

# Roux-en-Y Gastric Bypass Versus Medical Treatment for Type 2 Diabetes Mellitus in Obese Patients

## *A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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**Abstract:** The aim of the study is to compare Roux-en-Y gastric bypass (RYGB) surgery versus medical treatment for type 2 diabetes mellitus (T2DM) in obese patients.

Bariatric surgery can achieve remission of T2DM in obese patients. RYGB surgery has been performed as one of the most common surgical treatment options for obese patients with T2DM, but the efficacy of RYGB surgery comparing with medical treatment alone has not been conclusively determined.

A systematic literature search identified randomized controlled trials (RCTs) evaluating RYGB surgery versus medical treatment for T2DM in obese patients was conducted in PubMed, Embase, Cochrane Database, and Cochrane Clinical Trials Registry. This systematic review and meta-analysis were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The primary outcome was T2DM remission. Additional analyses comprised hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), body mass index (BMI), waist circumference, serum lipid level, blood pressure, medication use, and adverse events. Random-effects meta-analyses were calculated and presented as weighted odds ratio (OR) or mean difference (MD) with 95% confidence intervals (CI).

Six RCTs concerning 410 total obese T2DM patients were included. Follow-up ranged from 12 to 60 months. RYGB surgery was associated with a higher T2DM remission rate (OR: 76.37, 95% CI: 20.70–281.73,  $P < 0.001$ ) and serum level of high-density lipoprotein cholesterol (MD: 0.24 mmol/L, 95% CI 0.18–0.30 mmol/L,  $P < 0.001$ ) than medical treatment alone. HbA1c (MD: –1.25%, 95% CI: –1.88% to –0.63%,  $P < 0.001$ ), BMI (MD: –6.54 kg/m<sup>2</sup>, 95% CI: –9.28 to –3.80 kg/m<sup>2</sup>,  $P < 0.001$ ), waist circumference (MD: –15.60 cm, 95% CI: –18.21 to

–13.00 cm,  $P < 0.001$ ), triglyceride (MD: –0.87 mmol/L, 95% CI: –1.17 to –0.57 mmol/L,  $P < 0.001$ ), low-density lipoprotein cholesterol (MD: –0.32 mmol/L, 95% CI: –0.62 to –0.02 mmol/L,  $P = 0.04$ ), systolic blood pressure (MD: –2.83 mm Hg, 95% CI: –4.88 to –0.78 mm Hg,  $P < 0.01$ ) were lower after RYGB surgery. However, FPG (MD: –1.58 mmol/L, 95% CI: –3.58 to 0.41 mmol/L,  $P = 0.12$ ), total cholesterol (MD: –0.40 mmol/L, 95% CI: –0.92 to 0.12 mmol/L,  $P = 0.13$ ), and diastolic blood pressure (MD: 0.28 mm Hg, 95% CI: –1.89 to 2.45 mm Hg,  $P = 0.80$ ) were not significantly different between the 2 treatment groups. The medicine use and quality of life were solely improved in the surgical group. Nutritional deficiencies and anemia were noted more frequently in the RYGB group.

RYGB surgery is superior to medical treatment for short- to medium-term remission of T2DM, improvement of metabolic condition, and cardiovascular risk factors. Further RCTs should address the safety and long-term benefits of RYGB surgery on obese patients with T2DM.

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**Abbreviations:** BMI = body mass index, CI = confidence interval, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, MD = mean difference, OR = odds ratio, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, RYGB = Roux-en-Y gastric bypass, T2DM = type 2 diabetes mellitus.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity are 2 of the common chronic diseases that occur frequently among people in the whole world and remain an unsolved problem for global health care.<sup>1–4</sup> The association between obesity and diabetes is well established by that obese individuals are accompanied with an increased risk for T2DM, and 90% of patients with T2DM have an excess body weight.<sup>5,6</sup> Furthermore, effective weight loss in obese subjects with or without T2DM is associated with improvements of metabolic condition.<sup>7–9</sup> Conventional medical treatment of T2DM is usually a multimodal approach consisting of an appropriate diet, exercise, and various pharmacotherapeutics. However, few patients manage to satisfy the targets of T2DM treatment concepts.<sup>10</sup>

Although originally developed solely as a weight loss therapy, it has been shown that bariatric surgery not only leads to substantial weight loss but also to T2DM remission for patients with severe obesity.<sup>11</sup> Bariatric surgery has been recommended for severely obese patients with a body mass index (BMI) of >40 kg/m<sup>2</sup> or >35 kg/m<sup>2</sup> with obesity-related comorbidities.<sup>12</sup> Recently, more and more studies have indicated that bariatric surgery in nonseverely obese patients (BMI of <35 kg/m<sup>2</sup>) might be even superior to medical therapy with regard to diabetes

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remission, improvements of metabolic condition, and cardiovascular risk factors.<sup>13–15</sup> So far, it even appeared that a great number of T2DM patients with mild-moderate obesity (BMI of  $>30$  kg/m<sup>2</sup> and  $<40$  kg/m<sup>2</sup>) have becoming the majority of subjects undergone bariatric surgery.<sup>16–19</sup>

As a growing body of literature reported the outcomes of bariatric surgery for treatment of T2DM in obese patients, even some randomized controlled trials (RCTs) with longer-term follow-up outcomes have been completed recently.<sup>20–22</sup> Several reviews evaluating bariatric surgery against medical treatment in obese patients have been published recently.<sup>23–25</sup> However, a critically appraised pooled summary and meta-analysis of the available RCTs on solely Roux-en-Y gastric bypass (RYGB) surgery comparing with medical treatment alone is still missing, despite RYGB surgery is one of the most common bariatric surgery and RCTs were level I evidence for the clinical study.

The objective of this systematic review and meta-analysis was to evaluate the effectiveness of RYGB surgery versus medical treatment for T2DM in obese patients. T2DM remission served as the main outcome. Furthermore, hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), BMI, waist circumference, serum lipid level, blood pressure, medication use, and adverse events were evaluated.

