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ORIGINAL CONTRIBUTIONS

Does Metabolic Surgery Lead to Diabetes Remission in Patients with BMI < 30 kg/m^2?: a Meta-analysis

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Abstract

Background Bariatric surgery has demonstrated to be effective in remission of type 2 diabetes in obese patients, but it is unclear in non-obese patients. The aim of this study is to investigate if metabolic surgery is effective in diabetes resolution in patients with BMI < 30 kg/m^2.

Materials and Methods A systematic review was performed and the content of the PubMed, Ovid, and the Cochrane Library databases covering the period January 2008 to April 2018 was searched. Studies with metabolic surgery performed in patients with type 2 diabetes, BMI < 30 kg/m^2 and a follow-up ≥ 6 months were included. Type 2 diabetes remission rate and metabolic parameters changes were measured. A meta-analysis was conducted with the selected studies.

Results Twenty-six studies were included in the meta-analysis (1105 patients). The mixed-effects meta-analysis model for overall diabetes remission rate produced an estimate of 43% (95% IC 34–53%, $p < 0.001$). Moderator effects of the variables race, preoperative HbA1c, BMI, months of follow-up, duration of diabetes, and age on diabetes remission were also assessed, with no significant effects being found in any of them. A reduction in BMI (− 3.57 kg/m^2), fasting blood glucose (− 55.93 mg/dL) and HbA1c (− 2.08%) was observed after surgery.

Conclusions Metabolic surgery could be effective in remission of type 2 diabetes in BMI < 30 kg/m^2 patients but randomized and long-term studies are necessary. The scientific community should agree in a single definition of type 2 diabetes remission, in order to know the real effect of metabolic surgery in this group of patients.

Keywords Metabolic surgery · Type 2 diabetes · BMI < 30 kg/m^2 · Systematic review · Meta-analysis

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Introduction

The World Health Organization (WHO) reported a global diabetes prevalence of 8.5% in 2014 [1]. The increasing number of individuals with type 2 diabetes mellitus (T2DM) among children and young adults has become a serious health problem that requires urgent treatment [2]. Bariatric surgery has demonstrated to be effective in weight loss and the resolution of obesity comorbidities in individuals with a BMI > 35 kg/m^2, and several studies with subjects with BMI > 30 kg/m^2 have been carried out in the last few years [3, 4]. A type 2 diabetes remission rate between 30 and 63% has been reported in clinical trials. Different metabolic and hormonal weight-independent mechanisms could be involved in diabetes resolution, suggesting that BMI at baseline does not predict surgical benefits on glycemic outcomes [5]. However, it remains unclear whether bariatric surgery benefits T2DM patients with a BMI of < 30 kg/m^2 due to the small sample size of studies, most of them being non-randomized studies and using different types of surgeries.

The aim of this systematic review and meta-analysis is to investigate if different bariatric procedures are effective in type 2 diabetes resolution in subjects with BMI < 30 kg/m^2.

Materials and Methods

Search Strategy

This meta-analysis was conducted in accordance with the methodology of the PRISMA Statement Guidelines (Preferred Reported Items for Systematic Reviews and Meta-analysis) [6]. The content of the PubMed, Ovid, and the Cochrane Library databases covering the period January 2008 to April 2018 was searched. Keywords used in electronic searches included "(bariatric surgery OR metabolic surgery OR Roux-en-Y OR gastric band OR anastomosis OR sleeve gastrectomy OR biliopancreatic diversion OR duodenal jejunal bypass OR duodenal jejunal exclusion OR ileal transposition) AND (diabetes OR type 2 diabetes) AND (body mass index < 30 OR overweight OR normal weight OR non-obese)".

The review was carried out as follows: first, we checked the title and abstract of the studies in order to exclude inappropriate studies. Second, we reviewed the full text of the remaining studies to identify whether they met inclusion criteria. Articles that only showed the abstract were included if sufficient data were reported. Communications at congresses were excluded. Reviews were checked to find potential eligible studies. Only papers written in English, Spanish, and French were retrieved. We checked the studies for duplicate publications.

