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ORIGINAL CONTRIBUTIONS

Outcomes of Bariatric Surgery Versus Medical Management for Type 2 Diabetes Mellitus: a Meta-Analysis of Randomized Controlled Trials

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Abstract

Introduction Bariatric surgery improves type 2 diabetes (T2D) in obese patients. The sustainability of these effects and the long-term results have been under question.

Objective To compare bariatric surgery versus medical management (MM) for T2D based on a meta-analysis of randomized controlled trials (RCTs) with 2 years of follow-up.

Material and Methods Seven RCTs with at least 2-year follow-up were identified. The primary endpoint was remission of T2D (full or partial). Four hundred sixty-three patients with T2D and body mass index > 25 kg/m^2 were evaluated.

Results After 2 years, T2D remission was observed in 138 of 263 patients (52.5%) with bariatric surgery compared to seven of 200 patients (3.5%) with MM (risk ratio (RR) = 10, 95% CI 5.5–17.9, $p < 0.001$). Subgroup analysis of the Roux-en-Y gastric bypass (RYGB) showed a significant effect size at 2 years in favor of RYGB over MM for a higher decrease of HbA1C (0.9 percentage points, 95% CI 0.6–1.1, $p < 0.001$), decrease of fasting blood glucose (35.3 mg/dl, 95% CI 13.3–57.3, $p = 0.002$), increase of high-density lipoprotein (HDL) (12.2 mg/dl, 95% CI 7.6–16.8, $p < 0.001$), and decrease of triglycerides (32.4 mg/dl, 95% CI 4.5–60.3, $p = 0.02$). Four studies followed patients up to 5 years and showed 62 of 225 patients (27.5%) with remission after surgery, compared to six of 156 patients (3.8%) with MM (RR = 6, 95% CI 2.7–13, $p < 0.001$).

Conclusion This meta-analysis shows a superior and persistent effect of bariatric surgery versus MM for inducement of remission of T2D. This benefit of bariatric surgery was significant at 2 years and superior to MM even after 5 years. Compared with MM, patients with RYGB had better glycemic control and improved levels of HDL and triglycerides.

Keywords Type 2 diabetes mellitus · Obesity · Medical management · Bariatric surgery · Treatment outcome Randomized controlled trial

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Introduction

Obesity has become a major global health concern despite available medical and surgical management [1, 2]. In the comorbidities complicating morbid obesity, type 2 diabetes (T2D) has a substantial deleterious impact on patient quality of life and survival [1, 3, 4]. Despite emphasis on the importance of appropriate glycemic control in prevention of diabetes-related complications, less than 50% of patients are able to achieve the therapeutic goal of a glycated hemoglobin (HbA1C) level (less than 7% of total hemoglobin) with the currently available medical regimens [1, 2].

Bariatric surgery has been shown to dramatically improve T2D in morbidly obese patients [5, 6]. A meta-analysis by Buchwald et al. concluded that bariatric surgery is the better option for improvement or resolution of the clinical and laboratory manifestations of T2D [7]. Bariatric surgery is also referred to metabolic surgery because it can affect appetite, food intake, caloric absorption, and the neuroendocrine pathways leading to weight loss and improvement or resolution of T2D. The exact mechanism by which metabolic surgery affects obesity-related comorbidities, however, is yet to be determined. The beneficial effect of metabolic surgery on the improvement of T2D appears shortly after the operation even when substantial weight loss has not yet occurred [8]. Additionally, metabolic surgery has been shown to be effective in improvement of T2D in patients with class I obesity with a body mass index (BMI) of 30 to 35 kg/m^2 [9, 10].

In addition to retrospective studies, several randomized controlled trials (RCTs) have shown the benefits of bariatric surgery over medical treatment in achieving weight loss, glycemic control, and decreasing microvascular complications in patients with T2D [6, 11–13]. While several studies have shown the early substantial metabolic effects of bariatric surgery, the sustainability of these effects and the long-term results have been under question [6, 9–17]. Several RCTs comparing bariatric surgery with medical management have followed their patients for 2–5-year periods. This meta-analysis investigates remission of T2D after bariatric surgery versus medical management, using results of prospective RCTs with at least 2-year period of follow-up.

Methods

Study Design

This study was designed according to the Cochrane Handbook for Systematic Review and Meta-Analysis [18]. The Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations were followed throughout the study [19]. This meta-analysis was registered at the international prospective register of systematic reviews (PROSPERO) with the registration number CRD42016037105.

