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ORIGINAL ARTICLE

Effectiveness of Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy on Lipid Levels in Type 2 Diabetes: a Meta-analysis

Cecilia Closs[1] · Marianela Ackerman[2] · Walter Masson[3] · Martin Lobo[4] · Graciela Molinero[4] · Augusto Lavalle-Cobo[4] · Sophie Béliard[5] · Florian Mourre[5] · René Valéro[5] · Juan Patricio Nogueira[6]

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Abstract

Introduction Obesity and its co-morbidities, including type 2 diabetes (T2DM) and dyslipidemia, are accompanied by excess cardiovascular morbi-mortality. Aside from excess low density lipoprotein-cholesterol (LDL-C), atherogenic dyslipidemia (AD), mainly characterized by elevated triglycerides and decreased high density lipoprotein-cholesterol (HDL-C) levels, is often present in T2DM obese patients. Bariatric surgery, such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), has become a reference treatment in that population. However, the respective effects of RYGB vs SG on lipid metabolism in T2DM patients have been rarely studied.

Methods A meta-analysis of randomized controlled trials, comparing the effects of RGYBG vs SG on lipid metabolism 12 months after surgery in T2DM patients, was performed.

Results Four studies including a total of 298 patients (151 patients in the RYGB and 147 patients in the SG group) were examined. Despite a greater decrease in body mass index and greater improvement in glycemic control in RYGB compared to SG. RYGB vs SG was more effective in reducing total cholesterol, LDL-C, and non-HDL-C levels (mean difference [MD] −26.10 mg/dL, 95 % CI −38.88 to −13.50, p<0.00001; [MD] −20.10 mg/dL, 95 % CI −27.90 to −12.20, p<0.00001 and MD 31.90 mg/dl, 95 % CI −46.90 to −16.80, p<0.00001, respectively).

Conclusions The superiority of RYGB vs SG in reducing LDL-C, with an effect comparable to a moderate-intensity statin, suggests RYBG should be favored in hypercholesterolemic T2DM patients in order to further reduce cardiovascular risk.

Keywords Bariatric surgery · Type 2 diabetes mellitus · LDL-cholesterol · Sleeve gastrectomy · Roux-en-Y gastric bypass · Triglycerides · HDL-cholesterol · Lipids

✉ Juan Patricio Nogueira
nogueirajuanpatricio@gmail.com

1 Centro Medico Melian, Av. 9 de Julio 243, CP: 3600 Formosa, Argentina

2 Centro CIEN, Corrientes, Salta 1524, CP: 3400 Corrientes, Argentina

3 Hospital Italiano de Buenos Aires, Buenos Aires, Tte. Gral. Juan Domingo Perón 4190, CP:1199 Buenos Aires, Argentina

4 Consejo de Epidemiologia y Prevención, Sociedad Argentina de Cardiología, Azcuénaga 980, CP: 1115 Buenos Aires, Argentina

5 Aix Marseille Univ, APHM, INSERM, INRAE, C2VN, University Hospital La Conception, Department of Nutrition, Metabolic Diseases and Endocrinology, 147 Bd Baille, 13005 Marseille, France

6 Centro de Investigación en Endocrinología, Nutrición y Metabolismo (CIENM), Facultad de Ciencias de la Salud, Universidad Nacional de Formosa, Av. Gutnisky 3200, 3600 Formosa, Argentina

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Introduction

Obesity is a major health issue worldwide that is associated with several comorbidities including type 2 diabetes mellitus (T2DM) and dyslipidemia. The increasing prevalence of obesity is accompanied by an increasing prevalence of T2DM.[1] Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in patients with obesity and/or T2DM.[2] Elevated plasma low density lipoprotein-cholesterol (LDL-C) is the main cardiovascular lipid risk factor[3] but atherogenic dyslipidemia (AD), which is seen in insulin-resistant states, such as obesity and/or T2DM, accounts for a significant proportion of cardiovascular risk. AD is mainly characterized by elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs) from the liver (very low density lipoprotein or VLDL) and intestine (chylomicrons), small and dense low density lipoproteins (LDL) and decreased levels of high density lipoprotein-cholesterol (HDL-C).[4]

Bariatric surgery is currently the most effective treatment to induce weight loss in patients with severe and morbid obesity and leads to complete or partial remission of T2DM and improvement in cardiovascular risk factors such as hypertension and lipid abnormalities in a significant proportion of patients.[5] Bariatric surgery is superior to conventional medical treatment for weight loss and glycemic control in T2DM[6] and a significant body of evidence indicates that bariatric surgery reduces major cardiovascular events.[5]

Worldwide, the most commonly performed bariatric surgery procedures are sleeve gastrectomy (SG) and laparoscopic Roux-en-Y gastric bypass (RYGB). There is no strict recommendation for performing either SG or RYGB, and evaluating the differences in clinical trial outcomes would be very helpful in selecting the best surgical technique for a patient.

