly from the 40 Fr bougie (1.3 cm diameter and 32 cm^3 volume) someone could assume, but this difference inclines as the size increases into 60 Fr, reaching 1.9 cm diameter and 71 cm^3 volume. Taking under consideration the variable volume of the remaining antrum and the multiple meals that patients are postoperatively encouraged to consume during the day, this can add up to a serious difference in food volume absorption among the two edges of the bougie diameter, but it probably does not have any effect between 32 and 40 Fr. Furthermore, the actual size of the gastric tube may differ significantly from the bougie size since it depends solely on how closely to the bougie the linear staple is applied. Studies [4, 6], despite the use of different sized bougie 48 and 32 Fr, report the same gastric volume remnant (50–60 cm^3).

Nevertheless, many surgeons still believe that the diameter of the bougie used is a critical determinant of the final EBWL. Roa et al. using a 52-Fr bougie reported a mean EBWL% of 52.8 at 6 months postoperatively in patients with mean BMI of 41 [11], while others noted an EBWL% 35 with 60 Fr bougie in patients with 68 mean BMI [12]. Mognol, though, using 32 Fr bougie in 60 patients with mean BMI 64 marked a 41 EBWL% [3].

In a study of Perikh et al. [13], 135 patients were stratified in two groups according to the bougie size used: the first using the narrowest bougie size of 40 Fr and the second group with the largest 60 Fr. It is important to notice that there is a statistically significant BMI difference sustained among the two groups, with the 40-Fr group having lower BMI than the 60-Fr group (55.1 vs 63.1 kg/m^2, $p<0.001$). Despite this difference in BMI, the authors did not find any difference in EBWL% at 6 and 12 months postoperatively, an observation that supports even stronger the idea that bougie size does not actually matter.

Jacobs and co-workers reported no difference between 46-Fr, 40-Fr, and 36-Fr bougie regarding EBWL, weight loss, and BMI and, moreover, noted that no statistically significant difference between 4 and 7 cm antral pouch existed [14].

A recent analysis of ten LSG series came to no definite conclusions about the correlation between bougie size, EBWL%, and follow-up period [15]. On the other hand, LSG has been associated with a weight regain after several years depending on sleeve size, and primary large LSG showed short-term weight loss only [16].

It is difficult to reproduce the same gastric sleeve volume even by the same surgeon, since it depends on the lateral stretch applied to the fundus while stapling and the volume of fundus removed depending on the positioning of the stapler, right on the gastroesophageal junction or deviating from it. Furthermore, the exact length of pylorus left behind varies among surgeons. Baltasar et al. [17] prefer to start the LSG 2–3 cm from the pylorus, while other authors prefer to start at 6 cm [8] or even further away [7, 9, 13] from the pylorus. Moreover, utilization of a buttressing line or an oversewing line applied by most surgeons may result in further narrowing of the gastric lumen.

Yehoshua et al. reported that the gastric volume after LSG is somewhat less than 10% of the mean volume of the intact stomach, leading to higher intragastric pressures due to the markedly lesser distensibility of the gastric tube

compared to that of the whole stomach [18]. Distention of the stomach activates stretch receptors and mechanoreceptors that transmit satiety signals to the central nervous system (CNS) [19]. It is therefore logical to assume that the smaller the gastric tube, the faster it will reach its maximum volume capacity, activating the mechanoreceptors and diminishing the patient's appetite in CNS. Additionally, it has been shown that a small increase in volume in LSG's gastric tube results in a much earlier significant elevation of gastric pressure compared to the intact stomach [18]. It is known that during food ingestion an active relaxation of the gastric fundus occurs allowing a volume increase without a raise in the intragastric pressure [20]. Moreover, the fundus is the most easily expanded compartment of the reservoir part since it has only two layers of muscle [16], enabling that way the stomach to accommodate larger volumes. Therefore, resecting the fundus during LSG results not only in volume capacity reduction, but also in removal of the most distensible part of the stomach leading to high intraluminal pressure and consequently to early satiety feeling.

The possibility of a later dilatation of the remaining gastric tube and diminishing of the restrictive effect of the procedure is a common concern between both patients and physicians. The main cause of gastric dilatation is eating disorders, but so far, little is known about long-term failure of LSG due to gastric tube distention. Himpens, on the 2nd International Consensus Summit for LSG, warned about inadequate fundic resection that can lead to enlargement and formation of neofundus [21]. Up to now, only a few studies refer to late gastric dilatation after LSG. Langer et al. showed that only 1 out of 14 patients exhibited gastric dilatation at 1 year follow-up [10]. Gastric dilatation was defined by the authors as broadening of the gastric tube >4 cm in GI radiographic contrast imaging. Regardless of the preceding fact, the patient had achieved 59% EBWL, and 30 months postoperatively, his weight remained stable and still experienced early satiety. Gastric dilatation of sleeve gastrectomy as part of BPD-SG has also been reported, where the patient exhibited weight regain after successful weight reduction of 80% EBWL, 32 months postoperatively [22].

