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REVIEW ARTICLE

Resolving of diabetes mellitus post laparoscopic sleeve gastrectomy (LSG)

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ABSTRACT

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally with obesity as a risk factor for T2DM. Non-surgical and surgical methods are used to treat morbid obesity. Laparoscopic Sleeve Gastrectomy (LSG) is being recognized as an effective independent procedure for treating morbidly obese patients with T2DM by removing the gastric fundus and transforming the stomach into a narrow gastric tube. This paper discusses effects of LSG in T2DM resolution and remission, and its short-term and long-term influence on obese patients with T2DM with making comparison with other types of surgeries to resolve T2DM. LSG seems to have a substantial beneficial influence on T2DM, producing resolution in the majority of patients included in the studies. LSG has gained popularity for its relative operative ease and lower risk profile.

Keywords: Diabetes Mellitus, obesity, Gastric Surgery, Gastrectomy, Laparoscopic Sleeve Gastrectomy

Introduction

The prevalence of Type 2 Diabetes Mellitus (T2DM) is globally growing, especially in developing countries [1]. Obesity is the main risk factor of type 2 diabetes (T2DM), and majority of patients with T2DM (90%) are either overweight or obese [2]. The prevalence of T2DM is increasing and 439 million adults will develop diabetes by 2030 [3]. It has been estimated that the risk of chemical diabetes is about 50% with a body mass index (BMI) higher than or equal to 30 kg/m^2 and over 90% with a BMI of 40 kg/m2 or over [2]. In USA, the Centers of Disease Control (CDC) estimated that 68.0% of the people were overweight, followed by 33.8% were obese, and 14.3% were morbidly obese [4]. The relative risk of T2DM of morbidly obese patients is at least 5% among men and 8% to 20% in women [5]. To delay or prevent the risk of T2DM, it is important to lose weight in the overweight or obese patients with pre-diabetes or impaired glucose tolerance (IGT) and it can considerably improve blood glucose control in patients with T2DM [6].

Different strategies are used to treat morbid obesity including surgical and non-surgical methods. The common non-surgical methods comprise diet control, regular exercise, change of lifestyle, and pharmacologic intervention. These strategies are usually appropriate only for overweight and mildly obese patients, and their effects are not long-lasting. Overall, weight reduction by using a low calorie food rebounds in 2–4 years. However, physical activity and food control together can practically achieve long-lasting weight loss but obtaining long-term commitment from patients is challenging. In fact, lifestyle changes have minor long-term influences. Pharmacologic intervention, although beneficial for morbid obesity, causes unsatisfactory consequences [7]. This literature review aimed to review resolving of T2DM using surgical Laparoscopic Sleeve Gastrectomy (LSG) treatment.

Surgical treatment of obesity

Behavioral and medical methods to treat obesity result in weight loss of around 5–10% in a short period, which tends to decrease over time [8]. Globally, effective and long-term management of T2DM is a main challenge [9]. Surgery intervention is applied for the treatment of obese people with T2DM (BMI ≥ 40 kg/m^2 or BMI = 35–40 kg/m2 with co-morbidities) [10]. The quick and continuous influence of weight loss using metabolic surgery has been shown in previous studies [11]. Bariatric surgery for T2DM associated with obesity not only has significant therapeutic effects on weight loss but also reduces the symptoms of this disease [12]. It can also reduce the excess body weight (EBW) from 50 to 75% [12]. Interestingly, the result of the surgery is durable as confirmed by long-term follow-up evaluations [13]. Hence, based on the recent international guidelines,

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bariatric surgery is offered as the most effective method for morbid obesity [14]. It is also related with a high rate of remission of T2DM and other obesity-related illnesses, specifically hypertension, dyslipidemia and obstructive sleep apnea [11].

It is well documented that even a small degree of weight loss can considerably develop insulin resistance and consequently glucose homeostasis; however, other mechanisms underlying the favorable influence of these particular types of bariatric surgery are unclear [15]. Using surgical approach for obesity is also cost effective. For example, in USA, estimations of the cost of bariatric surgery per Quality Adjusted Life Year (QALY) are from $5,400 to $36,600/QALY, well under the $50,000/QALY benchmark that is generally regarded [16].