There is considerable ongoing investigation and debate regarding the mechanisms for postsurgical improvements in glycemic control.[7] In contrast, improvements in lipid levels have attracted less interest despite the fact that dyslipidemia (elevated LDL-C and AD) is an independent cardiovascular risk factor associated with the process of atherosclerosis, plaque formation, and rupture.[8] Many of the published randomized controlled clinical trials did not assess lipid parameters in their primary end points. Additionally, in many studies the percentage of patients undergoing prior and subsequent lipid-lowering treatments, or the class of lipid-lowering drugs used or their dose, were not reported.

Previously published studies have evaluated the association between bariatric surgery and changes in lipids in T2DM patients, although these results were conflicting.[6,9–11] To our knowledge, the only meta-analysis that has evaluated lipid parameters in diabetic but also in non-diabetic patients who underwent bariatric surgery was the study of Hayoz et al.[12]This study included overweight and obese patients and focused mainly on glycemic control. RYGB was found to be more effective than SG in improving weight loss and short- and mid-term glycemic and lipid metabolism control in patients with or without T2DM.[12]

The aim of this systematic review and meta-analysis of randomized clinical trials was to compare the effects of RYGB and SG on plasma lipid concentrations, specifically in T2DM patients, in order to identify the surgical procedure associated with the best outcomes in terms of lipids.

Materials and methods

Data extraction and quality assessment

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews.[13]

A literature search was performed that identified clinical trials published between January 1990 and December 2021, in English; 2 independent reviewers searched the electronic PubMed/MEDLINE, Embase and Cochrane Controlled Trials databases using the following terms: “obesity surgery OR bariatric surgery OR gastric bypass OR Roux-en-Y gastric bypass OR sleeve gastrectomy” AND “type 2 diabetes” AND “cholesterol OR lipids OR triglycerides”.

Data extracted were the following: plasma lipid concentrations, total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG), non-HDL-cholesterol, body mass index (BMI), plasma fasting glucose, and glycated hemoglobin (HbA1c).

Paired sample data were specifically chosen to minimize selection and publication bias. All of the analyzed studies met the following inclusion criteria: (a) Randomized clinical trials (RCTs); (b) Comparisons of RYGB versus SG therapy; (c) Follow-up duration of at least 12 months; (d) Evaluation of patients with T2DM; and (e) Report of the change in lipid values between baseline and follow-up. The exclusion criteria were the following: (a) Non-randomized studies, (b) Studies on procedures other than RYGB or SG, and (c) Non-diabetic patients.

This research focused on patients with diabetes because this population usually has an atherogenic lipid pattern, highly influenced by inflammatory cytokines related to overweight. Likewise, it is known that patients with diabetes have an overexpression of Nieman Pick C1-Like (NPC1L1) receptors at the intestinal level (cholesterol hyperabsorbers).[14] Consequently, it is highly attractive to determine the lipid impact of both surgical techniques specifically in patients with diabetes.

Decisions about the relationships between the publications were made to maximize information on the outcomes of interest and thus avoid repeating the count of patients. Several important studies produced numerous publications. In these instances, the data required for the study were extracted from all available literature and by e-mail of the authors. The primary endpoint of the study was defined by the change in plasma lipid concentrations (TC, LDL-C, HDL-C, TG, non HDL-C) after RYGB vs SG in diabetic patients between baseline and follow-up.

The secondary endpoints of the study were defined changes in BMI, plasma fasting glucose and HbA1c levels after RGYBG vs SG in diabetic patients between baseline and follow-up.

Potential risks of bias were evaluated using the Cochrane tool developed for this purpose.[15] This tool assesses bias in different domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and study staff (performance bias); blinding of outcome assessors (detection bias); incomplete results data (attrition bias); selective reporting of results (reporting bias); and other sources of bias. Each domain was rated as "High," "Low," or "Unclear" depending on the judgment of each author following the recommendations.[16]

Statistical Analysis

The summary effect of bariatric surgery on the lipid levels was calculated. To compare mean effects between subgroups, a Z test was used. The I^2 statistic was calculated to quantify between-study heterogeneity and inconsistency. Depending on the value of I^2, a fixed effect model ($I^2 < 40\%$) or a random effect model ($I^2 > 40\%$) was chosen. A p value ≤0.05 was considered statistically significant. The analyses were performed with the R statistical software package.[17]

Analysis of Publication Bias

Potential publication biases were explored using visual inspection of Begg's funnel plot asymmetry. Begg's rank correlation test and Egger's weighted regression test. The Duval and Tweedie's "trim and fill" method was used to adjust the analysis for the effects of publication biases.[18]

Results

The original search yielded 227 manuscripts for screening. After review of the abstracts, 104 studies were excluded. Of the 123 studies that remained, 8 were assessed for eligibility and 4 of them met the inclusion criteria and were included for quantitative synthesis.