## METHODS

### Search Strategy

We conducted a systematic review of the English-language literature published up to December 2015 by searching abstracts in PubMed, Embase, Cochrane Database, and Cochrane Clinical Trials Registry, using the search terms: [bariatric surgery OR obesity surgery OR metabolic surgery OR Roux-en-Y gastric bypass] AND [medical therapy OR nonsurgical treatment] AND [type 2 diabetes OR morbid obesity] AND [randomized controlled trial OR randomized clinical trial]. Additional cross-referencing was carried out for all the included studies. This systematic review was performed according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.<sup>26</sup> Two researchers (YY and YS) independently searched for literatures, selected studies, assessed quality, and extracted data from articles and then cross-checked. Any disagreement was resolved by consulting a third reviewer (GY). As all analyses were based on previous published studies, ethics approval was not required for this systematic review.

### Inclusion Criteria

RCTs evaluated RYGB surgery in patients with T2DM and investigated medical treatment as comparator were included in the meta-analysis if each treatment group included patients with BMI of 30 kg/m<sup>2</sup> or more and the mean BMI of each treatment group was 30 kg/m<sup>2</sup> or more. The RYGB procedure performed in order to improve metabolic conditions in patients with T2DM and obesity regardless of laparoscopic or open way. The rate of diabetes remission, HbA1c, FPG, BMI, waist circumference, serum lipid level, blood pressure, medication use, and adverse events were reported. Case reports, prospective studies, letters, comments, reviews, and animal studies were excluded.

### Data Extraction and Quality Assessment

The primary outcome was T2DM remission. Different definitions for diabetes remission were used as reported in

the article. Furthermore, secondary outcomes comprised HbA1c, FPG, BMI, waist circumference, serum lipid level, blood pressure, medication use, and adverse events. Outcome parameters of all the included studies were extracted by using a standardized data form. Additionally, general characteristics of studies, baseline characteristics of patients, inclusion and exclusion criteria of patients, details of interventions, and definition of outcomes were extracted from the included studies. In the case of missing data, the study authors were contacted for completion. Previously published follow-up data were also included to complete the outcome parameters. The methodological quality of the included RCTs was assessed as described by the *Cochrane Handbook for Systematic Reviews*.<sup>27</sup>

### Statistical Analysis

All statistical analyses were performed using Review Manager 5.2 software (the Cochrane Collaboration, <http://www.cochrane.org>). For dichotomous data, the odds ratio (OR) was calculated. For continuous data, the mean difference (MD) was calculated for the effect size based on the mean and standard deviation given in the retrieved studies. Missing mean and standard deviations at study end were calculated from other statistics if needed, such as values of mean change from baseline or baseline standard deviations. For all analyses, a random-effects model with 95% confidence intervals (CI) was used to adjust for possible variations in the treatment effect between the studies. Heterogeneity was assessed by the  $I^2$  statistic, with values of  $>50\%$  considered to indicate significant heterogeneity. The  $P$  value for the overall effect was calculated using the  $z$  test, with significance set at  $P < 0.05$ . Sensitivity analysis and estimation of publication bias were also performed.

## RESULTS

### Study Selection

The flow diagram of study selection procedure is shown in Figure 1. A total of 39 articles were retrieved by literature searches. A full-text review was performed on 15 articles. After evaluating articles according to selection, 6 eligible RCTs

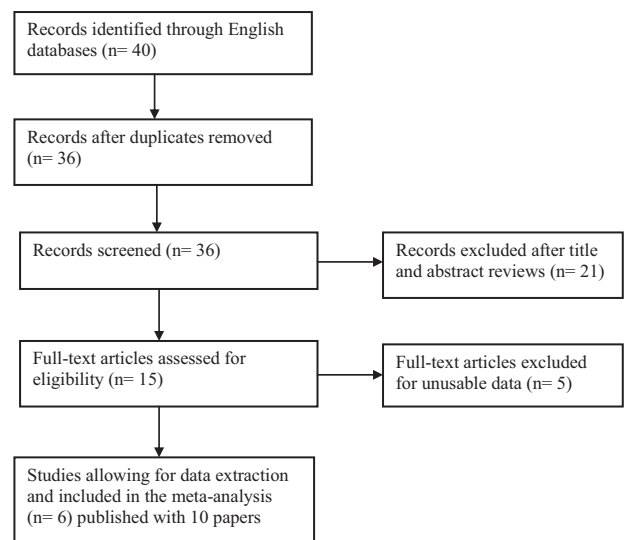


FIGURE 1. Flow diagram of included and excluded studies.

published with 10 full-length articles which met the inclusion criteria were finally included,<sup>20–22,28–30</sup> as the RCT by Courcoulas et al, Ikramuddin et al, Schauer et al, and Mingrone et al had additional 1-year, 1-year, 1-year, and 2 years outcomes published, respectively.<sup>31–34</sup>

**Study Characteristics**

These trials included a total of 410 diabetic patients with 204 who underwent RYGB and 206 who received medical treatment alone, and 57% were women. The baseline characteristics of patients in each treatment group are summarized in Table 1. The 6 included studies were conducted in USA (3), China (1), Italy (1), and in the USA and Taiwan (1). There were no significant differences among the study groups in baseline characteristics, except for serum lipid levels in study by Mingrone et al, in which higher values of total cholesterol, low-density lipoprotein, and triglycerides in the medical treatment group were found comparing with the RYGB group.<sup>34</sup> The mean BMI of the study population was >35 kg/m<sup>2</sup>, except for the RCT by Ikramuddin et al and Liang et al was <35 kg/m<sup>2</sup>, but the mean BMI was >40 kg/m<sup>2</sup> in study by Mingrone et al. In those 3 studies, the mean BMIs of the study population were 34.6 kg/m<sup>2</sup>, 30.4 kg/m<sup>2</sup>, and 45.2 kg/m<sup>2</sup>, respectively. All studies included patients with T2DM, and the mean duration of T2DM in each treatment group was ranged from 5.7 to 10.6 years. The mean HbA1c level of the study population was ranged from 7.9% to 10.5%. The mean age of the treatment group was ranged from 43.5 to 52.6 years. Study follow-up ranged from 12 to 60 months.