Recently, Keidar reported eight cases (1.1%) of LSG patients suffering from severe gastroesophageal dysmotility and reflux disease post-LSG that has been executed with various bougie sizes [23]. Radiographic imaging of these patients revealed a wide, dilated fundus with a relatively narrow mid-stomach, but without complete obstruction. In one of the cases, this dilatation was due to sort of kinking point in the mid-sleeve. Despite the fact that the authors concluded that the initial diameter of LSG does not implicate in later dilatation, they suggest that the anatomical changes in angle of His and gastroesophageal junction and most importantly the volume of fundus left behind lead to higher propensity of the stomach to distend, especially in view of functional obstruction [23].

In other studies though, the initial diameter of the LSG appears to be important for later dilatation, since a LSG with greater diameter will dilate earlier than a tighter one [16]. Nevertheless, postoperative endoscopic dilatations of narrowing points in the remaining gastric tube [23], seromyotomy for long stenoses [24], or even re-sleeve gastrectomy in cases of gastric dilatation or residual fundus remain a feasible and easy-to-perform option [16, 25]. In case of failure, conversion to biliopancreatic diversion or RYGB is the next option. Nowadays, usage of gastric band on the remaining gastric tube with success in EBWL has been reported [26, 27].

Therefore, apart from whether the bougie size actually affects the short- and possibly the long-term EBWL outcome of the procedure, the query whether its diameter has a significant long-term effect on pouch dilatation, loss of restriction, and weight regain still remains to be investigated.

Satiety vs Appetite: the Hormonal Benefit of SG

Gut hormone profiles following bariatric surgery have been shown to favor an anorectic state, improve metabolic parameters, and facilitate appetite reduction [28]. The only known peripheral hormone with orexigenic properties is ghrelin, a 28 amino acid peptide hormone that predominantly targets the same neuronal structures such as leptin and neuropeptide Y (NPY) [29]. It stimulates appetite, increases food intake, and reduces host metabolic state and fat catabolism in humans [30–32], while in weight reduction situations like diet, cancer cachexia, and anorexia, high levels of circulating ghrelin are observed [33–35]. Ghrelin represents an endogenous hormone that binds to the growth hormone secretagogue receptor and stimulates arcuate and solitary tract nucleus in hypothalamus for growth hormone (GH) release, playing a principal role in body weight regulation. It partly exerts its effects through vagal afferent loops [36], where it opposes leptin via disinhibition of NPY and agouti gene-related peptide (AgRP) [37].

Ghrelin receptors are also present in the stomach and other organs and tissues, suggesting effects beyond GH secretion stimulation. Ghrelin appears to stimulate appetite mainly through meal initiation, as it is suggested by its great preprandial rise and postprandial fall [38], favoring that way adiposity and contributing to obesity. Chronic administration of ghrelin in rodents resulted in hyperphagia and weight gain independent of growth hormone levels, suggesting a long-term effect on energy balance [39–42].

Comparison of ghrelin levels among lean and morbidly obese patients showed that lean controls have significantly higher plasma ghrelin levels at baseline [43–46]. This might be related to high caloric consumption, since body weight reduction in obese patients increases ghrelin's plasma levels [47]. Studying of a normal weight, overweight, and three subgroups with inclining BMI obese patients showed that obese patients had significantly lower ghrelin levels than normal and overweight patients, though no remarkable difference was noted within patients of various degrees of obesity [48].

Ghrelin is primarily produced by the stomach, though other sites of production like the duodenum, jejunum and lung do exist [49, 50]. Resection of its primary site of production may explain the lack of hunger that a large percentage of LSG patients report postoperatively, despite the extreme caloric restriction and the negative energy balance that follows the operation. During reoperation of a patient who has achieved complete weight regain 13 months postoperatively and exhibited ghrelin in its preoperative levels, Langer et al. found a remnant part of fundus unrecognized due to axial diaphragmatic hernia, emphasizing the importance of complete gastric fundus removal [10]. One cause of the rapid postprandial decline in ghrelin levels is postulated to be its response to nutrient passage through the cardia and fundus of an intact stomach and mediated in part by vagal parasympathetic signaling [49, 51]. It has been proposed that suppression of ghrelin secretion from the gastric fundus is secondary to a permanent deprivation of nutrient stimulation to cells responsible for producing and releasing ghrelin. Supporting evidence is derived from human subjects who exhibit gradual declines in circulating ghrelin levels during an overnight fast [52].