Search Strategy

We conducted a systematic literature review by searching PubMed, ISI Web of Science, Scopus, Embase, Cochrane Library Databases, ClinicalTrials.gov, and abstracts from the meetings of the American Diabetes Association (ADA), the International Federation for Surgery of Obesity and Metabolic Disorders (IFSO), the European Association for the Study of Diabetes (EASD), and the journal of *Surgery of Obesity and Related Diseases* (SOARD) as well as other obesity surgery journals. We selected all relevant RCTs conducted between January 1990 and April 2018. We used a combination of the following search terms: diabetes, bariatric surgery, sleeve gastrectomy, Roux-en-Y gastric bypass, gastric band, gastric banding, and biliopancreatic diversion. We also searched all eligible studies by manually searching the bibliographic list of key publications in English (Fig. 1).

Eligibility Criteria

Studies were included if they (1) were prospective RCTs, (2) included patients diagnosed with T2D, (3) compared remission rates of T2D with medical treatment versus bariatric surgery, and (4) had at least 2 years of follow-up. Two independent researchers (Z.K., S.S.) reviewed titles and abstracts of the studies for relevancy, and full texts of the eligible studies were retrieved for final assessment. There was an agreement value (κ) of 97% between the two reviewers for the included studies. Any disagreement was resolved by a third reviewer (G.M.S.) by coming to a consensus. From the initial 3122 records, seven studies were selected for the final review (Fig. 1).

Data Extraction

For each included study, we identified the number of patients, remission criteria used for the definition of remission of T2D, percentages of patients with diabetes who had full or partial remission, and changes in HbA1C, blood glucose, and lipid profile. Since Roux-en-Y gastric bypass (RYGB) was the most common surgical arm, continuous variables (HbA1C, blood glucose, and lipid profile) were compared only between RYGB and medical management.

Quality Assessment

Methodological quality assessment and risk of bias of the included studies were performed using elements of the Cochrane collaboration tool for assessing risk of bias [20]. Included studies were assessed on seven criteria, including random sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. For each category, studies

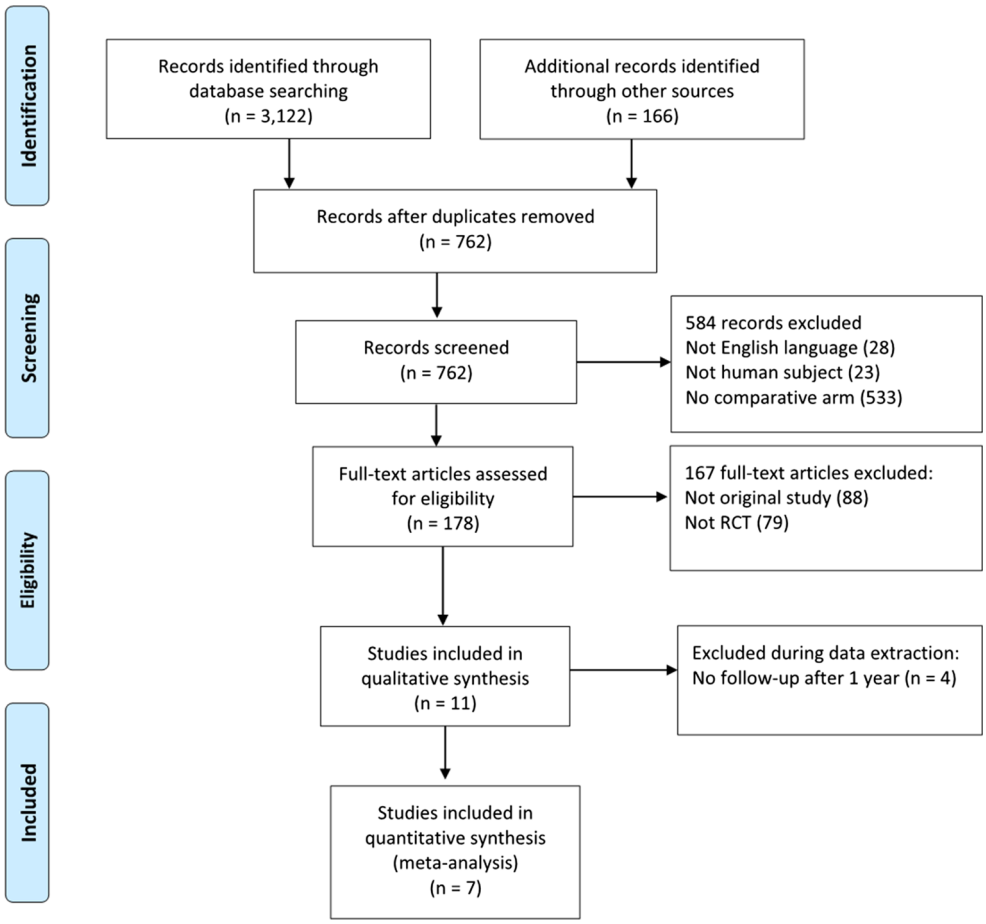

Fig. 1 PRISMA flowchart for search strategy and study selection

were classified as low, unclear, and high risk of bias. If there was a private industry sponsor funding the study, "other" category was considered as "unclear risk" for bias. Agreements across methodological quality assessment were obtained by discussion and consensus.