The characteristics of patient recruitment and intervention details of all included RCTs are summarized in Tables S1 and S6, <http://links.lww.com/MD/A931>, respectively. All 6 studies included patients with BMI of 30 kg/m<sup>2</sup> or more, and one<sup>22</sup> of which performed exclusively in patients with BMI of 35 kg/m<sup>2</sup> or more. Surgical treatment was standardized in all studies, and RYGB surgery was performed laparoscopically in 4 studies.<sup>21,22,29,30</sup> Within all included RCTs, bariatric surgery was compared with nonsurgical treatment which generally comprised reducing energy intake, increasing physical activity, weight management, and receiving medications for control of hyperglycemia, dyslipidemia, and hypertension, directed by a multidisciplinary team. Medical treatment was standardized in 4 studies, which was modeled on both the Diabetes Prevention Program<sup>35</sup> and the Look AHEAD trial protocol<sup>36</sup> in studies by Ikramuddin et al and Courcoulas et al, the Why WAIT program<sup>37</sup> in study by Halperin et al, and the American Diabetes Association guidelines<sup>38</sup> in study by Schauer et al. The details of medication use during the study follow-up were reported by all RCTs but one<sup>20</sup> (Table S5, <http://links.lww.com/MD/A931>). Furthermore, the goal of medical treatment was reported in 4 RCTs,<sup>21,22,29,30</sup> which was modification of medications until the patient reached the target HbA1c level <7.0% in 3 studies<sup>21,22,29</sup> and of 6.0% or less in a study by Schauer et al. The same medical treatment for the nonsurgical group was also offered to the RYGB group in 2 studies.<sup>21,30</sup>

Remission of T2DM was reported by 5 RCTs with different definition for diabetes remission in 4 studies according to the study reported,<sup>20–22,30</sup> and 1 study did not report a definition.<sup>29</sup> The target HbA1c level for T2DM remission ranged from 5.7% to 6.5%. What is more, 2 kinds of definition, full and partial remission, were given by studies by Ikramuddin et al, Courcoulas et al, and Mingrone et al. Two studies demanded solely a target HbA1c level of 6.0% or less without diabetes

**TABLE 1.** Description of Patients at Baseline From Studies Included in the Meta-Analysis

Study	Site	Intervention	No. (M/F)	Age (Years)	BMI (kg/m <sup>2</sup> )	Body Weight (kg)	T2DM Duration (Years)	HbA1c (%)	Follow-Up (Months)
Ikramuddin et al <sup>21</sup> 2015	USA and Taiwan	RYGB	60 (22/38)	49 ± 9	34.9 ± 3.0	98.8 ± 14.0	8.9 ± 6.1	9.6 ± 1.0	24
Courcoulas et al <sup>20</sup> 2015	USA	Medical	60 (26/34)	49 ± 8	34.3 ± 3.1	97.9 ± 17.0	9.1 ± 5.6	9.6 ± 1.2	36
		RYGB	24 (5/19)	46.3 ± 7.2	35.5 ± 2.6	99.8 ± 12.8	7.4 ± 4.5	8.7 ± 2.2	
Halperin et al <sup>28</sup> 2014	USA	Medical	23 (4/19)	48.3 ± 4.7	35.7 ± 3.3	102.6 ± 13.8	5.7 ± 5.6	7.0 ± 0.8	12
		RYGB	19 (6/13) <sup>†</sup>	50.7 ± 7.6	36.0 ± 3.5	104.6 ± 15.5	10.6 ± 6.6	8.24 ± 1.42	
Schauer et al <sup>30</sup> 2014	USA	Medical	19 (9/10) <sup>†</sup>	52.6 ± 4.3	36.5 ± 3.4	102.7 ± 17.0	10.2 ± 6.1	8.83 ± 1.01	36
		RYGB	50 (21/29)	48.3 ± 8.4	37.0 ± 3.3	106.7 ± 14.8	8.2 ± 5.5	9.3 ± 1.4	
Liang et al <sup>29</sup> 2013	China	Medical	50 (19/31)	49.7 ± 7.4	36.8 ± 3.0	106.5 ± 14.7	8.9 ± 5.8	9.0 ± 1.4 <sup>§</sup>	12
		RYGB	31 (22/9) <sup>†</sup>	50.81 ± 5.44	30.48 ± 0.94	81.97 ± 3.53	7.39 ± 1.69	10.47 ± 1.17	
Mingrone et al <sup>22</sup> 2015	Italy	Medical*	34 (24/10) <sup>‡</sup>	50.94 ± 5.89	30.28 ± 1.44	81.76 ± 3.67	7.17 ± 1.80	10.52 ± 1.49	60
		RYGB	20 (8/12)	43.90 ± 7.57	44.85 ± 5.16	129.84 ± 22.58	6.03 ± 1.18	8.56 ± 1.40	
		Medical	20 (10/10)	43.45 ± 7.27	45.62 ± 6.24	136.40 ± 21.94	6.08 ± 1.24	8.51 ± 1.24	

BMI = body mass index, HbA1c = hemoglobin A1c, No. (M/F) = number of patients (male/female). T2DM = type 2 diabetes mellitus.

\*This is the usual care plus exenatide treatment group in Liang 2013 with 2 nonsurgical groups.

<sup>†</sup>Excluded patients who lost to follow-up before intervention.

<sup>‡</sup>Excluded patients who did not complete the trial.

<sup>§</sup>Data from 40 patients included in 3-year outcome analysis.



medication,<sup>21,30</sup> the other 2 studies additionally demanded an FPG level <5.6 mmol/L.<sup>20,22</sup> The definition of outcome in each study was resumed in Table 2. We included the total (full and partial) T2DM remission data in meta-analysis. We calculated the mean values at study end from mean change variables and baseline values, and imputed baseline standard deviations in studies by Halperin et al and Courcoulas et al.

## Study Quality

The results of risk bias assessment are shown in Table S2, <http://links.lww.com/MD/A931>. The sequence generation for randomization was adequate in all studies. Concealment of group allocation was unclear in 1 study.<sup>29</sup> In none of these studies, patients and healthcare providers were blind. In 5 studies not all randomized individuals were analyzed.<sup>20–22,29,30</sup> Missing outcome data were not addressed in 1 study.<sup>29</sup> All but one<sup>29</sup> study were free of selective reporting.

## Medication Use

All the included studies reported the changes of medication use during follow-up (Table S3, <http://links.lww.com/MD/A931>). All studies reported the number of medicines for control of hyperglycemia, dyslipidemia, and hypertension in the surgical group was significantly reduced more than the medical treatment group. Furthermore, the quality of life was solely significantly improved after RYGB surgery in 2 studies (Table S4, <http://links.lww.com/MD/A931>).<sup>22,30</sup> However, medication use in patients who received medical treatment alone was frequently reported without significant improvement at study end.