Different types of surgeries

Using bariatric surgery such as Biliopancreatic Diversion (BPD), Adjustable Gastric Banding (AGB), Roux-en-Y gastric Bypass (RYGBP), Sleeve Gastrectomy (SG) and Gastric Banding (GB) can reduce weight and control most of the obesity-related co-morbidities, such as T2DM, hypertension, dyslipidemia, metabolic syndrome and sleep apnea syndrome [17,18]. Some of these surgical strategies are purely restrictive like AGB and some primarily malabsorptive like BPD, whereas others are a mixture of restrictive and malabsorbtive procedures such as RYGBP [3]. RYGB is one of the main bariatric procedures characterized by high therapeutic benefits and a low rate of adverse complications [19]. It is also the most frequently used bariatric surgical procedure for DM which impacts the structure of the digestive tract [20].

LSG as another type of bariatric surgery is restrictive in nature, weight loss and amelioration of obesity-related problems are comparable to RYGB. Moreover, LSG is considered easier, faster, and has less perioperative morbidity than RYGB [11]. LSG, originally considered as a first step for achieving weight loss in morbidly obese patients before conducting RYGBP or BPD, has appeared as a new restrictive bariatric technique [21,22]. To improve LSG's success, an additional intestinal bypass surgery combined with traditional SG (Sleeve Gasrectomy) side to side with jejunoileal anastomosis (JI-SG) has recently been examined and revealed favorable results in weight loss and enhancement of T2DM remission rate [23,24]. These two combined surgeries (JI-SG) comprise two physiological changes: the first is the exclusion of the gastric body and fundus of the stomach, which declines stomach capacity [25], and the second is side-to-side anastomosis of the ileum and jejunum, which transfers food more rapidly into the terminal ileum, without excluding or resecting any segments of the digestive tract. Based on the hindgut theory, this process of accelerating nutrient delivery to the hindgut produces better glycemic control [26]. Therefore, combined surgery with JI-SG has been recognized as a relatively new bariatric method. New findings support the effectiveness of this method. For example, Melissas et al. (2012) conducted laparoscopic JI-SG among 27 patients and found higher weight loss and an increased rate of diabetes resolution with JISG compared to SG alone [27]. In a systematic review study, Buchwald et al. (2004) compared the different surgical techniques and their effectiveness in weight loss. The results of meta-analysis showed that there was 95.1% resolution of T2DM in patients undergoing BPD/ duodenal switch, followed by GB (80.3%), SG (79.7%), and AGB (56.7%) [11]. Another systematic review compared the effectiveness of different bariatric surgery procedures on weight loss. The results showed that GB, LSG, and BPD change to decrease excess weight in patients by 47%, 62%, and 70%, respectively. While the reviews on LSG by Gill et al. (2010) and Brethauer et al. (2009) found that the mean percentage of loss was 47.3% and 60.4%, respectively [3].

The mechanism of surgery on T2DM remission

There are many available evidences confirming that bariatric technique increases T2DM control through mechanisms beyond weight loss [28,29]. The fundamental mechanism for T2DM remission after GBP is interesting. Four possible mechanisms have been offered comprising the starvation followed by weight loss hypothesis, the ghrelin hypothesis, the lower intestinal (hindgut) hypothesis, and the upper intestinal (foregut) hypothesis. None of these models essentially precludes the others; consequently any combination may be operational to some degree [30,31].

In RYGB, the food bypasses the duodenum and proximal jejunum; there are 2 related major theories including the hindgut and foregut theories [32]. The mechanism in LSG is different as it makes a small gastric reservoir and restricts food intake; so that food does not bypass the duodenum or proximal jejunum [33]. Although its mechanism is different, similar T2DM remission rates have been revealed as RYGB. The most recognizable mechanism for T2DM remission after LSG is the influence of weight loss and improved insulin sensitivity. Though weight loss is not the only consequence of food restriction, the results of new studies showed that there is no association between mean Excess Weight Loss% (EWL) and T2DM remission rate in LSG or RYGB patients. This result recommends that the control of T2DM is independent of %EWL. Other theories such as the ghrelin hypothesis [34,35] and farnesoid receptor hypothesis [36], have recently appeared. RYGB, which acts as both malabsorptive and restrictive mechanisms, helps early remission and sustains long-term control of T2DM [37].

