Long-term Metabolic Effects of Laparoscopic Sleeve Gastrectomy

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IMPORTANCE The prevalence of laparoscopic sleeve gastrectomy (LSG) is increasing, but data on its long-term effect on obesity-related comorbidities are scarce. Because the population of bariatric patients is young, long-term results of those comorbidities are highly relevant.

OBJECTIVE To investigate the long-term effects of LSG on weight loss, diabetes mellitus, hypertension, dyslipidemia, and hyperuricemia.

DESIGN, SETTING, AND PARTICIPANTS Cohort study using a retrospective analysis of a prospective cohort at a university hospital. Data were collected from all patients undergoing LSGs performed by the same team between April 1, 2006, and February 28, 2013, including demographic details, weight follow-up, blood test results, and information on medications and comorbidities.

MAIN OUTCOMES AND MEASURES Excess weight loss, obesity-related comorbidities, and partial and complete remission at 1, 3, and 5 years of follow-up.

RESULTS A total of 443 LSGs were performed. Complete data were available for 241 of the 443 patients (54.4%) at the 1-year follow-up, for 128 of 259 patients (49.4%) at the 3-year follow-up, and for 39 of 56 patients (69.6%) at the 5-year follow-up. The percentage of excess weight loss was 76.8%, 69.7%, and 56.1%, respectively. Complete remission of diabetes was maintained in 50.7%, 38.2%, and 20.0%, respectively, and remission of hypertension was maintained in 46.3%, 48.0%, and 45.5%, respectively. Changes in high-density lipoprotein cholesterol level (mean [SD] level preoperatively and at 1, 3, and 5 years, 46.7 [15.8], 52.8 [13.6], 56.8 [16.0], and 52.4 [13.8] mg/dL, respectively) and triglyceride level (mean [SD] level preoperatively and at 1, 3, and 5 years, 155.2 [86.1], 106.3 [45.3], 107.2 [53.4], and 126.4 [59.7] mg/dL, respectively) were significant compared with preoperative and postoperative measurements ($P < .001$). The decrease of low-density lipoprotein cholesterol level was significant only at 1 year ($P = .04$) and 3 years ($P = .04$) (mean [SD] level preoperatively and at 1, 3, and 5 years, 115.8 [33.2], 110.8 [32.0], 105.7 [25.9], and 110.6 [28.3] mg/dL, respectively). The changes in total cholesterol level did not reach statistical significance (mean [SD] level preoperatively and at 1, 3, and 5 years, 189.5 [38.2], 184.0 [35.4], 183.4 [31.2], and 188.1 [35.7] mg/dL, respectively). No changes in comorbidity status correlated with preoperative excess weight. Hypertriglyceridemia was the only comorbidity whose remission rates at 1 year of follow-up (partial/complete, 80.6%; complete, 72.2%) correlated with percentage of excess weight loss (76.8%) ($P = .005$).

CONCLUSIONS AND RELEVANCE Undergoing LSG induced efficient weight loss and a major improvement in obesity-related comorbidities, with mostly no correlation to percentage of excess weight loss. There was a significant weight regain and a decrease in remission rates of diabetes and, to a lesser extent, other comorbidities over time.

Obesity was recognized as a global epidemic by the World Health Organization 15 years ago and rates of obesity have since been increasing. Obesity is currently considered a severe health hazard and a risk factor for diabetes mellitus, hypertension, dyslipidemia, heart failure, and many other related comorbidities. Obesity causes increased risk for cardiovascular disease, even after eliminating other risk factors. It is also a significant independent predictor of renal failure, inflammation, and many other comorbidities.

Bariatric procedures are reportedly the most effective strategy to induce weight loss compared with nonsurgical interventions. Laparoscopic sleeve gastrectomy (LSG) is a common and efficient bariatric procedure with increasing popularity in the Western world during the last few years. Both intermediate and long-term data on LSG remain limited. Most of the earlier analyses had focused on weight loss and the remission of diabetes, even though hypertension, dyslipidemia, and hyperuricemia are also comorbidities commonly related to obesity. Moreover, most of the information on dyslipidemia is based on records from follow-up of 2 years or less, and there are relatively few data on the long-term effects of LSG on these and other comorbidities.