The flowchart for the selection procedure of eligible studies is shown in Fig. 1.

The characteristics of the included articles are summarized in Table 1. All of the studies evaluated were RCT and had T2DM patient sample sizes ranging from 15 to 120 patients and a follow-up of 12 months. All participants were adult subjects with obesity and T2DM and randomized to laparoscopic RYGB or SG. Overall, 298 patients with T2DM were included: 150 patients in the RYGB group and 148 patients in the SG group. The details of the techniques of RYGB the articles were as follows: Schauer et al. consisted of the creation of a 15–20-ml gastric pouch, a 150-cm Roux limb, and a 50-cm biliopancreatic limb; Ceperuelo-Mallafré V et al., a 100-mL gastric pouch is created along with a 200-cm biliopancreatic limb and an alimentary limb of 100 cm; Lee et al., a long-sleeved gastric tube was created (EndoGIA; Coviden), approximately 2.0 cm wide along the less curved side from the antrum to the angle of His, a loop gastroenterostomy (Billroth II anastomosis) was created with the small bowel approximately 120 cm distal to the ligament of Treitz; Murphy et al., a vertical lesser curve based 20–30 ml gastric pouch, a 100-cm antecolic antegastric Roux limb, a 50-cm biliopancreatic limb, with a 6.5- or 7-cm silastic ring placed around the gastric pouch, approximately 2 cm above the gastrojejunal anastomosis.

In the baseline comparisons between the 2 techniques RYGB vs SG, no significant differences were found it with BMI, TC, LDL-C, HDL-C, Non-HDL-C, TG levels, fasting blood glucose and Hba1c, there were not a significant difference between the two groups at baseline.

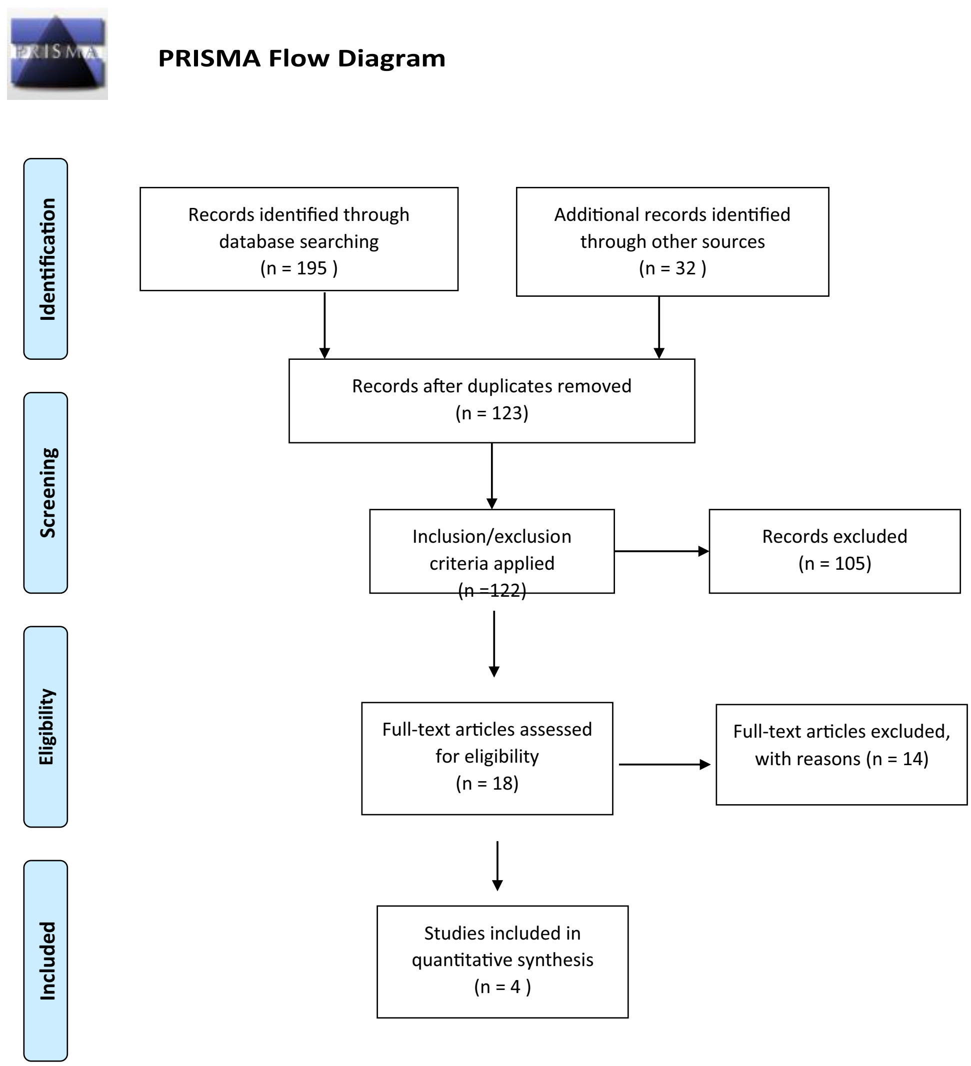
BMI (MD 0.16 k/m2, 95% CI -1.52 to 1.58; p=0.81), TC (MD −9.74 mg/dl, 95% CI −21.60 to 2.12; p=0.10), LDL (MD −7.37 mg/dl, 95% CI −17.07 to 2.33; p=0.13), HDL (MD 2.40 mg/dl, 95% CI −0.54 to 5.34; p=0.11), TG (MD −1.96 mg/dl, 95% CI −50.75 to 46.81; p=0.93), Non-HDL-C (MD 10.83 mg/dl, 95% CI −0.23 to 1.67; p=0.65), fasting blood glucose (MD −9.13 %, 95% CI −40.43 to 22.17; p=0.56), HbA1c (MD 0.05 %, 95% CI −0.35 to 0.47; p=0.78). The quality of the studies evaluated is shown in Fig. 2.