In comparison to RYGB, LSG can also control T2DM by engaging hormonal mechanism in addition to its restrictive component [38]. Bariatric surgery decreases food intake, restricts stomach volume, and changes the secretion of gastrointestinal hormones.

These hormones include incretin, peptide YY (YYP), and growth hormone-releasing peptides. Incretin comprises glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic hormone [39]. These hormones establish the entero-insular axis and are involved in the regulation of insulin release within the intestine [40]. Based on the hindgut theory, the quick delivery of undigested nutrients to the distal bowel up regulates the production of L-cell derivates, such as GLP-1 and peptide-YY-37. GLP- 1 action arouses insulin release and may grow the cell mass [41]. GLP-1 acts on receptors situated in -cells in pancreatic islets, thus causing glucose-dependent insulin secretion [42]. It affects receptors in the peripheral and central nervous systems, prevents secretion of gastric acid, slows gastric emptying, postpones food absorption, induces satiety, and reduces appetite [43,44]. GLP-1 also prevents glucagon secretion from βcells in pancreatic islets. In a study by Melissas et al., (2007), it was demonstrated that despite preservation of the pylorus in LSG, gastric emptying was enhanced, which supports the hindgut theory [45]. The resolution of T2DM has been considered as cessation of all hypoglycemic medications and/or insulin and a normal fasting plasma glucose level, normal postprandial glucose excursions, and normal hemoglobin A1c (HbA1c) [46]. A reduction in gastric emptying half time after LSG can probably contribute to better glucose homeostasis in patients with T2DM [47].

LSG and its benefits on resolving T2DM

LSG has been used progressively for its ease, safety, and lower rate of postoperative nutritional deficiencies. Studies have established that LSG successfully leads to weight loss and T2DM remission [48]. The positive influence of LSG on T2DM appears to be due to not only the fat mass loss but also the extensive resection of the gastric fundus that could be, per se, a factor that makes pathophysiological changes able to increase T2DM. It has been recommended that changes in ghrelin level after LSG can support to explain the rapid weight-independent glycemic effects of this surgical technique [45]. Despite of the ghrelin influence, LSG was also described to have a hindgut influence, growing GLP-1 and YYP due to increased transit time after LSG [49].

LSG is favorable because of the definitive effects upon weight loss, low changes to the gastrointestinal tract, avoidance of the need for reconstruction of the digestive tract, decreasing in surgical risks, and few postoperative problems [20]. Different studies have shown improvement in T2DM and hypertension (HTN) following LSG [50]. However, follow-up studies are also needed to evaluate the long-term durability of these results. LSG is a simple and quite effective surgical method in the treatment of morbid obesity. Newly LSG has been described to be effective in the complete remission of T2DM [51]. LSG is a new technique that has been subsequently found to have other substantial physiological implications. It is considered as the first stage surgery of a two-stage approach in which duodenoileostomy and ileoileostomy are conducted later; the significant weight loss seen after LSG has established it as an independent bariatric surgery method [52]. LSG has been revealed to create better weight loss than GB5 and is a less aggressive operation than GB with comparative outcomes [53]. It is also recognized as the main surgery option because of its easiness and outstanding results and safety. It also does not cause any malabsorption. It does not include placement of foreign bodies and needs less time [3]. On the other hand, this surgery like other types of surgery has some complications. For example in a study, 12.5% of patients who had LSG showed severe complications requiring invasive intervention comprised 1.6% of the complications (leakage, 0.5%; bleeding, 1.0%) which was slightly lower than those related with RYGB [54,55].