In this study, we aimed to determine the effect of LSG on diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia after 1, 3, and 5 years. We also sought to establish whether the remission of any of those obesity-related comorbidities is correlated with weight loss and which patients would be most likely to benefit from this procedure. The choice of bariatric procedure currently depends on the surgeon’s preference, and there are few objective data to compare the different approaches and their impact on specific comorbidities. This information is crucial to allow patients and physicians to choose the most appropriate procedure according to the specific needs of each patient. The primary end points of this study were excess weight loss and partial and complete remission of obesity-related comorbidities.

**Methods**

This cohort study is a retrospective analysis of prospectively collected data. Between April 1, 2006, and February 28, 2013, 1098 obese patients underwent bariatric surgery by the same surgical team. Of these, 443 underwent LSG. All patients had fulfilled the criteria for undergoing bariatric surgery established by the National Institutes of Health Consensus Conference. They were assigned to undergo an LSG based on clinical criteria, patient choice, and the consensus of the bariatric clinic team. Potential advantages, disadvantages, and risks of all procedures were explained in detail. The study was approved by the Rabin Medical Center Institutional Review Board. Owing to the retrospective nature of the study, a waiver of informed consent was granted.

**Surgical Technique**

All the LSGs were performed by the same surgical team. The gastric tube was created using a 32Fr to 40Fr bougie. Stomach resection started 2 to 4 cm from the pylorus. Sleeve volume ranged from 60 to 100 mL. Selective inversion of the staple line by seroserosal continuous suture (bougie in) was performed. Only the areas of bleeding or staples crisscrossing or where the staples seemed to not fit perfectly were oversutured.

The methylene blue dye leak test was used to ensure an intact staple line. The percentage of excess weight loss (%EWL) was calculated by assuming a normalized body weight at a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 25 and determined by dividing the postoperative weight loss by the preoperative excess weight and multiplying the result by 100.

**Patient Care**

Demographic data and the results of baseline blood tests were collected. Type 2 diabetes mellitus (T2DM) was defined as a fasting glucose level higher than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) and glycated hemoglobin greater than 6% of total hemoglobin (to convert to proportion of total hemoglobin, multiply by 0.01), or any levels in a patient receiving antihyperglycemic treatment. Impaired fasting glucose (IFG) was defined as a fasting glucose level higher than 100 mg/dL and lower than 126 mg/dL in patients with no use of antihyperglycemic treatment. Hypercholesterolemia was defined as a total cholesterol level higher than 200 mg/dL (to convert to millimoles per liter, multiply by 0.0259). Hypertriglyceridemia was defined as a triglyceride level higher than 150 mg/dL (to convert to millimoles per liter, multiply by 0.0113). Hypertension was defined as blood pressure higher than 140/90 mm Hg on more than 3 occasions or the use of medications to treat hypertension. Hyperuricemia was defined as a plasma uric acid level higher than 6.8 mg/dL (to convert to micromoles per liter, multiply by 59.485). Preoperative and postoperative laboratory assessments included a complete blood cell count and ferritin, albumin, fasting glucose, glycated hemoglobin, lipid profile, serum folate, vitamin B₁₂, vitamin D, and parathyroid hormone analyses. Information on medication use was also collected prior to the surgery.

The postoperative follow-up was scheduled to take place at 1, 3, 6, and 12 months and every year thereafter. Data were gathered from hospital medical records, postoperative office visit findings, and telephone interviews. Remissions of T2DM and IFG were defined as a normal fasting glucose level (<100 mg/dL) and a normal glycated hemoglobin level (<6% of total hemoglobin), respectively, with no use of insulin or oral medications. Partial remission for T2DM was defined as a reduction of medication dosage or cessation of medication use despite abnormal laboratory results. No partial remission was defined for IFG. For arterial hypertension, normal blood pressure without medication was considered remission and a decrease of medication dosage was considered partial remission. Remission of hyperlipidemia was defined as cessation of medication use with normal laboratory results. Partial remission was defined as reduction of medication dosage or cessation of medication use despite abnormal laboratory results.