Effect of RYGB vs SG procedures on plasma lipid levels (Fig. 3)

Total Cholesterol (TC)

TC levels were reported in 4 studies. RYGB significantly reduced TC plasma levels compared to SG (mean difference [MD] −26.10 mg/dL, 95 % CI −38.88 to −13.50,

Fig. 1 Flow diagram of the study screening process



p<0.00001). Heterogeneity was detected among the studies (I^2=33 %, *p*=0.21) (Fig. 3A).

LDL-Cholesterol

LDL-C levels were reported in 4 studies. RYGB significantly reduced LDL-C plasma levels compared to SG (mean difference MD −20.10 mg/dL, 95 % CI −27.90 to −12.20, *p*<0.00001). There was low heterogeneity detected among the studies (I^2=8 %, *p*=0.35) (Fig. 3B).

HDL-Cholesterol

HDL-C levels were reported in 4 studies. We did not find a significant difference between RYGB and SG (MD 1.60 mg/dl, 95 % CI −1.20 to 4.30, *p*=0.16). There was low heterogeneity detected among the studies (I^2=32 %, *p*=0.22) (Fig. 3C).

Triglycerides

Plasma TG levels were reported in 4 studies. We did not find a significant difference between RYGB and SG (MD 2.50 mg/dl, 95 % CI -22.30 to 27.40, *p*=0.85). There was high heterogeneity detected among the studies (I^2=70%, *p*=0.02) (Fig. 3D).

Non HDL-Cholesterol

Plasma non HDL-C levels were reported in 4 studies. RYGB significantly reduced non HDL-C levels compared to SG (MD 31.90 mg/dl, 95 % CI −46.90 to −16.80, *p*=<0.001). There was high heterogeneity detected among the studies (I^2=77%, *p*=0.01) (Fig. 3E).

Table 1 Mean baseline characteristics of included studies

First author (year)	N (RYGB/SG)	Follow-up (months)	Country	BMI-RYGB kg/m^2	BMI-SG kg/m^2	TC-RYGB mg/dl	TC-SG mg/dl	LDL-C-RYGB mg/dl	LDL-C-SG mg/dl	TG-RYBG mg/dl	TG-SG mg/dl	HDL-C-RYGB mg/dl	HDL-C-SG mg/dl	non HDL-C-RYBG mg/dl	non HDL-C-SG mg/dl
Schauer PR 2012	49/50	12	USA	37.0	36.1	180	187	91.8	105	160	167	44	46	135	141
Ceperuelo-Mallafré V 2019	15/15	12	Spain	38.6	39	188	175	116.	97	136	144	46	43	145	129
Lee WJ 2011	30/30	12	China	30.2	31.2	200	230	137	142.9	262	195	47	42	153	187
Murphy R 2018	56/53	12	New Zealand	36.9	38.4	191.4	205.4	123.6	132.5	100	153	45.6	43	145.4	162.4

BMI body mass index, *HDL-c* high density lipoprotein-cholesterol, *LDL-c* low density lipoprotein-cholesterol, *Non-HDL-c* non-HDL cholesterol, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *TC* total cholesterol, *TG*, triglycerides. *BMI, TC, LDL-C, HDL-C, Non-HDL-C, and TG levels, there were not a significant difference between the two groups at baseline

Effect of RYGB vs SG on BMI, fasting blood glucose (FBG) and HbA1c levels (Fig. 4)

BMI data were reported in 4 studies. RYGB significantly reduced BMI compared to SG (MD −1.60 kg/m^2, 95 % CI −2.80 to −0.40, p<0.0001). There was high heterogeneity detected among the studies (I^2=60 %, p=0.06).