Data Synthesis

Data were analyzed using Review Manager for windows (RevMan, version 5.3. Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Fasting blood glucose, changes in HbA1C, and cholesterol and triglyceride levels were presented as mean ± SD. Diabetes remission was presented as frequency (percentages) and analyzed using the Mantel-Haenszel method. Arms with zero events (four arms with medical treatment) were given an arbitrary value of 1 to prevent large values in risk ratios [21]. T2D remission was compared and analyzed based on "intention to treat," and all patients allocated to surgery versus all patients allocated to medical management were considered in analysis of remission of T2D. To quantify heterogeneity between studies, I^2 was calculated and considered representative of low heterogeneity at values < 30%, of moderate heterogeneity at values between 30 and 50%, and of considerable heterogeneity at values > 50%. The random effects model was used for analysis of studies with considerable heterogeneity, and the fixed effects model was used for studies with low or moderate heterogeneity. For categorical data, risk ratio (RR) was used as the quantity of interest. All values are reported with their corresponding 95% confidence intervals (CI). A $p < 0.05$ was considered statistically significant for both the pooled data and heterogeneity estimation.

Results

Characteristics of Included Studies and Intervention Arms

This meta-analysis reviewed seven studies with at least 2-year follow-up which included 463 patients with BMI ranging from 25 to > 45 kg/m^2 (Table 1) [3, 6, 14, 16, 22–24]. Patients were assigned to RYGB in five studies (146 patients, 31.5%), adjustable gastric banding in three studies (77 patients, 16.6%), sleeve gastrectomy in one study (20 patients, 4.3%), and biliopancreatic diversion with duodenal switch in one study (20 patients, 4.3%). Publication time frames ranged from 2008 to 2018. Remission criteria included HbA1C less than 6.5% in five studies [5, 14, 16, 22, 24], less than 6% in

Table 1 Characteristics of included randomized controlled trials comparing bariatric surgery versus medical treatment for management of type 2 diabetes mellitus

First author	Country	Year	BMI range at baseline (kg/m^2)	Mean diabetes duration (year)	Patients on insulin (%)	Arms (number of patients randomized)	Medical management	Glycemic goal/T2D remission criteria	Follow-up (year)
Courcoulas [14]	USA	2015	30–40	6.5	39%	MM (23) RYGB (24) AGB (22)	Weekly in person/telephone sessions in year 1 and twice monthly in year 2; energy-restricted diet (1200–1800 kcal/d); moderate-intensity exercise 300 min per week; T2D management by the original endocrinologist	HbA1C < 6.5%, FPG < 126 mg/dl, no glycemic medications	3
Dixon [16]	Australia	2008	30–40	< 2	2%	MM (30) AGB (30)	Open access to medical team; visits every 6 weeks; reduce fat intake < 30%; 10,000 steps per day and 200 min per week of structured activity; pharmacologic therapy by experienced endocrinologist	HbA1C < 6.2%, FPG < 126 mg/dl, no glycemic medications	2
Ikramuddin [22, 27, 45]	USA	2015, 2016, 2018	30–39.9	9	52%	MM (60) RYGB (60)	Weekly counseling sessions for 6 months, every 2 weeks in 7–9 months, monthly in 10–15 months, then every 3 months; physical activity 325 min per week; monthly endocrinologist visit for 6 months then every 3 months	HbA1C < 6.5%, no glycemic medications	2, 3, 5
Mingrone [5, 23]	Italy	2012, 2015	> 35	6	NR	MM (20) BPD (20) RYGB (20)	Visits at 0, 1, 3, 6, 9, 12, and then every 6 months; HbA1C target < 7%, reduced energy and fat intake < 30%; physical exercise ≥ 30-min daily brisk walking; pharmacologic therapy by experienced endocrinologist	HbA1C < 6.5%, FPG < 100 mg/dl, no glycemic medications	2, 5
Schauer/Kashyap [6, 9, 25]	USA	2012, 2013, 2017	> 30	8.3	43%	MM (20) SG (20) RYGB (20)	3-month visits; intensive medical therapy based on ADA guideline	HbA1C < 6.0%	2, 3, 5
Simonson [24]	USA	2018	30–42	10	60%	MM (19) RYGB (19)	Weekly sessions for 12 weeks for supervised group exercise, didactic sessions, and medication adjustments; 1500–1800 kcal diet; up to 300 min/week of exercise; monthly counseling for the next 9 months	HbA1C < 6.5%, FPG < 126 mg/dl	3
Wentworth [3, 26]	Australia	2014, 2017	25–30	3	10%	MM (26) AGB (25)	Visits every 3 months in year 1 and then every 6 months; multidisciplinary diabetes care based on ADA guidelines; HbA1C target < 7%; moderate-intensity physical activity 150 min per week	FPG < 7.0 mmol/l, and < 11.1 mmol/l 2 h after oral glucose (2 days after stopping glycemic medications)	2, 5