Inclusion Criteria

Inclusion criteria chosen for the analysis:

1) T2DM patients with BMI < 30 kg/m^2 before surgery.
2) Clinical trial or observational studies.
3) Studies with any kind of bariatric surgery technique.
4) Follow-up ≥ 6 months.
5) Metabolic outcomes were reported (at least two outcomes, one of them must be diabetes remission).

When results from all patients in a study were reported more than once, data were extracted from the highest quality study.

Exclusion Criteria

Exclusion criteria were as follows:

1) Studies involving patients with type 1 diabetes, gestational diabetes, children, or teenagers.
2) Gastrointestinal pathology at baseline before surgery.
3) Studies with a follow-up less than 6 months.
4) Unpublished reports.
5) Patients who underwent a second bariatric surgery.
6) Animal or in vitro studies.

Data Collection and Quality Assessment

Data were extracted independently by two authors (MR and JC) from all included studies using a standardized electronic form. Any disagreement between reviewers was solved by a third author (RC).

The following data were extracted from the included articles: first author, year of publication, study design, type of surgery, patient characteristics (age, sex, duration of diabetes), number of subjects, time of follow-up, complications, and adverse events of surgery and outcomes. The following variables were analyzed to assess glycemic control before and after surgery: BMI, fasting blood glucose, glycated hemoglobin (HbA1c), c-peptide, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and diabetes remission.

The Newcastle-Ottawa Scale was used to assess the risk of bias of the studies. Using this tool each study was judged according to three items: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or the outcome of interest [7].

Objectives

Our main objective was to perform a meta-analysis of T2DM remission (number of subjects who achieved a target of glycemic control, defined by each study) in patients with BMI < 30 kg/m^2 who had undergone bariatric surgery. Secondary end points were to conduct a meta-analysis of BMI, FBG, and HbA1c prior to and after surgery. Other glycemic parameters such as c-peptide, insulin, and HOMA-IR were described if they were reported in studies.

Statistical Analysis

An estimation was performed for each studied parameter adjusting meta-analytic mixed-effects models with R package metafor (version 2.0-0) using the restricted maximum-likelihood (REML) estimator method. In the case of differences in parameter values between pre- and post-intervention, a different estimate was performed for pre- and post-intervention, since the data included in the studies did not allow for estimates of pre-post variability (necessary for paired-data meta-analyses). All estimates included a 95% confidence interval. p values < 0.05 were considered statistically significant.

Results

Literature Search

The literature search identified 5983 potentially relevant articles in the initial electronic search (3588 in PubMed, 1773 in Ovid and 622 in the Cochrane library) (Fig. 1), of which 708 were excluded for duplication. Five thousand one hundred eight articles were excluded on the basis of the title and the abstract, leaving 167 articles for the full-publication review. One hundred thirty-five articles were excluded for the following reasons: 114 articles with BMI > 30 kg/m^2, 2 articles were meta-analyses, 13 articles were reviews, one article was a case report, 2 papers included patients with cancer, and 3 articles only showed the abstract but without sufficient information. Thirty-two articles were retrieved as potential studies to be included and 6 of them were withdrawn (4 had inadequate information and 2 were overlapped studies). Finally, 26 studies were determined to be appropriate for inclusion in this meta-analysis.

The quality assessment of the included studies is shown in the supplementary table. Quality assessment showed that only 4 of 26 studies had a non-exposed cohort and were adequately controlled for confounders. A follow-up rate < 100% was observed in 5 studies, and it is remarkable that the follow-up rate was < 50% in 2 studies. These aspects can lead to the risk of bias.