Plasma FBG levels were reported in 4 studies. RYGB reduced FBG compared to SG (MD 26.50 mg/dl, 95 % CI −45.90 to −7.70, p=0.008). The heterogeneity detected among the studies was high (I^2=80 %, p=0.01).

Hba1c levels were reported in 4 studies. RYGB significantly reduced Hba1c levels compared to SG (MD 0.70 %, 95 % CI −1.30 to −0.00, p=0.038). There was high heterogeneity detected among the studies (I^2=72%, p=0.01).

Discussion

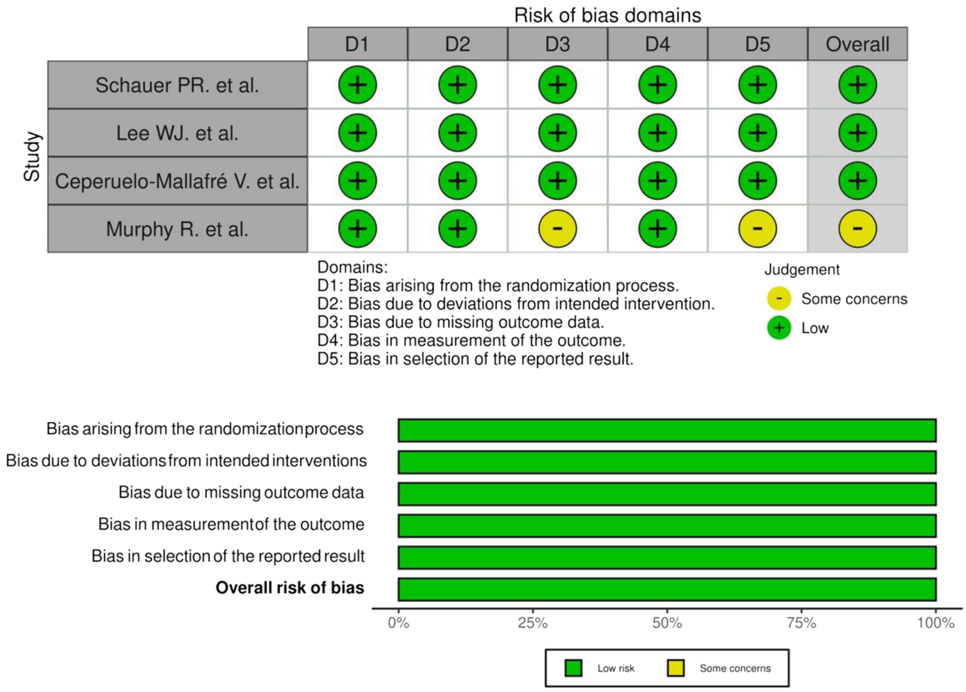
A reduction in cardiovascular morbidity and mortality has been shown following bariatric surgery.[19] This reduction has been attributed in part to a reduction in plasma lipid concentrations.

To our knowledge, the present study is the first meta-analysis showing, at 1 year after surgery, the superiority of RYGB compared to SG in reducing plasma TC, LDL-C, and non HDL-C concentrations in T2DM patients.

Despite a greater decrease in BMI and a greater improvement in glycemic control in RYGB compared to SG, the **2** procedures showed a similar improvement in **2** of the major AD abnormalities, lowering plasma TG and increasing HDL-C concentrations.

The 2 surgical techniques share common mechanisms to explain the improvement of AD parameters. The marked weight reduction, reduction in energy intake, improvement in insulin sensitivity, marked reduction of apolipoprotein C-III (apoC-III) and changes in its distribution between TRL and HDL are clear contributors to this improvement.[20] Hypertriglyceridemia is a major factor contributing to HDL catabolism and to the increased formation of small and dense atherogenic LDL particles,[21] and we have already shown that the increase of HDL-C after the 2 surgical techniques was positively associated with plasma adiponectin and negatively associated with BMI.[20] The decrease in plasma TG could partly explain the increase in HDL-C after bariatric surgery. Moreover, changes in ghrelin, adipocytokines, and glucagon-like peptide-1 (GLP-1) after bariatric surgery could also partly explain the improvement of AD.[21–23] In a recent lipoprotein kinetics study, we have shown that improved TRL metabolism after RYGB and SG, in non-diabetic obese humans, was due to a decreased production of VLDL and chylomicrons and an increased clearance of VLDL.[24]