MM medical management, *RYGB* Roux-en-Y gastric bypass, *AGB* adjustable gastric band, *SG* sleeve gastrectomy, *BPD* biliopancreatic diversion, *NR* not reported, *FPG* fasting plasma glucose, *ADA* American Diabetes Association, *FDA* Food and Drug Administration

one study [6], and based on fasting and postprandial plasma glucose in one study [3]. Non-surgical arms underwent intensive medical management including defined counseling, endocrinologist visits, exercise and physical activities, and management of other comorbidities.

Assessment of Publication Bias

The Cochrane risks of bias for each citation are included in Table 2. All studies performed random sequence generation. Three studies described allocation concealment [3, 14, 22]. Due to the nature of studies (comparing surgical and medical management), blinding was not possible and all studies have a risk of bias due to lack of blinding participants and personnel. In addition, blinding of outcome assessment was not clear in all trials. Intention-to-treat analysis for incomplete outcome data was described in all studies except one trial [9]. All trials followed their protocols for reporting outcomes and there was no selective outcome reporting. Five studies received funds by private industry sponsors with an unclear bias considered in the other category [3, 9, 16, 22, 24].

T2D Remission and Glycemic Control

Seven studies had at least 2-year follow-up [3, 5, 9, 14, 16, 22, 24]. Of these, T2D remission (partial or complete) occurred in 138 of 263 patients (52.5%) assigned to bariatric surgery compared to seven of 200 patients (3.5%) who were assigned to medical treatment (RR = 10, 95% CI 5.5–17.9, $p < 0.001$). Subgroup analysis based on the type of procedure is shown in Fig. 2. In the RYGB subgroups, remission rate was 52.7% versus 0.7% in medical group (RR = 15.2, 95% CI 6.3–36.5, $p < 0.001$). In AGB groups, remission rate was 51.9% versus 7.6% (RR = 5.8, 95% CI 2.8–12.1, $p < 0.001$). Biliopancreatic diversion and sleeve gastrectomy were assessed in only one study each. Efficacy of biliopancreatic diversion and sleeve gastrectomy in remission of T2D has been each assessed by one study. In the study by Mingrone et al., none of the 20 randomized patients to the medical management had diabetes remission at 2 years, as compared with 19 of 20 (95%) randomized patients to the biliopancreatic diversion ($p < 0.001$) [23]. In another study by Schauer et al., 12 of 49 (24%) patients who underwent sleeve gastrectomy achieved the study primary endpoint (HbA1C ≤ 6%) at 3 years, compared to two of 40 (5%) patients who treated with intensive medical therapy [6].

Analysis of RYGB arms showed superiority of RYGB over medical treatment after 2 years with a higher decrease of HbA1C (0.9 percentage points, 95% CI 0.6–1.1, $p < 0.001$) and decrease of fasting blood glucose (35.3 mg/dl, 95% CI 13.3–57.3, $p = 0.002$) (Fig. 3).

Four studies followed patients up to 5 years [5, 25–27]. After 5 years, 62 of 225 patients (27.5%) who had been randomized to surgery were in remission, compared to only six of 156 patients (3.8%) who were treated medically (RR = 6, 95% CI 2.7–13,

Table 2 Risk of bias based on methodological quality assessment of the 7 randomized controlled studies, comparing bariatric surgery versus medical treatment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Dixon [16]	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Mingrone [5]	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Wentworth [3]	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Kashyap [9]	Low risk	Unclear risk	High risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Courcoulas [14]	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Ikramuddin [22]	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Simonson [24]	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk

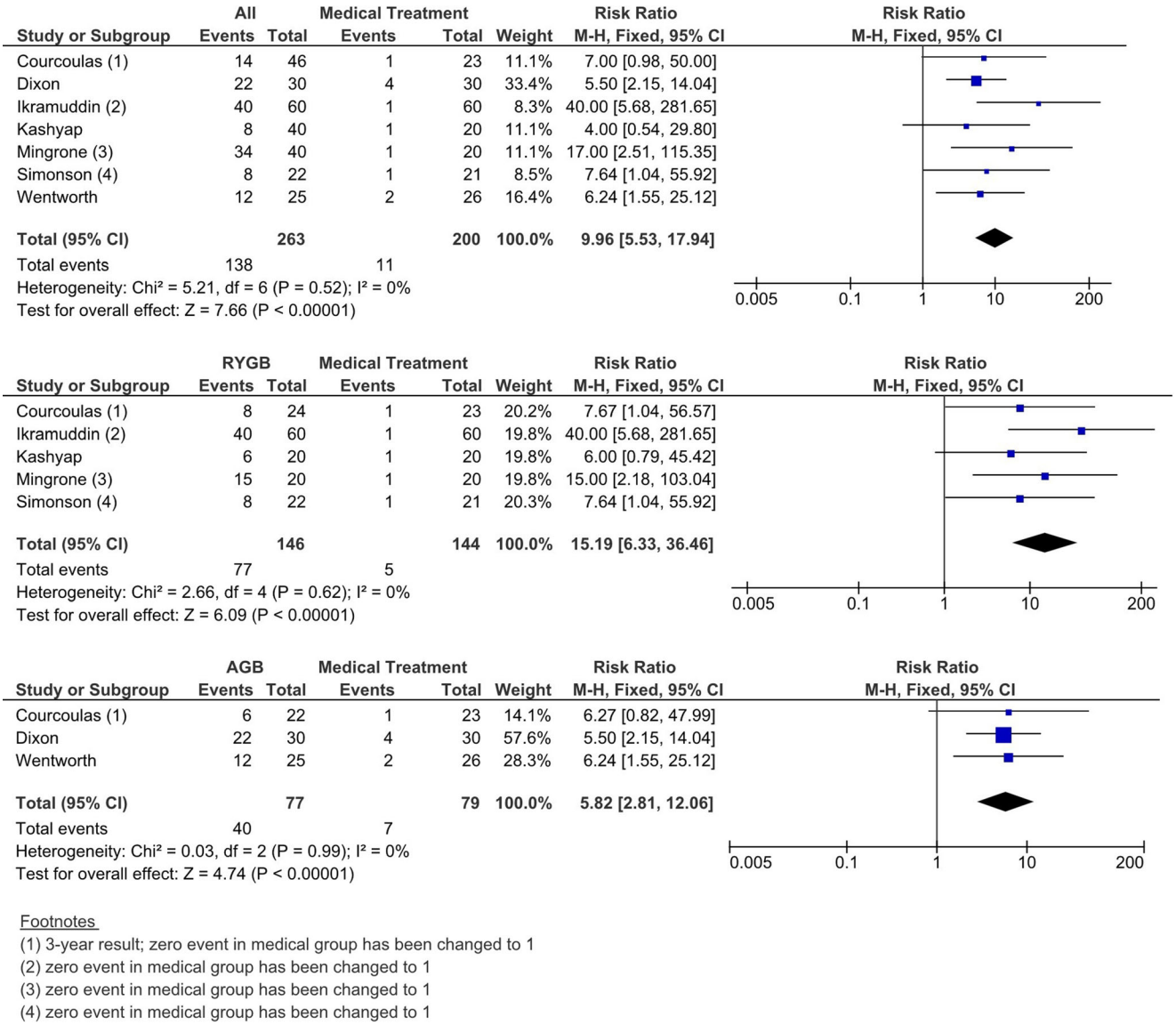

Fig. 2 Comparison of T2D remission (full or partial) between bariatric surgery and medical management after 2 years, and subgroup analysis in Roux-en-Y gastric bypass (RYGB) and adjustable gastric band (AGB)

$p < 0.001$) (Supplementary Fig. 1). Remission rate of surgical patients in these four studies was 63% at 2-year follow-up. Mingrone et al. compared remission of T2DM between medical management, RYGB, and biliopancreatic diversion up to 5-year follow-up. While none of the patients in medical group was in diabetes remission at 5 years, seven out of 19 (37%) patients in RYGB group and 12 out of 19 (63%) patients in biliopancreatic diversion group maintained the remission. Similarly, eight patients (42%) who underwent RYGB and 13 patients (68%) who underwent biliopancreatic diversion had HbA1C ≤ 6.5% with or without medication [5].

Serum Lipid Profile

Two years after RYGB, serum levels of total cholesterol (TCh) were reported by four studies (112 RYGB patients compared to 105 patients with medical treatment) [5, 14, 22, 24]. In these studies, the change in TCh level was variable, and the difference (8.3 mg/dl, 95% CI − 1.2 to 17.9) was not statistically significant (Fig. 4). Improvement of low-density lipoprotein (LDL) serum level 2 years after RYGB was reported by four studies (112 RYGB patients compared to 105 patients with medical treatment) [5, 14, 22, 24]; the change in LDL levels was not significant (7.4 mg/dl, 95% CI − 1.4 to 16.3) (Fig. 4). Improvement of high-density lipoprotein (HDL) serum levels after 2 years was reported by five studies (130 RYGB patients compared to 122 non-surgical patients) [5, 9, 14, 22, 24]; HDL levels showed an increase of 12.2 mg/dl (95% CI 7.6–16.8) in patients with RYGB compared to medical management ($p < 0.001$) (Fig. 4). Decrease in triglyceride (TG) serum levels 2 years after RYGB was reported by five studies [5, 9, 14, 22, 24]. Decrease in TG levels was 32.4 mg/dl lower in RYGB

