Original research

Sleeve gastrectomy and Roux-en-Y gastric bypass are equally effective in correcting insulin resistance

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A B S T R A C T

Background: Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are associated with glucose metabolism improvement although data on insulin resistance remission rates after these procedures are lacking.

Aims: Primary aim was to compare insulin resistance remission rates achieved after LRYGB and LSG, using population-specific HOMA-IR cut-off points. Secondary objectives were to analyze factors associated with type 2 diabetes mellitus (T2DM) complete remission according to the new American Diabetes Association criteria and to examine changes in HOMA-B during follow-up.

Methods: Non-randomized, prospective cohort study of patients undergoing LRYGB or LSG with a minimal follow-up of 24 months. Patients on insulin therapy were excluded.

Results: At baseline, 56 (48.7%) of the 115 LRYGB group and 48 (61.5%) of the 78 LSG group had insulin resistance, and 29 (25.2%) and 20 (25.6%) T2DM, respectively. No differences were detected in insulin resistance remission rate (92.9% LRYGB and 87.5% LSG, \( p = 0.355 \)) nor in T2DM complete remission at 2 years (62.1 vs 60% respectively, \( p = 0.992 \)). Factors independently associated with T2DM complete remission were diabetes treatment and a greater decrease in 3-month HOMA-IR index. The HOMA-B index showed a progressive decline during follow-up.

Conclusion: Both surgical techniques are equally effective in achieving insulin resistance normalization in the majority of severely obese patients. Three-month HOMA-IR reduction after surgery was the main predictor of T2DM complete remission.

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1. Introduction

In addition to weight loss, some bariatric procedures appear to have independent metabolic benefits associated with incretin effects and possibly other hormonal and neural mechanisms. In this respect, laparoscopic sleeve gastrectomy (LSG) has yielded better results than other restrictive techniques in terms of weight loss and improved glucose metabolism but similar or slightly inferior outcomes when compared with hybrid techniques such as laparoscopic Roux-en-Y gastric bypass (LRYGB). Although the beneficial effects of bariatric surgery on glucose metabolism are known, data on insulin resistance remission rates after surgery are lacking. In clinical practice, insulin resistance and beta-cell function have been assessed over the last 20 years by the homeostatic model assessment (HOMA-IR and HOMA-B, respectively). Despite a good correlation with the euglycemic hyperinsulinemic clamp method, the HOMA-B index varies widely among populations and in T2DM complete remission at 2 years. Therefore, specific cut-off points to define insulin resistance in each population should be established.

Given the terminological problems of “remission” versus “cure” and the great heterogeneity among studies in defining remission criteria for type 2 diabetes mellitus (T2DM), the American Diabetes Association (ADA) in 2009 defined and agreed the criteria for partial and complete remission that are stricter than those previously used. Given the short time elapsed, scant studies have evaluated...
the remission rate of T2DM after bariatric surgery in obese diabetic patients with these new criteria.\textsuperscript{5}

The primary aim of the present study was to compare insulin resistance remission rates achieved after LRYGB and LSG, using population-specific HOMA-IR cut-off points. Secondary objectives were to examine T2DM complete remission rates after both techniques according to the new ADA criteria and possible associated factors and to study changes in HOMA-B during follow-up.

2. Material and methods

2.1. Study protocol

A non-randomized, prospective cohort study was conducted on severely obese patients undergoing bariatric surgery at the Hospital del Mar, Barcelona. Patients were aged between 18 and 55 years and met the 1991 bariatric surgery criteria of the National Institutes of Health.\textsuperscript{11} Indication for the type of surgical procedure (LRYGB or LSG) was based on clinical criteria and the consensus of the Hospital del Mar Bariatric Surgery Unit. In this respect, LSG was preferred in younger patients, in

2 patients who did not complete two years of follow-up were excluded

4 patients who did not complete two years of follow-up were excluded

1 patient receiving insulin was excluded

1 patient receiving insulin was excluded

115 LRYGB patients completed primary outcome analysis

78 LSG patients completed primary outcome analysis

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Fig. 1. Study flow diagram. LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass. No fatal cases were observed.