**Statistical Analysis**

The statistical analysis was performed using SAS version 9.4 statistical software (SAS Institute, Inc). Continuous variables are presented as mean (standard deviation). Categorical variables are presented as number (percentage). The t test was used...
to compare the value of continuous variables between study groups, and the χ² test was used to compare categorical variables between study groups. The paired t test was used to assess changes in clinical measures for patients at different times. Statistical significance was reached at $P < .05$.

**Results**

Of the total of 1098 patients who underwent bariatric surgery between April 1, 2006, and February 28, 2013, 443 underwent LSG. Complete data were available for 241 of the 443 patients (54.4%) at the 1-year follow-up, for 128 of 259 patients (49.4%) at the 3-year follow-up, and for 39 of 56 patients (69.6%) at the 5-year follow-up. The study patients’ mean (SD) age was 42.2 (12.4) years (range, 13-72 years), and their relevant characteristics are listed in Table 1.

Prior to undergoing the surgery, 82 patients had been diagnosed as having T2DM, 65 as having IFG, 110 as having hypertension, 155 as having hypercholesterolemia, 109 as having hypertriglyceridemia, and 55 as having hyperuricemia. The rates of patients who had partial or complete remission at 1, 3, and 5 years of follow-up are shown in Table 2. The rates of patients who stopped using medications for T2DM were 64.5% at 1 year of follow-up, 48.3% at 3 years, and 55.5% at 5 years. In patients with preoperative insulin use, rates of cessation of medication use were drastically lower than in the general T2DM population: 36.8%, 9.1%, and 0.0% at 1, 3, and 5 years, respectively. Complete remission of diabetes was maintained in 50.7%, 38.2%, and 20.0%, respectively, and remission of hypertension was maintained in 46.3%, 48.0%, and 45.5%, respectively.

**Effect on Weight Loss**

The mean (SD) preoperative excess weight was 51.2 (18.4) kg, and the mean (SD) preoperative BMI was 43.9 (6.6). At 1 year of follow-up, the mean (SD) body weight was 81.4 (16.7) kg, the mean (SD) BMI was 29.9 (5.1), and the %EWL was 76.8%. At 3 years of follow-up, the mean (SD) body weight was 84.1 (17.2) kg, the mean BMI was 30.8 (5.3), and the %EWL was 69.7%. At 5 years of follow-up, the mean (SD) BMI was 32.3 (5.1), and the %EWL was 56.1%. There was a significant decrease in %EWL between patients with 1 and 3 years of follow-up or patients with 1 and 5 years of follow-up ($-4.8\%$, $P = .007$; and $-16.3\%$, $P < .001$, respectively). The decrease in %EWL between 3 and 5 years was not statistically significant ($P = .07$). The failure rates, determined as the percentage of patients with a %EWL less than 50%, were 13.3%, 21.1%, and 38.5% at 1, 3, and 5 years, respectively. There was no mortality, and the leak rates were 1.3% and 3.1% in the primary and conversion procedures, respectively. Eighteen patients underwent conversion to another bariatric procedure and were excluded from follow-up following the conversion.

**Postoperative Changes in Lipid Profiles**

The changes in the high-density lipoprotein (HDL) cholesterol and triglyceride levels were significant compared with the
Table 3. Changes in Lipoprotein Profile

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>Follow-up, y</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>189.5 (38.2)</td>
<td>184.0 (35.4)</td>
<td>183.4 (31.2)</td>
</tr>
<tr>
<td>HDL</td>
<td>46.7 (15.8)</td>
<td>52.8 (13.6)</td>
<td>56.8 (16.0)</td>
</tr>
<tr>
<td>LDL</td>
<td>115.8 (33.2)</td>
<td>110.8 (32.0)</td>
<td>105.7 (25.9)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>155.2 (86.1)</td>
<td>106.3 (45.3)</td>
<td>107.2 (53.4)</td>
</tr>
</tbody>
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Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