Systematic Review and Quality Assessment

Baseline characteristics of studies included in the meta-analysis are shown in Table 1. Seventeen studies were prospective, 8 retrospective, and 1 a cross-sectional study. Different types of surgical procedures were performed: Roux-en-Y gastric bypass (RYGB) in 13 studies, duodenal-jejunal bypass surgery (DJB) in three, laparoscopic sleeve gastrectomy with duodenal-jejunal bypass (LSG + DJB) in

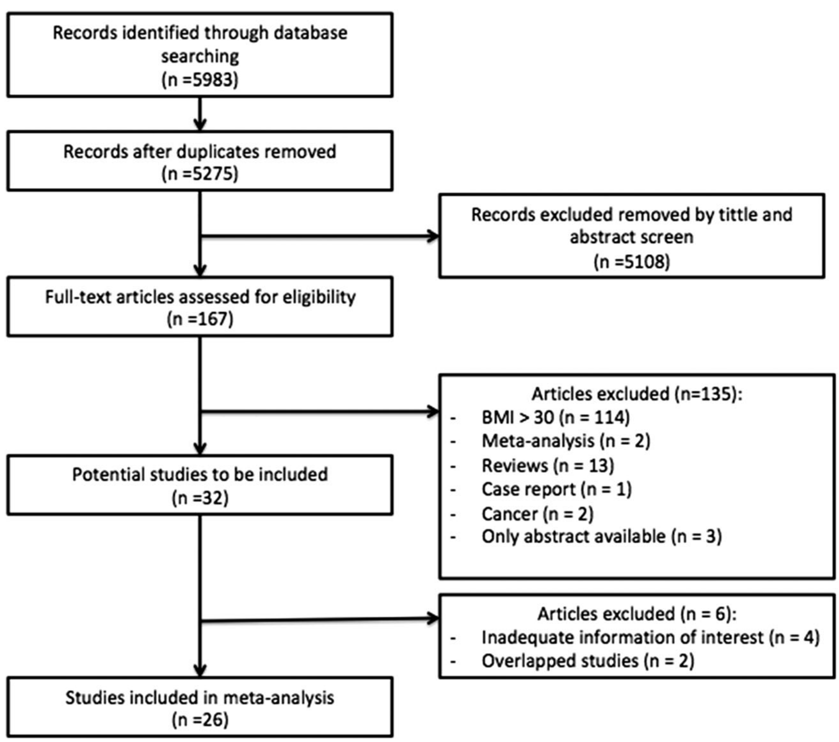

Fig. 1 Flow diagram showing the electronic search strategy for all included databases