2.2. Anthropometric and biochemical measurements

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The percentage of excess weight loss (% EWL) was calculated based on the excess weight above ideal weight (weight corresponding to BMI of 25 kg/m\textsuperscript{2}). T2DM diagnosis was defined as two fasting plasma glucose concentrations above 125 mg/dl or HbA\textsubscript{1c} $>6.5\%$ or treatment with oral hypoglycemic agents or insulin.\textsuperscript{12}

Glucose was determined by the oxidase method. HbA\textsubscript{1c} was quantified by chromatography (Biocheck, Barcelona, Spain). Insulin was measured by radioimmunoassay (Insulin kit, DPC, Los Angeles, USA). HOMA indexes were estimated using the following formulas:\textsuperscript{6} HOMA-IR = insulin (\textmu U/ml) $\times$ fasting glucose (mmol/l) / 22.5 and HOMA-B = $20 \times$ insulin (\textmu U/ml) / glucose (mmol/l) $- 3.5$.

In accordance with data from our population, the cut-off for the HOMA-IR index to define insulin resistance was a level $\geq 3.29$.\textsuperscript{7} Thus, HOMA $<$ 3.29 in patients not using insulin-sensitizing drugs (metformin or glitazones) was established as a criterion of insulin resistance normalization.

T2DM complete remission was defined based on the ADA consensus as a plasma glucose $< 100$ mg/dl with an HbA\textsubscript{1c} $< 6.0\%$ without drug therapy maintained for at least one year.\textsuperscript{10}

2.3. Surgical techniques

The LRYGB technique involved a 150-cm antecolic and antegastric Roux limb with 25-mm circular pouch-jejunostomy, with the exclusion of 50 cm of the proximal jejunum. In LSG, the longitudinal resection of the stomach from the angle of His to approximately 5 cm proximal to the pylorus was performed using a 36 French

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of severely obese patients undergoing LRYGB or LSG with a minimum of two years of follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LRYGB (n = 115)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.0 ± 8.6</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>87.8</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>119.8 ± 15.8</td>
</tr>
<tr>
<td>Body mass index (Kg/m\textsuperscript{2})</td>
<td>45.8 ± 4.3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>127.6 ± 11.0</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>110.2 ± 26.7</td>
</tr>
<tr>
<td>Insulin (\textmu U/ml)</td>
<td>14.7 ± 8.7</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.1 ± 2.8</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>140.4 ± 133.1</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>5.6 ± 0.8</td>
</tr>
<tr>
<td>Insulin resistance (%)</td>
<td>56 (48.7)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (%)</td>
<td>29 (25.2)</td>
</tr>
</tbody>
</table>

LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; HOMA, Homeostatic Model Assessment.

Data presented as mean ± standard deviation or percentages. Significance at $p < 0.05$ was determined using Student’s t-test for continuous variables and chi-square for categorical variables.
Changes in HOMA during follow-up after the bariatric surgical procedure. LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy. Data are expressed as means. Significance at p < 0.05 was determined using Student’s t-test.

**3. Results**

All 193 patients of the study were Caucasian, with a mean age of 45.2 ± 8.7 years, baseline BMI of 45.0 ± 4.7 kg/m² and mean follow-up of 2.9 ± 0.9 years. Baseline characteristics of LRYGB and LSG patients are listed in Table 1. Patients in the LRYGB group differed from the LSG group in a higher proportion of women and BMI.

Progressive weight loss, more marked during the first 3 months in the LSG group, was observed in both groups during the first year of follow-up. Thereafter, weight loss remained stable and without differences between groups (Fig. 2).