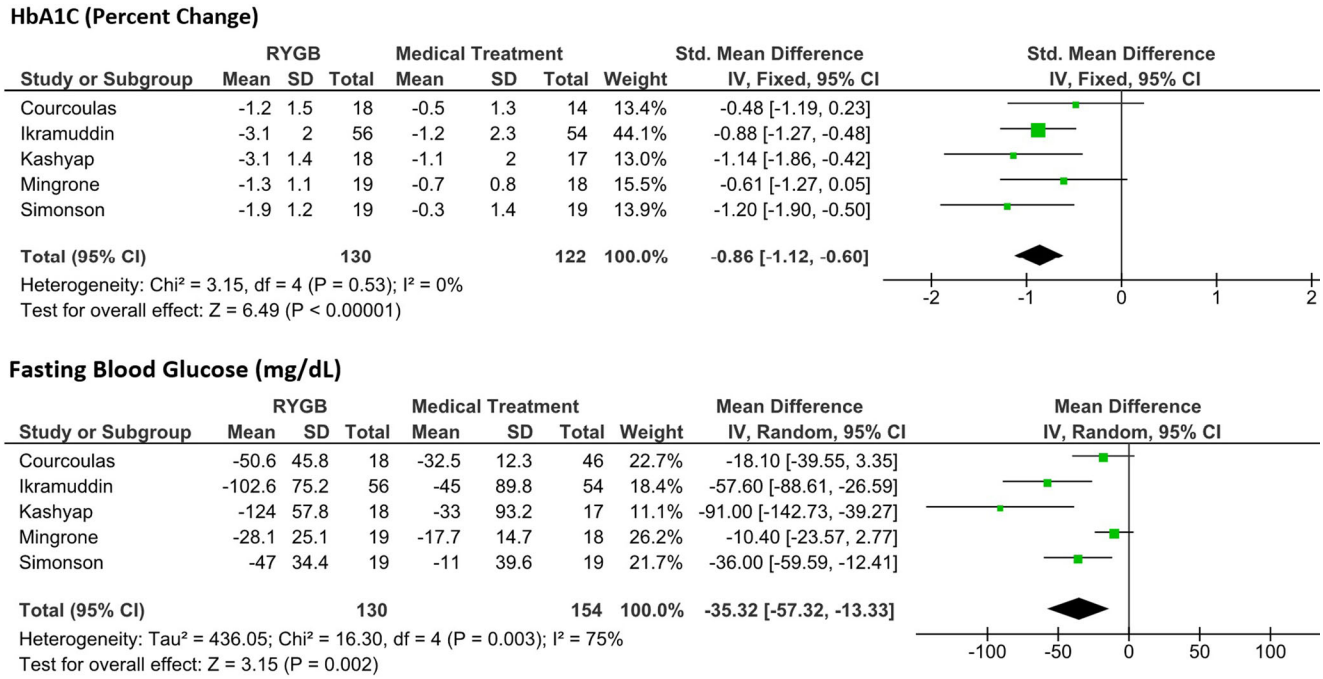

Fig. 3 Changes in HbA1C (%) and fasting blood glucose (mg/dl), 2 years after Roux-en-Y gastric bypass versus medical treatment

patients compared to medical treatment, and this difference was statistically significant (95% CI 4.5–60.3, $p = 0.02$) (Fig. 4).

Discussion

According to the Non-Communicable Diseases Risk Factor Collaboration (NCD-RisC), age-standardized, global prevalence of diabetes mellitus increased from 4.3 to 9% in men and from 5 to 7.9% in women between 1980 and 2014. The worldwide number of adults with diabetes mellitus has increased from 108 to 422 million over this time period, due to increase in age-specific prevalence, population growth, and aging [28]. These increases may be occurring due to urbanization, which reduces physical activity and increased caloric intake. The global burden of diabetes mellitus continues to increase exponentially with accompanying diabetes-related complications and comorbidities.

Intense lifestyle modification and pharmacologic intervention can decrease the incidence of T2D [29, 30]. Non-surgical management can induce remission in a minority of T2D patients [6]. Bariatric surgery has also been shown to reduce the incidence of T2D in patients with obesity [31, 32]. Bariatric surgery has been utilized increasingly in high-income countries over the past two decades, with evolving changes in surgical procedures, such as the now outdated gastric band and the emergence of sleeve gastrectomy [33]. With more evidence available about the metabolic effects of sleeve gastrectomy (similar to RYGB), including improvement in obesity-related comorbidities such as T2D [34], a greater number of obese patients with coexisting diabetes are now undergoing this procedure [33].