Table 1 Baseline characteristics of studies included in the meta-analysis

Study	Region	Study design	Type of surgery	*N*	Patients at the end of follow-up	Follow-up period (months)	Mean age	Mean duration of diabetes (years)	Mean BMI (kg/m^2)
DePaula et al. 2010 [8]	Brazil	Cross-sectional	LII + SG	72	72	24.5	51.3 (6.4)	10.5 (4.7)	27 (2.5)
Navarrete et al. 2011 [9]	Venezuela	Prospective	LSG + DJB	10	10	12	46.5	< 10	27.2
Scopinaro et al. 2011 [10]	Italy	Prospective	BPD	15	15	24	57.8 (6.7)	11.1 (6.1)	28.1 (1.4)
Geloneze et al. 2012 [11]	Bazil	Prospective	DJB	18	18	12	50 (5)	9 (2)	26.1 (1.7)
García-Caballero et al. 2012 [12]	Spain	Prospective	LOAGB	13	13	6	63.8 (8.2)	16.9 (8.7)	27 (7.5)
Heo et al. 2013 [13]	Korea	Prospective	DJB	31	15	12	46.6 (7.7)	8.3 (4.7)	23.1 (1.3)
Astarriaga et al. 2013 [14]	Caucasian	Prospective	BPD	15	15	12	55 (3.8)	16 (7.7)	28.3 (2.3)
Dixon et al. 2013 [15]	Korea + China	Prospective	LRYGB or LOAGB	103	103	12	47.5 (9.6)	8.2 (5)	26 (3)
Chen et al. 2014 [16]	China	Retrospective	RYGB	35	35	12	45.3 (8.5)	3.7 (2.4)	22.3 (1.1)
Kim et al. 2014 [17]	Korea	Prospective	LOAGB	172	51	36	46 (11)	9.6 (5.2)	25.3 (3.2)
Malapan et al. 2014 [18]	Taiwan	Prospective	LRYGB	29	29	12	53	10.4	24.2 (1.8)
Ugale et al. 2014 [19]	India	Retrospective	LIISG or LIIDSG	22	22	12,7			24.2 (4.3)
Wentworth et al. 2014 [20]	Australia	Prospective	LAGB	25	23	24	53 (6)	2.2 (1.7)	29 (1)
Yin et al. 2014 [21]	China	Retrospective	LRYGB	28	28	12	51.6	9.6	24.7
Cui et al. 2015 [22]	China	Prospective	RYGB	58	58	12	48.5 (12.3)	< 15	23.4 (2.8)
Liang et al. 2015 [23]	China	Prospective	RYGB	80	80	12	48.5	7	24.6
Lee et al. 2015 [24]	China	Prospective	LRYBG or LOAGB or LSG	80	80	12	47.7 (9.1)	6.5 (5.1)	26.9 (2.2)
Kwon et al. 2017 [25]	Korea	Prospective	LRYGB	15	15	24	51	10	26.1
Wang et al. 2016 [26]	China	Retrospective	LRYGB	40	40	24	49.1 (8.1)	6.3 (4.2)	24.5 (1.9)
Celik et al. 2016 [27]	Turkey	Prospective	DSIT	33	33	12			
Di et al. 2016 [28]	China	Retrospective	LRYGB	66	66	42,1	50.4 (11.4)	8.9 (5.2)	28.2 (1.2)
Ramakrishnapillai et al. 2016 [29]	India	Retrospective	LSG + II	31	31	12	45 (10.2)	8.14 (4.8)	26.6 (2.6)
Zhang et al. 2017 [30]	China	Retrospective	LRYGB	28	25	38,7	51.3 (11.1)	9.6 (5.5)	27.1 (0.6)
Kim et al. 2017 [31]	Korea	Retrospective	LDJB	8	8	36	51.1 (7.1)	7.5 (2.5)	27 (2.5)
Gong et al. 2017 [32]	China	Prospective	LRYGB	31	31	6	46.2 (11.1)	8.3 (5.7)	26.5 (1.4)
Ke et al. 2017 [33]	China	Prospective	LRYGB	47	39	24	47.4 (8.6)	5.5 (4.4)	26.7 (2.5)

N, number of patients included in the study; *LII + SG*, laparoscopic ileal interposition with sleeve gastrectomy; *LSG + BPD*, laparoscopic sleeve gastrectomy with biliopancreatic diversion; *DJB*, duodenal-jejunal bypass; *LOAGB*, laparoscopic one anastomosis gastric bypass; *LRYGB*, laparoscopic Roux-en-Y gastric bypass; *LIISG*, laparoscopic ileal interposition with sleeve gastrectomy; *LIIDSG*, laparoscopic ileal interposition with diverted sleeve gastrectomy; *LAGB*, laparoscopic adjustable gastric band; *RYGB*, Roux-en-Y gastric bypass; *DSIT*, diverted sleeve gastrectomy with ileal transposition. *II*, ileal interposition; *LDJB*, laparoscopic duodenal-jejunal bypass