Fig. 2 Individual bias assessment of included studies and summary bias assessment of included studies



Several studies have already shown that RYGB is more effective than SG surgery in reducing cholesterol levels[4,25] and more specifically that TC and LDL-C are significantly reduced 12 months after RYGB but not after SG.[26] A previous meta-analysis has shown the superiority at 12 months of RYBP vs SG in reducing TC and LDL-C, but no superiority in reducing TG and in increasing HDL-C in diabetic and non-diabetic patients.[12] Here, we confirm a significantly greater reduction in plasma TC, LDL-C, and non HDL-C and no difference in TG and HDL-C concentrations after RYGB compared to SG, in the specific population of T2DM patients.

The intestine plays a crucial role in cholesterol metabolism and is involved in the absorption of cholesterol (from food and bile) and in trans-intestinal cholesterol excretion. It has long been known that ileal bypass (creating malabsorption, without closing the stomach as in bariatric surgery) decreases cholesterol levels and cardiovascular disease.[27] The RYGB's malabsorptive effect significantly alters the flow of food in the gut and the metabolic changes observed after this surgery are partly independent of weight loss. These changes are multifactorial and complex and constitute a large field of study. The potential factors that may be involved in cholesterol-lowering after RYGB are (i) changes in cholesterol metabolism (decreased intestinal absorption, increased intestinal excretion, increased hepatic catabolism, decreased hepatic synthesis); (ii) increased conversion of intestinal cholesterol to coprostanol (an inactive form of sterol that is not absorbed and eliminated in the feces); (iii) changes in metabolism of bile acids (critical players in intestinal cholesterol metabolism); (iv) changes in intestinal hormones; and (v) changes in the intestinal microbial ecosystem (microbiota).[20,28] In RYGB compared to SG surgery, it has been shown that intestinal cholesterol absorption is decreased leading to decreased plasma TC and LDL-C concentrations, accompanied by enhanced hepatic cholesterol synthesis and catabolism.[28] The other technique is biliopancreatic diversion with duodenal switch (BPD/DS) which has shown effects on LDL-C levels. A 30% decrease in LDL-C levels and a parallel 12% decrease in convertase subtilisin/kexin type 9 (PCSK9) levels have been observed after performing this surgical technique,[29] Interestingly, PCSK9 is a key regulator in the catabolism of LDL-C levels.

It is known that there is regain of weight with both RYGB and SG in a few years. However, certain data reflect that LDL-C levels decrease between 17% and 24% over 2–6 years after DS.[30,31]

Interestingly, most studies examining the effect of RYGB on plasma LDL-C concentrations showed a consistent 20–30% decrease in LDL-C after RYGB, that was maintained at 5 years.[28,32] The linear association between achieved LDL-C and the rate of cardiovascular outcomes is clear and the clinical benefit of lowering LDL-C with statins remains widely accepted, as does the concept demonstrated by the Cholesterol Treatment Trialists' Collaboration, that the magnitude of clinical benefit observed with statins is proportional to the absolute reduction in LDL-C.[3] The 20–30% decrease in LDL-C after RYGB