With better techniques and more favorable long-term benefits of weight loss surgery compared to its initial risk and cost, bariatric surgery is increasingly being considered as a treatment option for obese patients with T2D [35–38]. One reason for this change in the approach of treatment of T2D is the publication of recent RCTs comparing surgical and medical management [11, 14–17]. However, the long-term results of these RCTs need to be pooled in order to better measure the differences in the two treatment options. Our meta-analysis of seven RCTs showed a remission rate of 52.5% with bariatric surgery comparing to 3.5% with medical management for T2D after 2 years of treatment initiation. Four studies followed their patients for 5 years and reported a remission rate of 27.5% for the surgical group and 3.8% in the medical group. Bariatric surgery was superior to medical management for improved glycemic control at 5 years; however, more studies with longer follow-up are needed to evaluate if this effect will disappear with time or will reach a plateau.

A prospective, matched cohort study of obese Swedish patients revealed a T2D remission rate of 72.3% for bariatric surgery patients versus 16.4% for control patients at 2 years, and 30.4% in the bariatric group versus 6.5% in the control group at 15 years (both statistically significant) [38]. A retrospective study in 134 obese patients with T2D who underwent sleeve gastrectomy reported long-term outcomes (> 5 years). There was a partial remission rate of 26% (HbA1C < 6.5% and off medications), a complete remission rate of 11% (HbA1C < 6% and off medications), and continuous (>

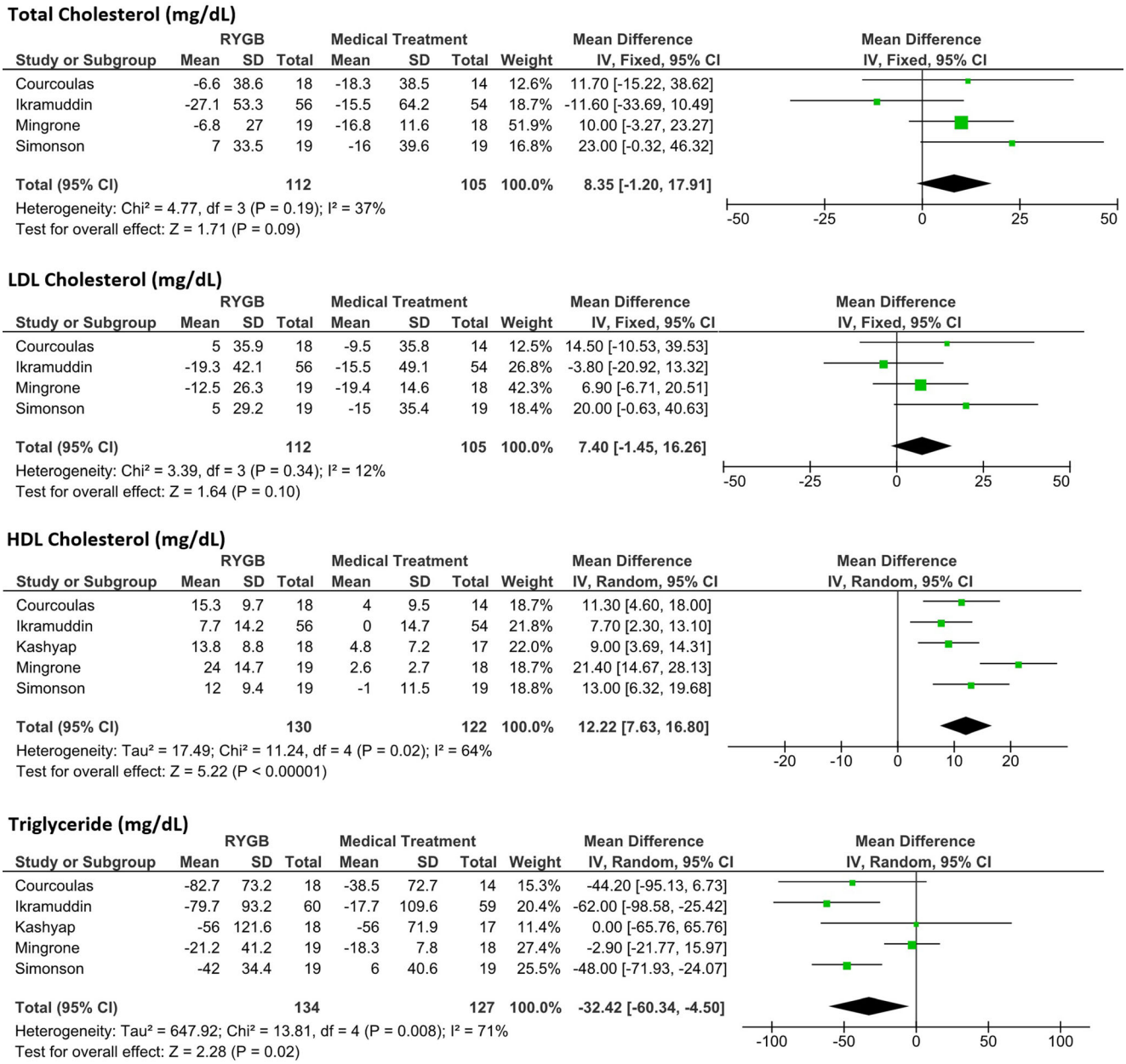

Fig. 4 Comparison of changes in lipid profile (total cholesterol, low-density cholesterol, high-density cholesterol, and triglyceride) all in mg/dl, 2 years after Roux-en-Y gastric bypass versus medical treatment