Influence of sleeve gastrectomy on resolving T2DM

Comparing with RYGB

The results of newly conducted research as well as systematic reviews and randomized controlled trials (RCTs) confirmed that LSG has become more and more acceptable as a stand-alone bariatric surgery technique [30,56]. Wide ranges of results have been reported showing different influence of LSG on weight loss and T2DM remission compared with other types of surgeries. In a systematic review, data showed EWL after LSG was not significantly different from EWL following RYGB in 24 months post-surgery [57]. This finding is in line with that of Peterli et al. (2012) showing no significant differences in 12 month post-operation EWL between LSG and RYGB [56]. A similar weight loss effect with SG and RYGB has been observed, especially in the early postoperative period. In a retrospective study conducted by Lakdawala et al., (2010), the results demonstrated the mean percentage of EWL 6 and 12 months after SG to be 50.8% and 76.1%, respectively [53]. In another systematic review which compared different types of surgeries such as LSG, RYGB, and AGB, the results revealed that LSG was associated with a similar weight loss pattern as that seen with RYGB [58]. In a study, Cutolo et al., (2012) compared the clinical efficacy of RYGB and SG among 31 obese T2DM patients; fifteen patients had undergone LSG and 16 had LRYGB. A BMI reduction in body weight was seen at 18–24 months which was 29 ± 8 and 33 ± 11% in LSG and LRYGB, respectively [14].

In another systematic review, Buchwald et al. (2009) found that bariatric surgery makes an overall remission of T2DM of 78% that remained at 62% during 2 years follow-up with malabsorptive procedures being more effective than the restrictive ones (95 vs. 57%). The results for LRYGB include 80% remission rate of T2DM over 2 years follow-up [12]. Lots of evidences confirm that the remission of T2DM happens early after bariatric procedures before a significant weight loss [59]. It can be associated with the changes in gut hormones consequent to the anatomic modifications of intestinal nutrient transition [60]. Quick transfer of indigested food to the distal intestine results in a greater release of some enterohormones such as GLP-1 [16] which is identified to exert variety of beneficial effects on glucose homeostasis. Actually, plasma GLP-1 levels grow up to ten fold after bariatric surgery [14].

Other retrospective clinical studies showed the remission rate of approximately 80–90%, and the rate was lower in RCTs as they are more reliable. For example, the results of two RCTs revealed the remission rate of LSG was significantly lower than that of RYGB. In a study conducted by Lee et al. (2011), the remission rates for SG and RYGB were 47% and 93%, respectively, so they concluded that RYGB was more likely to achieve T2DM remission [30]. Schauer et al. (2012) demonstrated a lower rate of remission which was 27% and 42% for SG and RYGB, respectively, showing similar effects on T2DM remission, though the rates were somewhat higher in the RYGB group [61]. Other studies reported a higher effect of T2DM remission using LSG compared with RYGB. For example, in a systematic review of SG alone reports a remission rate of 66.2% and a remission and improvement rate of 97.1% for T2DM [46]. While, in another study using RYGB a remission rate was 83.3% and a remission and improvement rate was 90.6% for T2DM. These results reveal that SG can successfully improve glycemic control in T2DM patients [11]. Other studies reported different rates of remission from 40 to 90%, which depends on the operation type, as diabetes remission is stated as 60–90% in RYGBP, 86% in BPD; the long-term results are 60% diabetes remission in RYGBP and SLG and 50–70% in insulin dependent diabetes [62,63].

Short-term effects of LSG

LSG has recently been considered as a first stage of BPD with Duodenal Switch (BPD-DS), and is proposed as potential single restrictive bariatric technique. It is well documented that LSG is associated with a high rate of resolution of T2DM and other obesity-related comorbidities such as hypertension, hyperlipidemia and sleep apnea [64,65]. In a study which was conducted to cure T2DM, a high rate of resolution of 74.5%, at a mean follow-up of 36 months was observed. In the LSG group, a cure rate of 66.6% after 3.3 months was reported when EWL was 36.3 ± 7.2%. Lacy described a high resolution of T2DM at 4 months after LSG, and this resolution was similar to that in GBP (51.4% and 62% respectively, $p = 0.332$) [50]. In another study, Rizzello et al., (2010) evaluated the short-term effects on insulin resistance following LSG among 17 consecutive obese T2DM patients. Patients' fasting serum glucose and insulin concentration were measured at 5, 15, 30, and 60 days. The results displayed that all obese patients had a sharp and significant decrease of serum glucose and insulin concentration after LSG in different measured days [66].