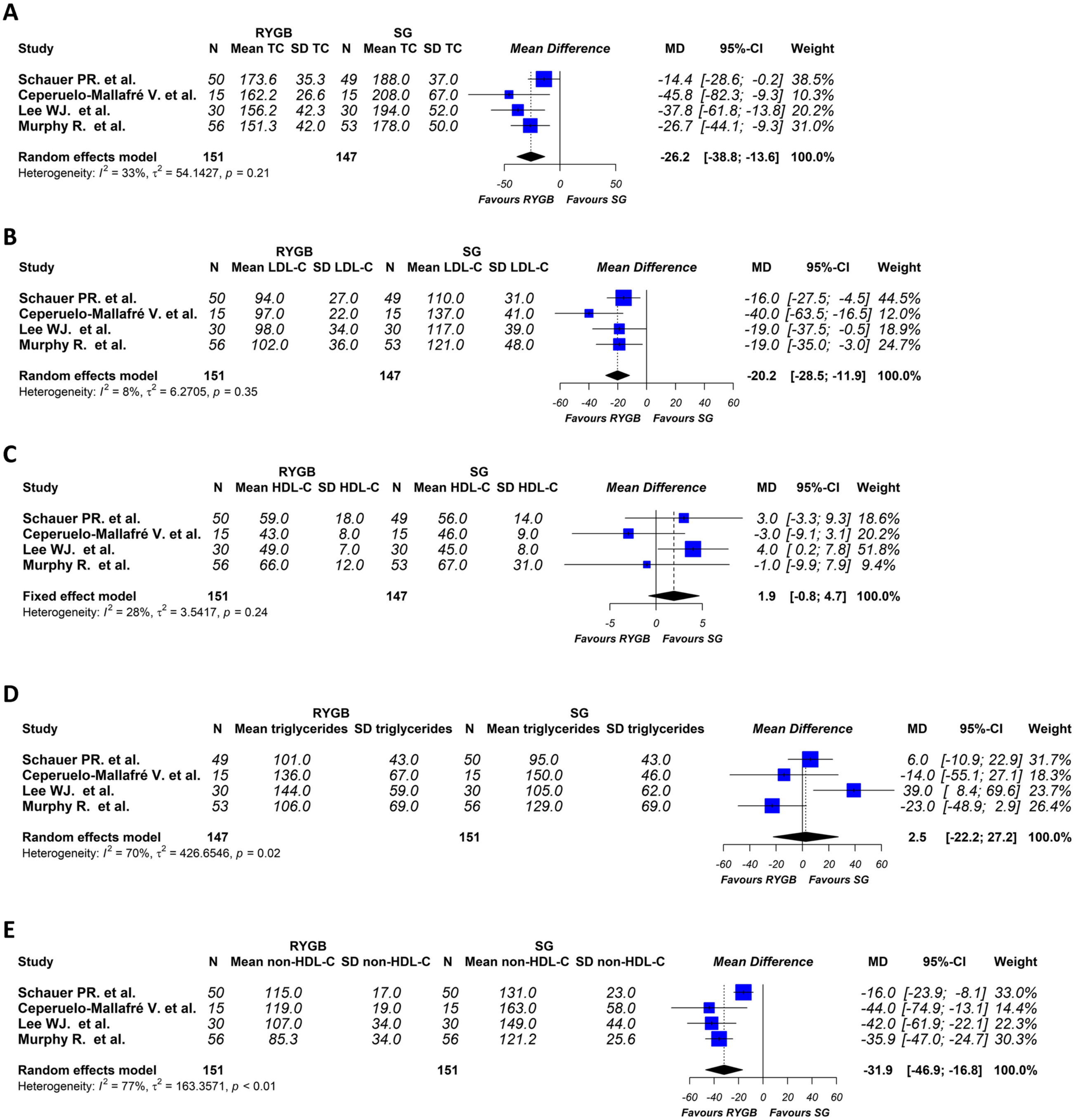


Fig. 3 Mean difference (MD) change in plasma TC (**A**), LDL-C (**B**), HDL-C (**C**), Triglycerides (**D**), and non-HDL-C(**E**) concentrations (mg/dl) at 12 months after RYGB vs SG.

is equivalent to that obtained with a moderate-intensity statin such as low-dose rosuvastatin or atorvastatin or simvastatin in association with ezetimibe.[33] As well as in association studies of moderately potent statins with ezetimibe, the greatest decrease in LDL-C was found in diabetics compared to non-diabetics, the RYGB could be more powerful in lowering LDL-C in diabetics related to non-diabetics.[34]

Moreover, in a meta-regression analysis, the use of statin and non-statin therapies that reduce LDL-C levels were associated with a similar risk reduction of major vascular events per change in LDL-C.[35] It is thought that weight may play a role in atherogenic dyslipidemia in diabetic patients, a recent study with regain of weight at long term has shown that lipid levels are maintained for the first 12 months.[36]