At baseline, 56 (48.7%) patients of the LRYGB group and 48 (61.5%) of the LSG had insulin resistance. Three months after surgery, HOMA-IR had decreased dramatically in both groups (Fig. 3A), with a remission rate of 91.1% in the LRYGB patients and 91.7% in the LSG, p = 0.914. Insulin resistance remission rate achieved after 2 years of follow-up was 92.9% in LRYB group and 87.5% in LSG (p = 0.355). The HOMA-B index progressively decreased in both groups during follow-up; however, it was significantly higher in the LSG group at the second and third year post-bariatric surgery (Fig. 3B).

No differences were observed in baseline characteristics of T2DM patients between groups (Table 2). According to the applied bariatric surgery technique, no differences were found in the T2DM complete remission rate (62.1% for LRYGB and 60% for LSG, p = 0.992). Factors independently associated with T2DM complete remission were preoperative diabetes treatment with diet only, compared with oral drug treatment, and a greater decrease in HOMA-IR index values three months post-surgery (Table 3).

**4. Discussion**

The present study showed that two different bariatric surgery techniques, LRYGB and LSG, are equally effective in achieving insulin resistance normalization using a population-specific HOMA-IR cut-off.

Insulin resistance normalization was attained with both surgical techniques in almost all patients as early as 3 months after surgery. This finding suggests that weight loss was not the only factor responsible for the decline in HOMA-IR after bariatric surgery. Previous studies found that surgical techniques with a malabsorptive component like LRYGB produce a greater HOMA-IR reduction than that obtained after restrictive techniques such as vertical banded gastropasty. Furthermore, this reduction occurred soon after the procedure, when significant weight loss had not yet been achieved.1 These findings could be explained by changes in gut hormonal mechanisms, such as increased secretion of incretins that enhance insulin sensitivity.13,14 In the present study, LSG, despite being a restrictive technique, produced an early improvement in insulin sensitivity of a similar magnitude to that achieved with LRYGB. A possible explanation for this finding could be related to the characteristics of the LSG technique. LSG includes a gastric fundus resection, unlike other restrictive techniques, that causes a decrease in ghrelin concentration, a hormone that produces insulin resistance.15–27

In the present study, all patients met the criteria for partial remission and approximately 60% for complete T2DM remission after a 2 year-follow-up. In other studies comparing LRYGB and LSG,
the overall remission rate of T2DM was above 80% with both techniques.18–24 The lower T2DM remission rate found in the present study could be explained by at least two facts. First, in previous studies there was a wide heterogeneity in the criteria used for diabetes remission. In some studies, remission criteria were non-specified19,20,22 others only included diabetes medication withdrawal23,24 while others used HbA1c < 6.5% and fasting glucose < 125 mg/dl once medication had been withdrawn.18,21 And second, in addition to stricter biochemical criteria for T2DM remission (fasting glucose < 100 mg/dl and HbA1c < 6.0%), the new ADA criteria require these biochemical parameters to be maintained for at least one year.10

In obese patients with short T2DM duration, such as those in our study population, insulin resistance predominates over beta-cell dysfunction.25 Therefore, in these patients, enhancement of insulin sensitivity is a key factor for glucose metabolism improvement. This is consistent with the finding that HOMA-IR reduction 3 months post-surgery was a predictor of T2DM complete remission two years after the procedure. Moreover, the short duration of diabetes of the subjects included in this study may explain the lack of association of diabetes remission with other factors previously described such as waist circumference and T2DM duration.20,27

The HOMA-B index is a marker of pancreatic beta-cell function. In a healthy subject with a normal BMI and no family history of diabetes mellitus, the HOMA-B index is expected to be close to 100, indicating optimal beta-cell function (100%). Subjects in the present study had a mean baseline level above 100 that progressively decreased during follow-up. These results suggest that, preoperatively, beta cells in these patients had a compensatory hyperfunction and, after bariatric surgery, insulin resistance remission caused a decline in this compensatory insulin secretion, reflected in a reduction in the HOMA-B index. On the other hand, surgical techniques with a malabsorptive component cause an increase in hormones with an incretin effect. These hormones raise insulin secretion, but only in the postprandial period. Therefore, the HOMA-B index, which estimates beta-cell function in the fasting state, would not be the optimal method of evaluating postprandial insulin secretion improvement in these patients.28