## Adverse Events

All studies reported adverse events in the publication, and adverse events are listed in Table S5, <http://links.lww.com/MD/A931>. There was heterogeneity in the definitions of adverse events among studies. Although there were no deaths during operation, 1 postoperative complications merit particular attention in a study by Ikramuddin et al.<sup>32</sup> That was 1 patient undergone RYGB surgery developed a leak from the jejunojejunostomy ultimately led to anoxic brain injury, lower extremity amputation, and long-term disability. In a study by Mingrone et al, 1 patient in the medical group suffered fatal myocardial infarction that led to the death during the 5-year follow-up.<sup>22</sup> After RYGB surgery, 160 adverse events were reported in 199 patients, included 35 developed hypoglycemic episode, 11 developed anemia, 8 developed anastomotic ulcer, 4 developed intestinal obstruction, and 2 developed anastomotic leak. In the medical treatment group, 119 adverse events were reported in 190 patients, included 39 developed hypoglycemic episode, 7 developed renal calculus, and 6 developed anemia. Depression with suicide attempt developed in 1/199 of surgically treated and in 1/190 of medically treated individuals. It is worth mentioning, nutritional deficiencies were noted more frequently in the RYGB group, mainly a greater incidence of iron-deficiency anemia.

## Meta-Analysis Results

### T2DM Remission

Five of the 6 studies reported T2DM remission rates.<sup>20–22,29,30</sup> The T2DM remission rate was 56.81% (100/176) in the surgical group and 0% (0/162) in the medical treatment group. The pooled analysis of T2DM remission rates revealed a significantly higher remission rate after RYGB

surgery than after medical treatment alone (OR: 76.37, 95% CI: 20.70–281.73,  $P < 0.001$ ) (Figure 2).

### Serum HbA1c Level

All the included studies reported HbA1c levels in the study end. The pooled analysis revealed that the serum HbA1c level was lower by the end of postsurgical follow-up than after medical treatment alone (MD: -1.25%, 95% CI: -1.88% to -0.63%,  $P < 0.001$ ) (Figure 3A).

### FPG

Four of the 6 studies reported FPG levels in the study end.<sup>20–22,28</sup> Meta-analysis revealed no statistical significance between the 2 groups in terms of FPG level (MD: -1.58 mmol/L, 95% CI: -3.58 to 0.41 mmol/L,  $P = 0.12$ ) (Figure 3B).

### BMI

All the included studies reported the BMI at study end as a parameter of weight loss. Meta-analysis showed a significant lower BMI in individuals undergone RYGB surgery than those received medical therapy alone (MD: -6.54 kg/m<sup>2</sup>, 95% CI: -9.28 to -3.80 kg/m<sup>2</sup>,  $P < 0.001$ ) (Figure 4A). The result suggested that RYGB surgery is associated with a more powerful effect on weight loss.

### Waist Circumference

Five of the 6 studies reported the waist circumference as the index of abdominal fat mass.<sup>20–22,28,30</sup> Meta-analysis showed a significant lower waist circumference in individuals undergone RYGB surgery than those received medical therapy alone (MD: -15.60 cm, 95% CI: -18.21 to -13.00 cm,  $P < 0.001$ ) (Figure 4B). The result suggested that RYGB surgery can more powerfully reduce abdominal fat mass.

### Serum Lipid Profiles

Triglyceride concentrations are available for 5 studies.<sup>20–22,28,29</sup> Triglyceride concentrations decreased more after RYGB surgery than after medical treatment alone (MD: -0.87 mmol/L, 95% CI: -1.17 to -0.57 mmol/L,  $P < 0.001$ ) (Figure 5A). Furthermore, high-density lipoprotein cholesterol increased more (MD: 0.24 mmol/L, 95% CI: 0.18–0.30 mmol/L,  $P < 0.001$ ) and low-density lipoprotein cholesterol decreased more (MD: -0.32 mmol/L, 95% CI: -0.62 to -0.02 mmol/L,  $P < 0.05$ ) after RYGB surgery than after medical treatment alone (Figure 5C and D). However, total cholesterol was not significantly different between surgical and medical treatment (MD: -0.40 mmol/L, 95% CI: -0.92 to 0.12 mmol/L,  $P = 0.13$ ) (Figure 5B).

### Blood Pressure

All 6 studies reported systolic blood pressure, but diastolic blood pressure was available for 5 studies. The pooled analysis revealed that systolic blood pressure was lower by the end of postsurgical follow-up than after medical treatment alone (MD: -2.83 mm Hg, 95% CI: -4.88 to -0.78 mm Hg,  $P < 0.01$ ) (Figure 6A). However, diastolic blood pressure was not significantly different between the 2 treatment groups (MD: 0.28 mm Hg, 95% CI: -1.89 to 2.45 mm Hg,  $P = 0.80$ ) (Figure 6B).

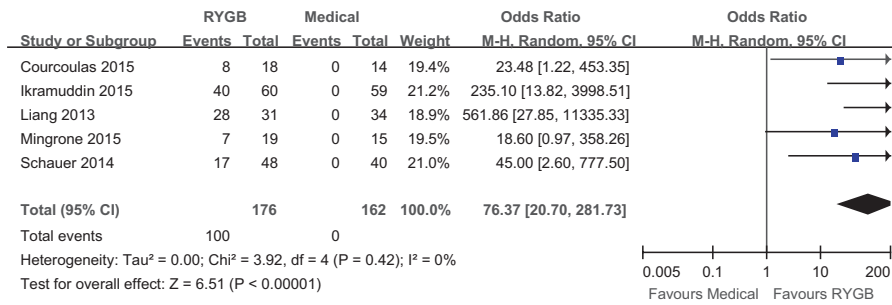
### Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed to determine the significance of results by sequentially repeating the meta-analysis