A systematic review on T2DM outcomes after LSG 5] showed T2DM remission of 93.1%. For weight loss outcomes, the results revealed a mean %EWL of 65% after GBP at 12 months similar to 67.1% as previously reported. The results also showed that %EWL was 66.8% at one year after LSG which was higher than that stated at 47.3% after LSG with a mean follow-up of 13.1 months [46]. It is also reported that both GBP and LSG caused considerable early T2DM remission (67% and 56% at 3 months), with modest extra T2DM remission at one year (76 and 68%), despite more substantial weight loss at this time point. This can be described by the contribution of acute caloric restriction to achieve early T2DM remission in both GBP and LSG and reduced bowel transit times leading to increased incretin hormones [67].

In a systematic review study of LSG, the results showed T2DM remission of 56.3% at 3 months based on HbA1c criteria of <6.5%. Small differences in glycemic definitions were caused by large differences in reported T2DM remission at one year of 44.0%, 67.8%, and 75.8% based on HbA1c of <6%, <6.5%, and <7%, respectively [15]. In another retrospective review study, Tritsch et al., (2015) examined the postoperative medical management of 88 T2DM patients using consecutive LSG. Those who received an average of 1.41 oral T2DM medications (24 patients) showed a reduction up to an average of 0.70 ($p < 0.01$) postoperative in one month. Medication changes continued over the 6-months follow-up. For those who required insulin therapy, the mean insulin dose 42.1 units decreased to 16.8 units immediately post operation ($p < 0.01$) which resumed at 1 month. The mean insulin dose was 13.3 units for 6 months [68]. In another prospective study by Dasgupta et al., (2013), 43 obese Indian patients with T2DM who received LSG were followed up for 12-month. The results showed a significant difference in mean glycated hemoglobin (HbA1c) levels at baseline and 12 months after surgery (7.94–1.9% and 5.80–0.7%, respectively, $P < 0.001$). More than two thirds of those patients (78%) reached the primary end point of HbA1c level <6% without medication. HbA1c level less than 7% occurred in 91.4%. The mean body weight was reduced from 122.08–23.32 kg to 83.43–15.12 kg in one year ($P < 0.001$). The weight loss and percentage of EWL noted in one year were significantly reduced (31.14–7.8% and 61.52–15%, respectively). It was also found that anti-diabetic medication usage reduced from 88.57% to 11.4% [3].

In another study conducted by Shah et al. (2010) among 53 patients who underwent LSG, the results revealed that euglycemic status was achieved by 96.2% without any anti-diabetic medications [69]. Other studies reported diabetes resolution values at one year after LSG changing from 14% to 98% [53,70]. In a systematic review of total 27 studies and 673 patients undergoing LSG for morbid obesity, the results showed that two-thirds of the patients had completed diabetes resolution, 27% had significant improvement, and the disease continued in 13.1% of patients [46]. In another review of 24 studies using LSG, the mean preoperative BMI was 46.6 kg/m^2 which was decreased to 32.2 kg/m2 postoperatively over a mean period of follow-up between 3 to 36 months [71].

The Modified LSG (MLSG) is known as a safe method with a low morbidity rate (2.7%). In a study, 150 patients with BMI of 35 to 60 kg/m2 were monitored after undertaking a MLSG. Approximately, 87% of participants were presented with normal glycemic levels between 77 and 99 mg/dL. Participants also had increased average serum insulin levels by 9 mlU/L and average glycosylated hemoglobin levels by 5.1%. Those who had BMI less than 45 kg/m2 experienced an average weight loss of 44.6% while it was 58% for patients with a BMI greater than 50 kg/m^2 [72]

Mihmanli et al. (2016) conducted a study to evaluate the effects of LSG on the treatment of T2DM. Laboratory results as HbA1c and fasting plasma glucose of 88 patients were assessed preoperatively and postoperatively at the 6th and 12th months. Most of participants (55 patients) were using oral anti-diabetic medication and 33 patients were using insulin. The complete T2DM remission was observed in 80 patients (90.9%), while 3.4% had partial remission and 5.6% had persistent diabetes after 6 months. After 12 months, complete remission was observed in 95.4% of participants and 1.1% had partial remission and 3.4% had persistent diabetes [73].