The present study was not without limitations. First, patients were not randomly assigned to either of the bariatric surgery techniques and therefore the baseline characteristics of patients included in each group were not comparable. Second, diabetic patients included in the present study had a short disease duration, the majority did not require pharmacological treatment and those on insulin therapy were excluded. Therefore, the results found cannot be generalized to the whole diabetic population. Finally, insulin resistance was assessed using the HOMA-IR index; however, a more accurate method for quantifying insulin resistance, the euglycemic hyperinsulimemic clamp, was not used since it is invasive and time-consuming.

5. Conclusion

In conclusion, LRYGB and LSG are equally effective in achieving insulin resistance normalization in almost all patients. Furthermore, both techniques achieved similar T2DM complete remission rates and HOMA-IR reduction at 3 months after surgery was the main predictor. The HOMA-B index should be carefully interpreted in these patients.

Ethical approval

Study protocol was approved by the hospital del mar (Barcelona) Ethics Committee.

Funding

None.

Author contribution

BD contributed for the study design, data collection, data analysis and writing.
FLRJA contributed for the study design and writing.
PBJ contributed for the data analysis and writing.
CJJ contributed for the data analysis and writing.
PA contributed for the data collection.
RM contributed for the data collection.
RJM contributed for the study design.
PM contributed for the study design.
GA contributed for the study design, data analysis and writing.

Conflict of interest

The authors declare no potential conflicts of interest relevant to this article.

References


Table 2

| Baseline characteristics of severely obese patients with type 2 diabetes mellitus undergoing LRYGB or LSG with a minimum of two years of follow-up. |
|---------------------------------|--------------------------|--------------------------|
| Age (years) | 49.2 ± 6.2 | 50.6 ± 7.4 | 0.488 |
| Gender (% female) | 79.3 | 75.0 | 0.492 |
| Body mass index (Kg/m²) | 45.7 ± 4.6 | 45.6 ± 5.8 | 0.954 |
| Treatment | | | |
| Diet alone (%) | 16 (55.2) | 7 (35) | 0.164 |
| Oral hypoglycemic drugs (%) | 13 (44.8) | 13 (65) | 0.227 |
| Duration of diabetes (years) | 1.3 ± 2.4 | 1.5 ± 2.5 | 0.746 |
| Fasting glucose (mg/dl) | 143.1 ± 31.0 | 150.0 ± 25.9 | 0.415 |
| HbA1c (%) | 6.5 ± 0.8 | 6.9 ± 0.7 | 0.113 |
| HOMA-IR | 6.1 ± 3.3 | 7.6 ± 4.8 | 0.212 |
| HOMA-B | 123.0 ± 207.6 | 91.3 ± 81.9 | 0.553 |

HbA1c, glycosylated hemoglobin; HOMA, Homeostatic Model Assessment.
Data presented as mean ± standard deviation or percentages. Significance at p < 0.05 was determined using Student’s t test for continuous variables and Chi-square for categorical variables.

Table 3

<table>
<thead>
<tr>
<th>Factors related to complete remission of type 2 diabetes mellitus two years after surgery</th>
<th>OR (95% confidence interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.91 (0.78–1.06)</td>
<td>0.217</td>
</tr>
<tr>
<td>Diet therapy alone</td>
<td>9.69 (1.36–69.10)</td>
<td>0.023</td>
</tr>
<tr>
<td>LRYGB</td>
<td>0.71 (0.11–4.77)</td>
<td>0.722</td>
</tr>
<tr>
<td>Decrease in HOMA-IR units at 3 months</td>
<td>1.31 (1.01–1.70)</td>
<td>0.045</td>
</tr>
<tr>
<td>% EWL at 3 months</td>
<td>1.07 (0.99–1.14)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

LRYGB, laparoscopic Roux-en-Y gastric bypass; HOMA, Homeostatic Model Assessment; % EWL, percentage excess weight loss.