**TABLE 2.** Outcome Definition

Study	Main Outcome	Secondary Outcomes	Definition of T2DM Remission
Ikramuddin et al <sup>21</sup> 2015	Achievement of the composite triple endpoint of HbA1c <7.0%, LDL < 2.59 mmol/L and SBP < 130 mm Hg	Weight loss, FPG, HDL cholesterol, C-peptide, and triglyceride concentrations, DBP, waist circumference, and use of medicines to control glycemia, cholesterol, blood pressure, and occurrences of diabetes remission	Partial remission: HbA1c ≤ 6.5% with no medicines for hyperglycemia Full remission: HbA1c ≤ 6.0% with no medicines for hyperglycemia
Courcoulas et al <sup>20</sup> 2015	The rate of diabetes remission	Bodyweight, BMI, and waist circumference, glycemic control, the use of glucose-lowering medications (categorized; none, insulin only, insulin/other medication, and oral/other medication), lipid levels (total cholesterol, triglycerides, HDL, LDL), blood pressure, and body composition (percentage of body fat, lean mass, and bone mass)	Partial remission: the absence of antidiabetics with HbA1c < 6.5% and FPG ≤ 6.9 mmol/L; Full remission: the absence of antidiabetics with HbA1c < 5.7% and FPG ≤ 5.6 mmol/L
Halperin et al <sup>28</sup> 2014	The rate of glycemic control (HbA1c < 6.5% and FPG < 7.0 mmol/L), regardless pharmaceutical interventions	Weight and glycemia (weight loss, waist circumference, fat and lean mass, HbA1c, FPG), blood pressure and lipid levels, cardiometabolic risk, patient-reported outcomes, and adverse events	Not available
Schauer et al <sup>30</sup> 2014	Proportion of patients with HbA1c ≤ 6.0%, regardless diabetes medications	Measures of glycemic control, weight loss, blood pressure, lipid levels, renal function, carotid intima-media thickness, medication use, adverse events, disease-related complications, and quality of life (evaluated by the RAND 36-Item Health Survey)	HbA1c ≤ 6.0% without diabetes medications
Liang et al <sup>29</sup> 2013	Cardiac function (left ventricular mass index)	Metabolic parameters (BMI, HbA1c, HOMA-IR, and lipids), inflammatory cytokines (hs-CRP, TNF-α, HMW-adiponectin), adverse events	Not reported
Mingrone et al <sup>22</sup> 2015	The rate of diabetes remission at 2 years	Durability of diabetes remission and relapse of hyperglycemia, glycemic control, bodyweight, BMI, waist circumference, arterial blood pressure, plasma total cholesterol, HDL cholesterol and triglycerides, cardiovascular risk, medication use, quality of life, adverse effects of surgery, and diabetes-related complications	Partial remission: 5.6 ≤ FPG ≤ 6.9 mmol/L and HbA1c < 6.5% for at least 1 year without treatment; Full remission: FPG < 5.6 mmol/L and HbA1c < 6.0% for at least 1 year without treatment

BMI = body mass index, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL = high-density lipoprotein, HMW = high-molecular weight, HOMA-IR = homeostasis model assessment of insulin resistance, hs-CRP = high-sensitive C response protein.



**FIGURE 2.** Forest plot of the type 2 diabetes mellitus remission rate after RYGB surgery compared to medical treatment. The remission rate was higher in the RYGB group than the medical group (OR: 76.37, 95% CI: 20.70–281.73,  $P < 0.001$ ). CI = confidence interval, OR = odds ratio, RYGB = Roux-en-Y gastric bypass.

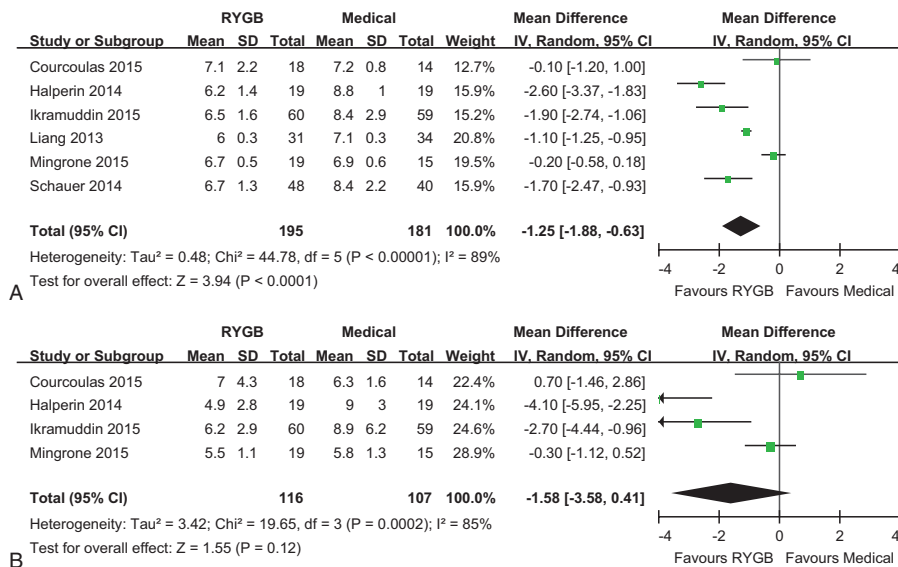
excluding 1 study at a time. The results of this analysis suggested that the pooled OR and MD values were not significantly affected except for FPG result. The pooled MD value of FPG was significantly affected after excluded 2 longer-term follow-up studies (data not shown).<sup>20,22</sup> As statistically significant data are published more frequently than nonsignificant data, our results may be influenced by publication bias (Figure 7).

**DISCUSSION**

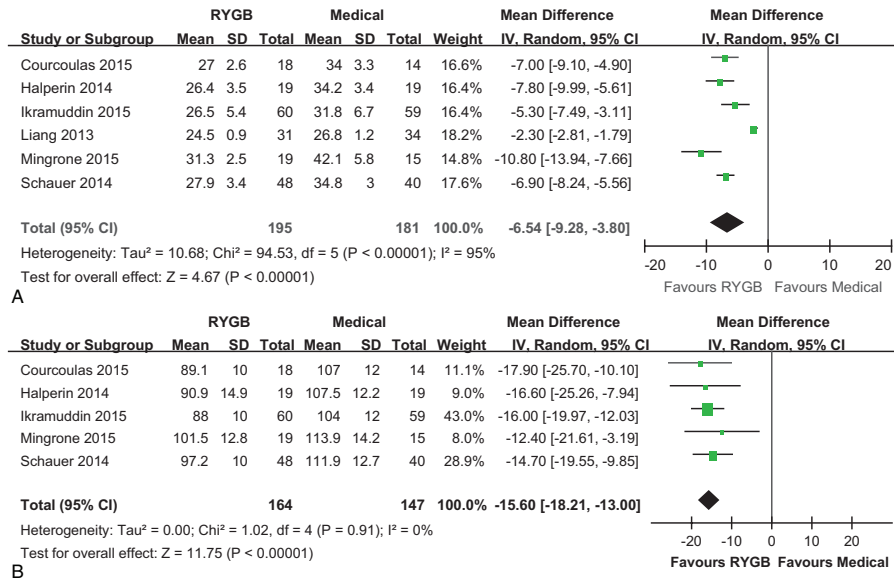
This systematic review and meta-analysis demonstrates that RYGB surgery is more efficient than medical treatment alone for T2DM in obese patients. According to the results of pooled analysis, RYGB surgery is superior in terms of short- to medium-term (12–60 months) T2DM remission. After RYGB surgery, HbA1c, triglycerides, and low-density lipoprotein cholesterol decreased more, and high-density lipoprotein cholesterol increased more. Furthermore, RYGB surgery led to greater weight loss and abdominal fat mass reduction, and