Langer et al. [53] in a prospective study of 20 patients (ten with LSG and ten with LAGB), all balanced for age, sex, and BMI, compared plasma ghrelin levels before and after LSG and LAGB. The investigators showed a significant reduction of its levels on postoperative day 1 after LSG. It is interesting that ghrelin levels remained significantly low and stable both at 1 and 6 months postoperatively, implying a more permanent hormonal effect of LSG. On the other hand, no reduction on ghrelin levels at postoperative day 1 was noted in the LAGB group, although these patients exhibited increased plasma ghrelin levels at 1 and 6 months postoperatively, justifying that way the effect of hormonal superiority of LSG in EBWL compared to LAGB. Enhancing the hypothesis of long-term reduced ghrelin levels, the study of Ariyasou et al. [49] showed that gastrectomized patients had 65% reduced ghrelin levels compared to normal subjects, with no correlation between time after gastrectomy and plasma ghrelin effect, implying a permanent result. Wang and Liu [54] showed a significant reduction of plasma ghrelin levels 2 years after of LSG, while its levels increased statistically significant 2 years after LAGB.

On the other hand, Adami et al. [55] studied ghrelin levels in patients that underwent BPD-DS that included SG and found that decrease of ghrelin levels exists only during the immediate postoperative period and it reaches preoperative values at 2 months postoperatively. The lack of fundus extraction in their patients may be blamed for the compensation of ghrelin levels, suggesting the existence of a recuperating mechanism of the human body in reaching satiety appetite homeostasis.

Karamanakos et al. [56], in a prospective double-blind study of 32 patients, 16 with LSG and 16 with LRYGBP, reevaluated the patients' fasting and postprandial ghrelin and peptide-YY (PYY) levels on the 1st, 3rd, 6th, and 12th month postoperatively and noted in the LSG group a decline in ghrelin values along with an increase in PYY levels. PYY is known to induce the feeling of satiety [57]. It is a gastrointestinal hormone that is produced by the enteroendocrine L cells and acts on the intestinal epithelium [58] and on hypothalamus [59], while its secretion is correlated to the amount of ingested calories [60]. Both findings were associated with markedly greater appetite suppression and EBWL compared to the 16 patients that had undergone LRYGBP. Interestingly, PYY is stated as a powerful inhibitor of gastrointestinal motility and pancreatic, gastric, and chloride secretions [61], actions that could be involved in post-bariatric surgery EBWL, though no such studies have been executed yet. Furthermore, low blood levels of PYY have been associated with both insulin resistance (IR) and insulin hypersecretion in response to maximal stimulatory glucose concentrations [62], probably contributing that way to the improved IR of diabetic patients after LSG.

Although LSG's actual hormonal impact is only on ghrelin, its hormonal effects turn to be a very complicated issue, since ghrelin reduction, directly or indirectly, affects the very complicated hormonal system of appetite that involves AgRP, neuropeptide Y, and leptin. AgRP is a neuropeptide produced in the hypothalamus that has been demonstrated to be an inverse agonist of the melanocortin receptors MC3-R and MC4-R, which are directly linked to metabolism and weight control [63]. It is co-expressed with NPY, increases appetite, and decreases metabolism and energy expenditure, consisting one of the most potent and long-lasting appetite stimulators. Its appetite stimulating effects are inhibited by leptin and activated by ghrelin [64]. Leptin is an anorectic hormone, produced and released by the adipocytes. It enters blood circulation and can pass through the blood–brain barrier [65], exerting its function by inhibiting the NPY and activating the proopiomelanocortin (POMC) neurons in the arcuate nucleus. Kotidis et al. [66] confirmed reduction of leptin levels, along with

ghrelin, in a study of 40 obese patients. Both hormones were decreased 18 months post-BPD-DS, and this was attributed to the sleeve gastrectomy part of the operation. Moreover, leptin has recently been demonstrated to counteract ghrelin's actions in NPY neurons [67].

Furthermore, weight loss surgery ameliorates and even resolves type 2 diabetes mellitus (T2DM) in patients with obesity. Changes in IR with rapid improvement have been demonstrated following LRYGBP, LAGB, and BPD-DS [68–70], and studies suggest that T2DM and IR improvement after LRYGBP and BPD-DS is unrelated to weight loss, implying a hormonal effect of the bariatric procedure through the enter-insular axis [71]. Regarding LSG, studies have also shown a high rate of T2DM resolution [6, 72, 73] independent to EBWL and fat mass normalization [74]. These data suggest an additional mechanism that contributes to changes in T2DM and IR patient's profile following LSG and confirms that LSG is more than a restrictive procedure. Ghrelin seems to suppress the insulin-sensitizing hormone adiponectin, block the hepatic insulin signaling, and inhibit insulin secretion. It has been proposed that decreased ghrelin levels increase the maximal capacity of glucose-induced insulin release and enable islets to secrete more insulin in order to meet the increased demand associated with obesity [75]. Thus, part of the glycemic improvement in T2DM after LSG may rise from ghrelin reduction.