Discussion

The increasing prevalence of obesity and the consensus that bariatric procedures are the most effective methods of weight loss have led to the spiraling growth of these procedures. Indeed, they are among the most commonly performed gastrointestinal operations worldwide. Initially LSG had been described as part of the duodenal switch, but its success led to the suggestion that it could be used as a single and definitive procedure for morbid obesity. In 2012, the American Society for Metabolic and Bariatric Surgery noted that several matched-cohort, prospective, and case-control studies demonstrated that LSG was equivalent to or exceeded Roux-en-Y gastric bypass (RYGB) surgery as well as laparoscopic adjustable gastric bypass surgery in terms of weight loss outcomes and improvements in a variety of obesity-related comorbidities after a short-term follow-up. Some of the advantages of LSG include technical cost efficiency and easy learnability, lack of an intestinal anastomosis, normal intestinal absorption, and pylorus preservation. Long-term follow-up data on the status of those comorbidities following LSG, however, are sparse.

Reports on long-term results of LSG usually focused on weight loss. In 2004, Sjöström et al reported a significant regain of body weight after 2 and 10 years following bariatric operations. Long-term %EWL reportedly varied widely (46%-86%), with a decline at longer follow-ups. Our findings agree with those results. The %EWL in our study groups decreased from 76.8% at 1 year to 69.7% at 3 years and 56.1% at 5 years of follow-up. The difference in %EWL between 1 and 3 years as well as between 1 and 5 years was statistically significant, but the difference in %EWL between 3 and 5 years was not. This might imply that a major part of the weight regain occurs in the first few years following the surgery. Furthermore, the failure rate, defined as the percentage of patients with a %EWL less than 50%, increased from 13.3% at 1 year of follow-up to 21.1% at 3 years and 38.5% at 5 years.

The success of bariatric surgery is usually defined by long-term weight loss, enduring improvement in comorbidities, and low mortality and morbidity rates. Rather than being considered a priority, the effect of these procedures on obesity-related comorbidities is usually not taken into consideration when analyzing the results. Because the mean age of patients undergoing bariatric surgery is usually 40 to 50 years, long-term results of those comorbidities are both attainable and highly relevant.

Vest et al performed a meta-analysis of different types of bariatric surgery and cardiovascular outcomes. Ten of the 73 articles they reviewed included information on LSG, and the length of follow-up ranged from 3 months to 14.5 years (mean, 4.8 years). The rates of partial or complete remission were 73% for diabetes, 63% for hypertension, and 73% for hyperlipidemia. Gill et al systematically reviewed the effect of sleeve gastrectomy on diabetes mellitus and reported that the complete and partial remission rates at 13 months of follow-up were 66% and 27%, respectively. Sarkhosh et al reviewed the effect of LSG on hypertension and found that 58% of patients showed remission at a mean of 17 months. The success of LSG on hyperlipidemia was recently reviewed by Al Khalifa et al, who reported that the partial and complete remission rate at 17 months was 83.5% and that the mean (SD) preoperative and postoperative cholesterol levels were 194.4 (12.3) mg/dL (range, 178-213 mg/dL) and 181 (16.3) mg/dL (range, 158-200 mg/dL), respectively.
Reports on partial and complete remission of obesity-related comorbidities after 3 or more years of follow-up after LSG are scarce. In a systematic review by Brethauer et al, only 1 of the 10 studies on postoperative comorbidity status had data from follow-up longer than 24 months. The range of partial and complete remission is quite wide in the studies on the effect of surgery on such comorbidities with a longer follow-up. In their randomized trial, Schauer et al compared the remission rates of T2DM after LSG, RYGB, and medical therapy at 3 years of follow-up and found that 24% of the patients who underwent LSG had complete remission compared with 38% who underwent RYGB and 5% who underwent medical therapy. Atkins et al described remission rates of 74.5%, 49.5%, and 26.5% for T2DM, hypertension, and hyperlipidemia, respectively, at 4 years of follow-up. Other studies with medium-term follow-up reported remission rates of 67% to 86% for T2DM, hypertension, and hyperlipidemia. Our complete remission rates were lower: 38.2% for T2DM, 48.0% for hypertension, 45.6% for hypercholesterolemia, and 66.0% for hypertriglyceridemia at 3 years of follow-up. Lower remission rates could be attributed to stricter criteria, definition of remission, and interpretation of the laboratory results. Studies also use different end points, making it difficult to compare data. The definition of remission is especially important in the current context. A consensus statement of the American Diabetes Association defined complete remission of diabetes as normal glycemic measures without the use of pharmacologic therapy for 1 year or longer. In this study, however, we defined remission as normal postoperative glycemic measures without medications, as reported in several other studies. One major additional drawback is the definition of the term partial remission. Some studies define it as the reduction of medication, some as reduced severity of associated symptoms, and some as the normalization of laboratory results. Clearly, different definitions cause vagueness of data. In this study, we defined partial remission as the reduction of medication dosage or the cessation of medication use despite abnormal laboratory results. Moreover, our study showed that 64.5% of patients with preoperative use of antidiabetics stopped using medications after 1 year of follow-up, with the rates at 3 and 5 years decreasing to 48.3% and 55.5%, respectively. The majority of the patients with preoperative insulin use did not require insulin treatment postoperatively: 63.2% and 54.5% of patients stopped using insulin or were treated with oral diabetic agents only at 1 and 3 years of follow-up, respectively. These results are lower than the rates of reduction of insulin and oral diabetic agents reported by Schauer et al following RYGB.