greater reductions in use of antidiabetic, antihypertensive, and lipid-lowering drugs. Although nutritional deficiencies and anemia were noted more frequently in the RYGB group, the quality of life was improved more in the surgical group.<sup>22,30</sup> There was no significant difference of FPG level between the 2 groups after included 2 longer-term studies, which may due to relapsed hyperglycemia during longer-term follow-up in the surgical group and more efficient antidiabetic drugs used in the medical group.<sup>20,22</sup> As a consequence, RYGB surgery should be considered an efficient treatment option for T2DM in obese patients, but continued monitoring of glycogenic control is warranted because of potential relapse of hyperglycemia in some patients.

The effect of RYGB surgery on diabetes remission seems to be strictly different compared to the effect of medical treatment alone, as 56.81% (100/176) of patients undergone RYGB surgery and none of the 162 patients received medical treatment alone attained diabetes remission. In the Swiss Multi-centre Bypass or Sleeve Study (SM-BOSS), 67.9% of obese



**FIGURE 3.** Forest plot of HbA1c (A) and FPG (B) level after RYGB surgery compared to medical treatment. The HbA1c level was lower in the RYGB group than the medical group (MD: -1.25, 95% CI: -1.88 to -0.63,  $P < 0.001$ ). The FPG level was similar in RYGB and medical groups (MD: -1.58, 95% CI: -3.58 to 0.41,  $P = 0.12$ ). CI = confidence interval, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, MD = mean difference, RYGB = Roux-en-Y gastric bypass.



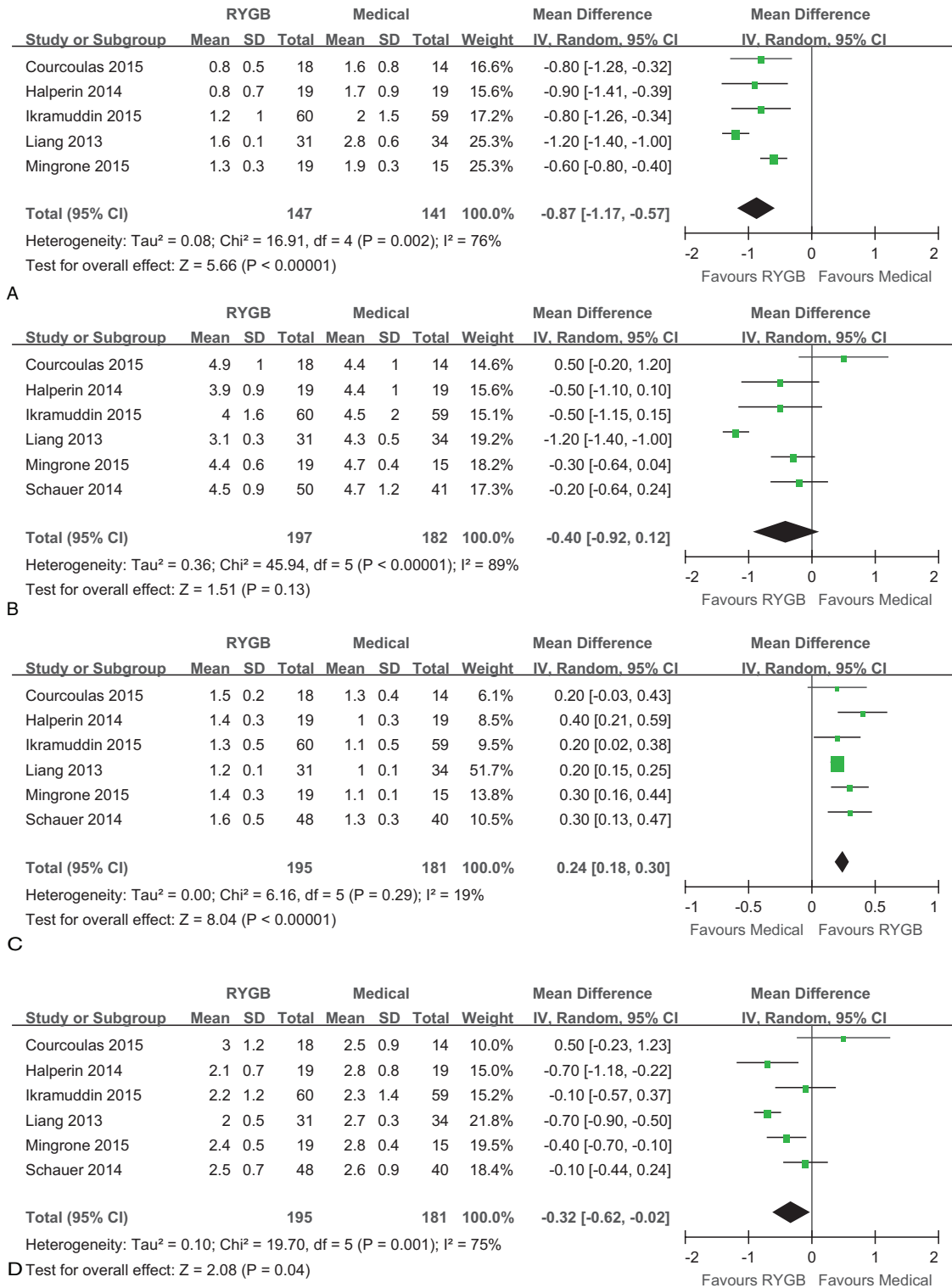
**FIGURE 4.** Forest plot of BMI (A) and waist circumference (B) level after RYGB surgery compared to medical treatment. Both BMI (MD: -6.54, 95% CI: -9.28 to -3.80, P < 0.001) and waist circumference (MD: -15.60, 95% CI: -18.21 to -13.00, P < 0.001) were lower in the RYGB group than the medical group. BMI = body mass index, CI = confidence interval, MD = mean difference, RYGB = Roux-en-Y gastric bypass.