Table 2 Diabetes remission of the studies included in the meta-analysis

Study	HbA1c at baseline (%)	HbA1c after surgery (%)	Patients in diabetes remission	Number of patients at the end of follow-up	Diabetes remission rate (%)	Definition of diabetes remission in each study
DePaula et al. 2010 [8]	8.5 (1.8)	6.1 (0.9)	36	72	50	HbA1c < 6%
Navarrete et al. 2011 [9]	9	6.3	4	10	40	HbA1c < 7% without any antidiabetic medication
Scopinaro et al. 2011 [10]	9.1 (1.3)	6.9 (1.1)	4	15	26.7	FBG ≤ 125 mg/dL, HBA1c ≤ 6%, without any antidiabetic medication
Geloneze et al. 2012 [11]	8.9 (1.4)	8 (0.8)	3	18	16.7	HbA1c < 7%
García-Caballero et al. 2012 [12]	8.3	6.6	10	13	76.9	No antidiabetic medication
Heo et al. 2013 [13]	8.2 (1.6)	7.7 (1.9)	2	15	13.3	HbA1c < 6% and any antidiabetic medication
Astarriaga et al. 2013 [14]	8.5 (1.5)	6 (3.8)	6	15	40	HbA1c < 6.5%, FGB < 7 mmol/L, 2-h plasma glucose (OGTT) < 11.1 mmol/L, without any antidiabetic medication
Dixon et al. 2013 [15]	9.1 (1.6)	6.8 (1.7)	31	103	30.1	HbA1c ≤ 6%
Chen et al. 2014 [16]	9.8 (2.3)	5.9 (7)	2	35	5.7	HbA1c < 6%, FBG < 6.1 mmol/L, without any antidiabetic medication
Kim et al. 2014 [17]	9 (1.7)	6 (0.8)	46	51	90.2	HbA1c < 7%
Malapan et al. 2014 [18]	10 (1.8)	7.2 (1.4)	11	29	37.9	HbA1c < 6.5%, without any antidiabetic medication
Ugale et al. 2014 [19]	Nr	Nr	9	22	40.9	HbA1c < 6,5% without any antidiabetic medication
Wentworth et al. 2014 [20]	6.9 (1.2)	6.1 (1)	21	23	52.2	FBG < 7 mmol/L, 2-h plasma glucose (OGTT) < 11.1 mmol/L
Yin et al. 2014 [21]	9.3 (2.9)	7 (1.3)	19	28	67.9	FBG < 100 mg/dL, HbA1c < 6%, without any antidiabetic medication
Cui et al. 2015 [22]	9 (1.8)	4.5 (1.5)	48	58	82.8	FBG < 7 mmol/L, 2-h PBG < 11.1 mmol/L, RBG < 11.1 mmol/L
Liang et al. 2015 [23]	8.5 (2)	6.5 (1)	20	80	25	FBG < 110 mg/dL, HbA1c < 6%, without any antidiabetic medication
Lee et al. 2015 [24]	9.1 (1.8)	6.8 (1.3)	20	80	25	HbA1c < 6%, without any antidiabetic medication
Kwon et al. 2017 [25]	8.8	Nr	7	15	46.7	HbA1c < 6.5%, without any antidiabetic medication
Wang et al. 2016 [26]	8.2 (1.8)	7.8 (2.2)	14	40	35	HbA1c < 6.5%, FBG < 5.6 mmol/L, 2-h PBG < 7.8 mmol/L without any antidiabetic medication
Celik et al. 2016 [27]	9.9 (1.7)	6.8 (1.1)	15	33	45.5	HbA1c < 6.5%
Di et al. 2016 [28]	8.3 (1.9)	6.6 (1)	38	66	57.6	HbA1c < 6.5%, FBG < 7.0 mmol/L, without any antidiabetic medication
Ramakrishnapillai et al. 2016 [29]	8.8	6.8	16	31	51.6	HbA1c < 6%, without any antidiabetic medication
Zhang et al. 2017 [30]	8.5 (1.7)	6.3 (0.7)	12	25	48	HbA1c < 6%, FBG < 5.6 mmol/L, without any antidiabetic medication.
Kim et al. 2017 [31]	7.7 (1.3)	7.3	0	8	0	HbA1c ≤ 6.5%, without any antidiabetic medication
Gong et al. 2017 [32]	7.8 (1.7)	6.5 (0.6)	22	31	71	HbA1c < 6.5%, without any antidiabetic medication
Ke et al. 2017 [33]	8.2 (2.1)	6.3 (0.8)	11	39	28.2	HbA1c < 6%, FBG < 5.6 mmol/L, without any antidiabetic medications