Complete remission rates in patients with preoperative insulin use were much lower than complete remission rates in the general T2DM population. This demonstrates the effect of preoperative characteristics on remission rates. It is well known that the severity of diabetes prior to surgery affects the remission rates. Therefore, diabetic patients with a long-standing disease who are referred to the bariatric clinic as a last resort cannot be compared with patients who undergo surgery shortly after being diagnosed as having diabetes. As such, the differences between the reported remission rates may reflect the differences in the levels of awareness of diabetologists.

The influence of LSG on hyperlipidemia warrants special attention. Hyperlipidemia comprises 4 variables: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. In a recent analysis of changes in lipid profile in patients after LSG, Zhang et al noted that only HDL cholesterol and triglyceride levels changed significantly. We also observed a significant change in LDL cholesterol, HDL cholesterol, and triglyceride levels, but the change in total cholesterol level did not reach statistical significance. In addition, there was no significant difference between the changes in the different follow-up points, which means that the improvement in HDL cholesterol and triglyceride levels did not deteriorate significantly over time. A confounding factor of these results could be the cessation of use of antihyperlipidemic agents.

Many authors have focused their studies on the comparison of different bariatric procedures. In a recent meta-analysis, RYGB and LSG were found to have an equivalent effect on hypertension and dyslipidemia, although RYGB was found to achieve better control of T2DM. It should be noted that most studies included in that meta-analysis reported data that were retrieved after a follow-up of 2 years or less. Schauer et al also found RYGB to be superior to LSG in terms of the likelihood of achieving a glycated hemoglobin level of 7% of total hemoglobin or less with no use of diabetes medications after 3 years of follow-up. Another study that compared the improvement of the lipid profile following LSG and RYGB found that RYGB had a clear benefit in all lipid fractions.

Surprisingly, our results showed that none of the changes in obesity-related comorbidity status correlated with excess weight prior to the surgery. Patients with preoperative T2DM were less likely to show a remission of hypertension and hypertriglyceridemia. As described by others, age was a negative predictive factor for partial or complete remission of hypertension in our study. Partial and complete remission of hypertension also correlated with preoperative hypertriglyceridemia. Hypertriglyceridemia was the only comorbidity whose remission rates correlated with %EWL. Finally, there was a decline in the rates of remission of diabetes at 1, 3, and 5 years of follow-up.