5 years) complete remission in 3% of patients [39]. In a prospective RCT by Schauer et al. comparing 3-year outcomes of obese patients with uncontrolled T2D (randomized into either intensive medical therapy alone, RYGB, or sleeve gastrectomy), 36% of RYGB patients, 24% of sleeve gastrectomy patients, and 5% of medical treatment patients achieved a HbA1C level of < 6% [6]. No patient achieved a complete remission with intensive medical treatment. These trials suggest that in addition to a greater partial remission rate, bariatric surgery may have the potential of achieving complete remission of T2D compared to medical management. Our meta-analysis did observe a large heterogeneity among RCTs based on study populations in the following categories: initial BMI at the time of enrollment, type of bariatric procedure, medical regimen for treatment of T2D, and counseling for management of T2D. These variations along with different

criteria for definition of T2D remission may be responsible for the differences in remission rates.

Bariatric surgery is associated with operative and metabolic complications which include anastomotic leak, stricture, bleeding, and marginal ulcers, as well as gallstones, dumping syndrome, hypoglycemia, nutritional deficiency, malnutrition, and possibility of weight regain [13, 25]. These procedures have a 2% risk of diagnosed complications in the index admission and 5% risk of 30-day readmission after RYGB and sleeve gastrectomy, based on an analysis of the 2012 and 2013 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database [40]. These complications should be considered when surgical intervention is compared with medical treatment of T2D.

Our meta-analysis showed the superiority of RYGB over medical treatment in elevation of serum levels of HDL and decreasing TG. Consistent with other studies, we did not find any significant difference between the two groups for TCh and LDL [6, 41]. Sleeve gastrectomy and biliopancreatic diversion have been shown to have metabolic efficacy in improvement of HbA1C and lipid profile in obese patients [7, 34]. We did not perform subgroup analysis for these procedures due to the limited number of patients and studies. The study by Mingrone et al. was the only one which included biliopancreatic diversion (beside two other arms of RYGB and medical management). After 5 years, biliopancreatic diversion showed a significantly higher efficacy than medical management in improvement of fasting glucose, HbA1C, lipid panel, cardiovascular risk, and some aspects of quality of life. Furthermore, biliopancreatic diversion was superior to RYGB in some of the metabolic benefits such as lower rate of relapse of T2D at 5 years (37% of biliopancreatic diversion vs. 53% of patients with RYGB) [5]. On the other hand, Schauer et al. showed that sleeve gastrectomy had a superior effect compared to medical management in terms of weight loss, TG and HDL level, and quality of life measures at 5 years [25]. RYGB was the most common arm in these studies and it may stem from the conventional belief in RYGB as the most effective procedure for treatment of T2D. Further studies are warranted to evaluate the long-term results of bariatric surgery compared to medical management with a special focus on sleeve gastrectomy.

Limitations

This meta-analysis suffers some limitations due to the inherent flaws of included RCTs. None of the included studies in our meta-analysis analyzed the potential modification effects by age, initial HbA1C level, or duration of T2D which have been shown to have an effect on the remission rate [42]. Additionally, these studies are different in the percentage of patients on insulin at baseline. Variations in the criteria for remission of T2D may also be a limitation of this review [43, 44]. Lack of blinding which was not possible due to the type interventions is a potential factor for bias. Future prospective RCTs with large sample sizes in each intervention group would be helpful to compare the long-term efficacy of specific bariatric surgery procedures compared to available medical treatment options for improvement of glycemic control, T2D remission, and potential cure. This would better guide clinicians in developing their management plans for obese patients with T2D.

Conclusions

Bariatric surgery seems to be superior to medical therapy for remission of T2D based on the meta-analysis of seven randomized, controlled trials comparing the efficacy of bariatric surgery versus medical treatment for T2D after 2 years. Based on 5-year reports of four RCTs, this benefit of bariatric surgery reduced at 5 years but still remained significantly superior to medical management. Significantly better improvement of levels of HbA1C, fasting plasma glucose, HDL, and TG were also demonstrated up to 2 years after RYGB.

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Registration This study has been registered in the international prospective register of systematic reviews (PROSPERO, registration number CRD42016037105).

Compliance with Ethical Standards

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

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Does not apply.

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