patients with T2DM in the RYGB group were not taking medication 1 year after surgery.<sup>39</sup> In the recent meta-analysis from Ribaric et al, relative to diabetes and weight in comparative studies of bariatric surgery versus conventional medical therapy, the overall T2DM remission rate for surgery versus conventional group was 63.5% and 15.6%, respectively.<sup>25</sup> Nowadays, more and more nonseverely obese patients (BMI < 35 kg/m<sup>2</sup>) with T2DM received bariatric surgery have also achieved ideal goals, as 5 of the 6 included studies in our meta-analysis recruited participants with BMI < 35 kg/m<sup>2</sup>.<sup>20,21,28-30</sup> In fact, less obese patient who choose to receive bariatric surgery are more likely to have severe diabetes, as the mean duration of T2DM in each treatment group was ranged from 5.7 to 10.6 years in our meta-analysis. Our results of T2DM remission are somewhat lower than previous reported studies; such differences could be explained by the greater severity, longer duration of diabetes and longer-term follow-up in our population, as well as a stricter definition of diabetes remission based on American Diabetes Association guidelines used in studies conducted in recent years.<sup>20,21,30</sup> With regard to the pooled analysis of T2DM remission, our results (OR: 76.37, 95% CI: 20.70-281.73) is consistent with a network meta-analysis from Muller-Stich et al compared RYGB surgery with medical treatment in nonseverely obese patients (OR: 55.1, 95% CI: 12.2-248.5).<sup>24</sup>

The results of our meta-analysis showed that RYGB surgery was significantly more efficient than medical treatment alone, with regard to improving of obesity, hyperglycemia, hyperlipidemia, and arterial hypertension, indicating the improvements of metabolic condition and cardiovascular risk factors.<sup>40,41</sup> Unlike specific medical treatment with poor outcomes associated with massive quantities of medication used to stringently control hyperglycemia, hyperlipidemia, and arterial hypertension, RYGB surgery seems to have a multifactorial effect on T2DM and its associated comorbidities.<sup>42</sup> Although the significant and durable caloric restriction and body weight

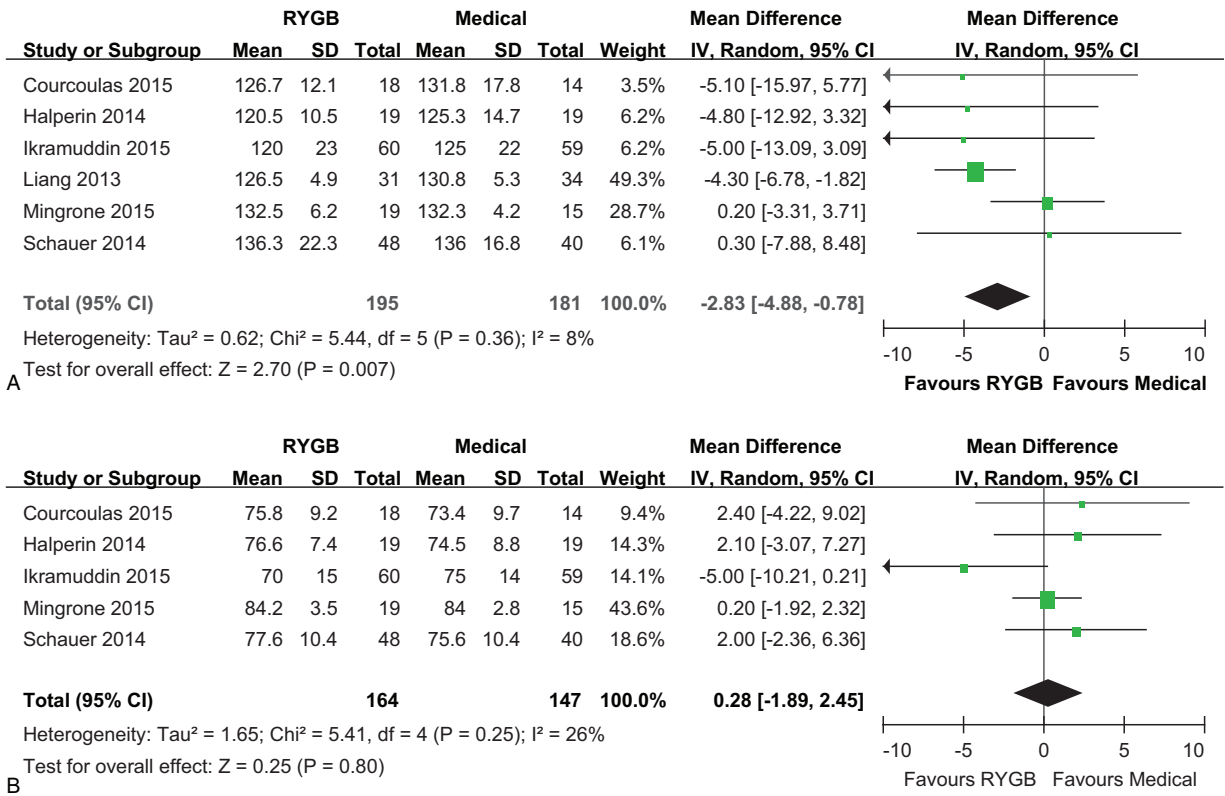
loss might explain some of the greater improvements in hyperglycemia, hyperlipidemia, and arterial hypertension after RYGB surgery compared with medical treatment alone, numerous studies have indicated that RYGB surgery caused favorable outcomes independent of caloric restriction and weight loss.<sup>43</sup> Currently several potential mechanisms are being discussed, the bile acid-mediated regulation of metabolism via activation of farnesoid X receptor and TGR5,<sup>44-46</sup> the jejunal nutrient sensor that may be enhanced by bypassing the jejunum,<sup>47</sup> the altered microbiota in small intestine,<sup>48</sup> the reprogramming of intestinal glucose metabolism after intestinal reconstruction,<sup>49</sup> as well as the decreased obesity-induced and inflammation-mediated insulin resistance,<sup>50</sup> all of which has been linked to improvements of metabolic condition after RYGB surgery. Unraveling the precise mechanisms underlying the effects induced by RYGB surgery may potentially lead to promising targets of novel drugs for treatment metabolic diseases.