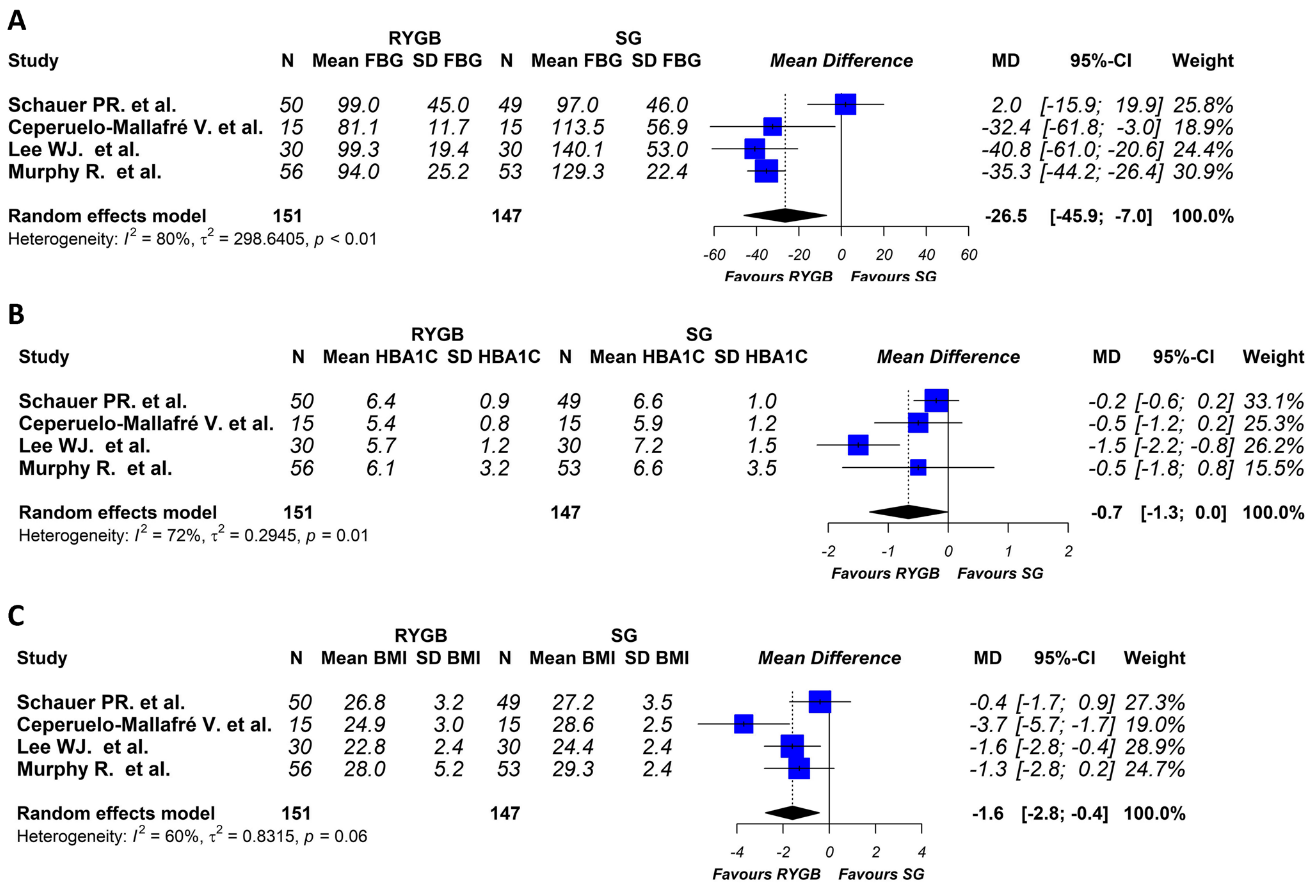


Fig. 4 Mean difference (MD) change in BMI (**A**), plasma fasting blood glucose (FBG) (**B**), and HbA1c (**C**) levels at 12 months after RYGB vs SG

Limitations

One important limitation in this analysis is the small number and short duration of the studies included. There was also significant clinical and statistical heterogeneity among the included studies. Therefore, larger and longer-term studies are now required. Additionally, the patients included in the studies analyzed in this meta-analysis were very well supervised and their follow-up was short. Therefore, the lipid effects related to the surgical techniques evaluated could be related to the exhaustive management of the diet observed in this type of study and not necessarily be maintained in the long term.

Finally, the baseline use of statins in each of the articles included is not known. Also, the details of the techniques in in terms of limb lengths or pouch size that could influence the absorption of lipid parameters the articles are not described.

Conclusion

In this study, we have demonstrated the equivalence between RYGB and SG in improving atherogenic dyslipidemia (plasma decrease in TG and increase in HDL-C) and the superiority of RYGB in lowering plasma TC, LDL-C, and non HDL-C, 1 year after surgery, in T2DM patients. The magnitude of the decrease in LDL-C after RYGB is comparable to that achieved with a moderate-intensity statin. These improvements in lipid profiles (AD for both surgical techniques) and more specifically cholesterol in RYBP partly explain the decrease in cardiovascular events after bariatric surgery. Our meta-analysis would suggest favoring RYGB surgery over SG in patients with hypercholesteremia and T2DM.

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Author Contribution Nogueira Juan Patricio was the main coordinator of the project and was responsible for the study design. Closs Cecilia, Ackerman Marianela, and René Valéro drafted the manuscript of the present paper. Sophie Beliard, Mourre Florian, and Molinero Graciela were involved in the supervising of data collection and stratification. Lobo Martin and Nogueira Juan Patricio contributed to data assembly and analysis. Lavalle-Covos Augusto contributed with manuscript revision. All authors contributed intellectually to this manuscript and have approved this final version.

Declarations

Ethical Approval Does not apply.

Informed Consent Does not apply.

Conflict of Interest The authors declare no competing interests.

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