Nevertheless, more studies are still required to determine LSG's actual hormonal effects on obesity-related metabolic disturbances and the complex mechanisms through which they interrelate. Table 1 summarizes the three major hormones that have been studied post-LSG up to now, but still a lot remains to be clarified. Despite the fact that the major impact of LSG in hormonal regulation of weight is ghrelin, whether the physiologic advantage of its reduced production post-LSG will be lost over time, through other mechanisms like post-surgical gastric hyperplasia, or other sites of ghrelin production such as the duodenum and the brain will compensate its normal values over time still remains unknown, and more studies with longer follow-up should be performed.

Gastric Emptying

Another possible mechanism of LSG action on EBWL that has been recently suggested is its possible effect on gastric emptying rate through various mechanisms. Up to date, only a few studies have addressed that, showing conflicting results. Studies have been demonstrating that accelerated gastric emptying of solid meals may be the cause of reduced satiety and hunger in individuals [76], while other studies showed no difference in gastric emptying rate between lean and obese subjects [77]. Control of gastric emptying is under the influence of duodenal and distal ileum receptors that have a common antro-pyloric target. When the hypertonic meal passes through the distal ileum and the colon, L cells stimulated by fat and glucose secrete glucagon-like peptide (GLP-1), which decreases gastric emptying and intestinal peristalsis [78]. It has been demonstrated that GLP-1 concentration in serum is increased in normal weight people after a meal, but not in morbidly obese patients [79]. Furthermore, GLP-1 has been also shown to promote satiety and decrease energy intake through its interaction with its receptors in the brain [80, 81]. In a study by Pereferrer et al., baseline GLP-1 levels in non-obese rats were lower than those of obese animals, while its levels post-sleeve gastrectomy in obese rats have been shown to be lower than pre-interventional levels [82].

Melissas et al. [83] found that gastric emptying for solids occurs more quickly after LSG, something that could be explained by alterations in the contractility of the proximal stomach, the absence of receptive relaxation after LSG, the removal of the ghrelin-producing fundus, and possible antral distention which leads to changes in enterohypothalamic axis.

Table 1 Weight control hormones that have been studied after LSG

Hormone	Origin	Site of action	Mechanism of action in obesity	Effect on weight	Levels post-LSG	References
Ghrelin	Primarily stomach fundus	Acts on arcuate and solitary hypothalamic nuclei	Stimulates GH release	Stimulates appetite	Reduced	[31–33]
				Reduces metabolic rate		[50, 51]
	Pancreas		Opposes leptin actions			[54, 55]
	Intestine			Reduces fat catabolism		[57]
PYY	Enteroendocrine L cells of ileum and colon	Gastrointestinal epithelium, arcuate nucleus	Associated with IR and insulin secretion	Induces satiety	Increased	[57–60] [63]
Leptin	Adipocytes	Acts on arcuate nucleus	Inhibits NPY and activates POMC neurons	Anorectic	Reduced	[66–68]

A very interesting study by Bernstine et al. [84] measured gastric emptying in patients before and 3 months after LSG with multiple scintigraphic imaging minute intervals. According to this study, LSG performed with antrum preservation has no effect on gastric emptying since both mean time of gastric emptying and retention among the different time intervals failed to show any significant differences.

Since gastric emptying may play role not only in EBWL, but also in postoperative symptoms like gastroesophageal reflux and vomiting, it is important that further research towards defining LSG mechanism of action and efficacy on gastric motility is performed.

Conclusion

Although long-term efficacy of LSG is yet unclear, data so far demonstrate a very promising bariatric surgical option that will be here to stay. Nevertheless, both indications and boundaries of the operation need further clarification. This review concentrates on two major aspects of LSG: the optimal bougie size and the exact mechanism of early satiety that is often observed in these patients. Regarding bougie size, most studies support the use of a narrow bougie in order to ensure the complete removal of the fundus, but no consensus has been reached to date. Early satiety after LSG is an even more challenging aspect of the procedure since multiple factors seem to be involved: alternations in hormone levels, impaired gastric motility, and elevated pressure within the sleeve. Up to now, the major effect of LSG on patients' metabolic profile is exerted by ghrelins' reduction after fundus removal. This effect though implicates and counteracts with many other hormonal signals that still remain to be elucidated with further studies so as to consolidate the position of LSG in bariatric surgery.

LSG has emerged as a restrictive operation, but its ability to extend beyond that through hormonal modifications raises a promise that it will play a leading role in the future of bariatric surgery, either as a sole operation or as part of a more extended procedure.

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

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