Despite the discussions above, it is important to notice that there are some negative metabolic consequences after RYGB surgery, the rate of overall adverse events was higher in the surgical group with 80.40% (160/199) compared to the medical group with 62.63% (119/190). As the RYGB procedure comprised of gastric restriction and intestinal bypass, malabsorption of micronutrients (including vitamins, calcium, zinc, and iron) is a problem after surgery. Despite protocol requirements for supplementation, nutritional deficiencies and iron deficiency anemia were common after RYGB surgery.<sup>51,52</sup> There are also other complications after RYGB surgery and all we need to focus on, which included a variety of different forms, such as anastomotic leaks, stenosis, small bowel obstruction, gastrointestinal hemorrhage, internal hernias, and so on. Other negative effects such as dumping syndrome and gastroesophageal reflux disease are more likely to torment patient undergone RYGB surgery.<sup>53</sup> The complication rate, mortality rate, and reoperation rate not mentioned here are also important determinants in recommending surgical intervention for diabetes management.



**FIGURE 5.** Forest plot of triglyceride (A), total cholesterol (B), high-density lipoprotein cholesterol (C), and low-density lipoprotein cholesterol (D) after RYGB surgery compared to medical treatment. The levels of triglyceride (MD: -0.87, 95% CI: -1.17 to -0.57, P < 0.001) and low-density lipoprotein cholesterol (MD: -0.32, 95% CI: -0.62 to -0.02, P = 0.04) were lower in the RYGB group than the medical group. The total cholesterol level was similar in RYGB and medical groups (MD: -0.40, 95% CI: -0.92 to 0.12, P = 0.13). The high-density lipoprotein cholesterol (MD: 0.24, 95% CI: 0.18-0.30, P < 0.001) level was higher in the RYGB group than the medical group. CI = confidence interval, MD = mean difference, RYGB = Roux-en-Y gastric bypass.



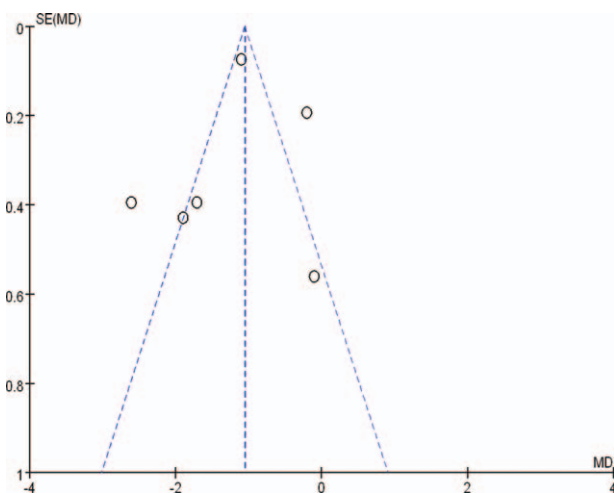


**FIGURE 6.** Forest plot of systolic blood pressure (A) and diastolic blood pressure (B) after RYGB surgery compared to medical treatment. The systolic blood pressure was lower in the RYGB group than the medical group (MD: -2.83, 95% CI: -4.88 to -0.78, P < 0.01). The diastolic blood pressure was similar in RYGB and medical groups (MD: 0.28, 95% CI: -1.89 to 2.45, P = 0.80). CI = confidence interval, MD = mean difference, RYGB = Roux-en-Y gastric bypass.

Bariatric surgery is not without risks, the mortality up to 30 days was 0.16% for RYGB surgery in a meta-analysis included 361 studies of 85 048 patients.<sup>54</sup> In the American College of Surgeons Bariatric Surgery Network database, the 30-day complication rate was 5.9% for RYGB surgery.<sup>55</sup> It is important to

notice that the merit of RYGB surgery treatment of obese patients with T2DM depends on whether potential risks make benefits acceptable.

Although this meta-analysis provided comprehensive evidence that to which extent efficacy of RYGB surgery for T2DM in obese patients compared with medical treatment alone, some limitations must be taken into account. First, we included a small number of studies and as the included participants, as available RCTs on RYGB surgery against medical treatment alone in obese patients with T2DM is rare to date. Additionally, we only searched for English literature and significant data are published more frequently than non-significant data, our results may be influenced by publication bias. Second, there were certain differences in respect to baseline characteristics of patients, length of follow-up, implementation of interventions, and criteria for T2DM remission among the different studies. Third but not the last, the quality assessment of the included studies revealed moderated quality within all RCTs, as patients and health providers were not blinded in all included studies. As all of above limitations may affect the accuracy of this meta-analysis, data were pooled conservatively with random-effects models.<sup>56</sup> The quantity and quality of available evidence limit our conclusion. However, most of the treatment effect could be reproduced in a sensitivity analysis by sequentially repeating the meta-analysis excluding 1 study at a time, and the fixed-effects model did not change significantly. Despite the discussions above, the pooled data of currently available evidence showed that RYGB



**FIGURE 7.** Funnel plot of HbA1c for assessing publication bias. HbA1c = hemoglobin A1c.

surgery is more efficient for treatment of obese T2DM patients than medical treatment alone.

As there is no consensus on reporting adverse events of surgical and medical interventions, and little available data, we could not perform a meta-analysis on surgical risks. This meta-analysis included studies with follow-up periods ranged from 12 to 60 months just represented short to medium-term benefits of improvements of metabolic condition and cardiovascular risk factors. Theoretically, such improvements have the potential to reduce cardiovascular morbidity and mortality in the long term, as shown in nonrandomized studies.<sup>41,57</sup> Long-term outcomes of RYGB surgery for metabolic conditions, diabetes-related complications, and mortality, should be evaluated among obese patients. Surgeons should focus on the potential surgical risks and long-term benefits fully of using RYGB surgery to reduce the complications and mortality associated with T2DM. Well-designed studies evaluating surgical risks and long-term outcomes should be conducted in the future.

### CONCLUSION

This meta-analysis showed the short to medium-term superiority of RYGB surgery to medical treatment, with regard to T2DM remission, improvement of metabolic condition, and cardiovascular risk factors. Additionally, well-designed studies with consistent definition of adverse events, as well as a larger number of RCTs with long-term follow-up (>60 months) are needed to evaluate the safety and long-term benefits of RYGB surgery on obese patients with T2DM.

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