In our opinion, the presence of obesity-related comorbidities should play a major role when choosing the appropriate procedure for a specific patient. For example, performing an operation that yields a low resolution rate of hyperlipidemia translates into lifelong medical treatment in a young patient with significant hyperlipidemia. In that case, a malabsorptive procedure might be more beneficial than an LSG procedure. If the recurrence of obesity is known to be followed by the remittance of an existing comorbidity in a specific procedure, an alternative procedure should be considered. For example, the weight loss durability failure of almost 40% at 5 years of follow-up of the LSG should be one of the deciding factors in such cases.

Our study has several limitations. First, patients lost to follow-up may cause a bias because their characteristics and reasons for not arriving at follow-up visits are unknown. However, the follow-up rates in this study are comparable to those in other long-term studies and our data included all patients’ relevant laboratory results. Another limitation is that the follow-up was not continuous for all patients and some follow-up data were available for only 1 year. Also, the small
sample size at 5 years of follow-up precludes arriving at firm conclusions regarding the changes in their obesity-related comorbidities.

Conclusions
The results of this analysis demonstrated that %EWL decreased with longer follow-up. Furthermore, partial and complete remission rates of T2DM were significantly lower when follow-up was longer. Undergoing LSG induced a reduction in %EWL and a major improvement in obesity-related comorbidities in the short-term. The longer follow-up data revealed weight regain and a decrease in remission rates for T2DM and other obesity-related comorbidities. These data should be taken into consideration in the decision-making process for the most appropriate operation for a given obese patient.

REFERENCES
No Rush to Judgment for Bariatric Surgery

Anita P. Courcoulas, MD, MPH

It is unclear whether current studies will address critical questions about the long-term outcomes of bariatric surgery, including the sustainability of weight loss and comorbidity control and long-term complication rates. These critical gaps in knowledge pose a significant problem for people considering a potential surgical option to treat severe obesity.

Contributing to these deficits are the paucity of comparative trials, incomplete follow-up, a lack of standardized definitions for changes in health status (eg, diabetes mellitus remission), and the tendency to rush to judgment in favor of surgical treatment options.

Laparoscopic sleeve gastrectomy is a good case in point, evolving very quickly during the last several years into the dominant procedure in use despite a complete void of information about the longer-term effects. Golomb et al3 try to address this by documenting 1-, 3-, and 5-year results in a cohort of 443 sleeve gastrectomy cases but clearly raise more issues than they can answer. They show that both weight loss and type 2 diabetes remission degrade substantially over time: excess weight loss from 77% to 56% and complete remission of diabetes from 51% to 20% between 1 and 5 years. The results are from only 56 people available for 5-year follow-up and with rates of loss to follow-up of 50%, on average, at 1 and 3 years. One must assume that people lost to follow-up may differ in important ways. In addition, there are no standards to report comorbid health changes following bariatric surgery, which limits the ability to compare results across studies. Golomb and colleagues do an excellent job of outlining the study’s own specific definitions of prevalence, incidence, and remission of type 2 diabetes and other health outcomes, but these are neither standard nor shared between members of the research community.

How can these problems be addressed? Large, prospective observational studies such as the Longitudinal Assessment of Bariatric Surgery Consortium study report standardized definitions and do better with long-term retention, but the burden of work and subsequent high cost are problematic in a highly competitive funding environment. The issues of cost and feasibility also make a large randomized trial that could compare surgical procedures across heterogeneous populations impractical. There is hope for the use of large electronic databases to contribute to these knowledge gaps, but the handling of large amounts of missing data is a critical feature that is often not well articulated by the authors or well understood by the readers. The answers will likely be generated over time not only by a few of these large-scale efforts but also by thoughtful inference that will be made through pooled analyses of data like that from Golomb and colleagues and from many other disparate randomized and nonrandomized studies of bariatric surgery. It will take time, patience, and a willingness to avoid a rush to judgment. In the meantime, clinicians and prospective patients will need to discuss and weigh the evidence in a dynamic exchange driven not always by final conclusions but by the most current available data.