Long-term influence of LSG on T2DM

Data regarding long-term diabetes remission after LSG are contradicting amongst authors. Himpens et al (2006), in a RCTs study, compared the outcomes between LSG and AGB. The results of this study found significantly better weight loss in three years after LSG compared to AGB [52]. In another study, Himpens et al (2010) reported the longterm weight loss information on 41 patients who underwent LSG. The results of the study showed that the mean EWL overall was 72.8% after three years, while it was 57.3% after 6 years. After conducting a second-stage duodenal switch procedure among 11 patients, their EWL increased to 70.8% in six years (mean BMI 27). Among those who were considered as standalone LSG patients (n = 30) they experienced 53% EWL and a mean BMI of 31 in six years. It can be concluded that some patients do regain weight in the long term after LSG is carried out as a primary method and that weight loss can be developed by conducting a secondstage procedure in selected patients. The results of the study also showed that Gastroesophageal reflux disease (GERD) remains a concern after LSG and 26% of the patients experienced GERD with long-term follow-up. They can be re-sleeved to control the symptoms. Overall, patients were contented with LSG procedure in six-plus years [74].

In another study conducted by Bohdjalian et al. (2010), the long-term effects of LSG were assessed. In this study, five-year weight loss data for 26 patients who underwent LSG were recorded. Before the surgery, the mean BMI of patients was 48.2kg/m^2 and one-third of the patients were considered as super-obese. Mean EWL was 55% after five years. Four patients (15%) experienced a secondstage gastric bypass for weight regain and gastric reflux. One third of patients were treated for GERD after 5 years using chronic acid suppression medication. The results also showed reduction in plasma ghrelin levels after five years of LSG that continued to significantly reduce as compared to preoperative levels [35].

In another study, Eid et al (2012) revealed that, among patients with very high BMI, LSG can also make excellent long-term weight loss and co-morbidity reduction without conducting the second-stage procedure. The results of long-term follow-up of data showed that the mean %EWL at 72 and 96 months was 52% and 46%, respectively [75].

In another study, Gill et al (2010) conducted a systematic review of 28 studies including 673 patients with a mean preoperative BMI of 47.4. LSG caused diabetes remission in 66.2% of patients and in these studies that stated improvement and remission of diabetes, 97% of patients had either improvement or remission. The mean HbA1c reduced from 7.9 to 6.2 in the 11 studies [46]. Lee et al (2011) conducted a comparison study of gastric bypass to LSG among Taiwan patients. LSG caused remission of diabetes in 47% of patients in one year and was associated with an average of three percent decrease in HbA1c levels [30].

In another study, Capoccia et al., (2015) carried out a study on T2DM among obese patients who underwent LSG. Continuous Glucose Monitoring (CGM) was implemented in each patient to better clarify the remission of diabetes after three years follow-up. The results showed that the diabetes resolution after LSG happened in 40% of patients; in the other 60%, even if they displayed a normal fasting glycemia and HbA1c, patients spent a lot of time in hyperglycemia [76].

Park et al., (2014) conducted a study among 192 consecutive Korean patients who underwent LSG and their mean preoperative BMI was 40.0 ± 7.2 kg/m^2, and most of them (62.5%) had at least one obesity related comorbidity. The results of the study demonstrated that at the postoperative 1, 2, 3, and 4 year follow-ups, the mean percent of EWL values were 72.6%, 80.6%, 71.1%, and 57.8%, respectively, with follow-up rates of 81%, 56%, 58%, and 30% respectively. The results of the study confirmed that the overall mean %EWL reached 68.3% ± 27.2% at a mean follow-up of 25 months. Moreover, after the surgery, the obesity-related co-morbidities were resolved in >70% of the patients [77].

Conclusion

Laparoscopic Sleeve Gastrectomy (LSG) is one of the preventive surgical techniques useful for treating morbid obesity by removing the gastric fundus and transforming the stomach into a narrow gastric tube [78]. This surgical technique aims to decrease operation risks for super-obese or high-risk patients; however, it has been validated as a stand-alone bariatric surgery nowadays [79]. Furthermore, LSG has gained increasing popularity with both bariatric surgeons and patients, mainly due to its relative operative ease and lower risk profile [80]. In conclusion, LSG seems to have a substantial beneficial influence on T2DM, producing resolution in the majority of patients included in the studies.

List of Abbreviations

T2DM	Type 2 Diabetes Mellitus
LSG	Laparoscopic Sleeve Gastrectomy

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