FBG, fasting blood glucose; *OGTT*, oral glucose test tolerance; *RBG*, random blood glucose. *2-h PBG*, 2-h postprandial blood glucose

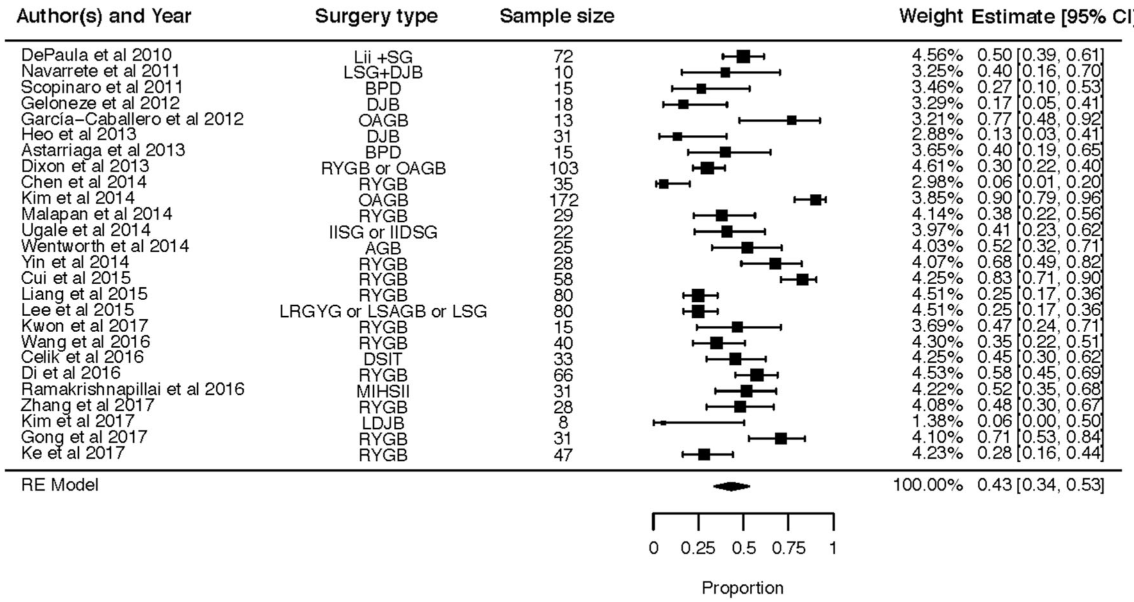

Fig. 2 Effect of metabolic surgery for T2DM patients with BMI < 30 kg/m^2: diabetes remission. CI confidence interval

one study, diverted sleeve gastrectomy with ileal transposition (DSIT) in two, one anastomosis gastric bypass (OAGB) in four, laparoscopic ileal interposition with sleeve gastrectomy (LII + SG) in three, laparoscopic adjustable gastric band (LAGB) in one, and only sleeve gastrectomy (SG) in one study. One thousand one hundred five patients with type 2 diabetes were assessed preoperatively. The mean age of the subjects ranged from 45 to 63.84 years and the mean duration of diabetes from 2.2 to 16.9 years. The mean follow-up was from 6 to 42.1 months (13 studies had a follow-up of 12 months). Three of 26 papers did not report complications and adverse events. There was no mortality in any of the studies. Two studies reported no major complications occurred. The most frequent complications described were gastrointestinal bleeding (7 studies), marginal ulcer (5 studies), nausea (4 studies), cholecystectomy (4 studies), persistent diarrhea, anastomotic leakage, anastomotic stenosis, and adhesions (3 studies). Nutritional deficiencies (vitamin B1, B12, and iron) were described in 3 studies.

The studies were developed with subjects from South Korea (3), China (12), Brazil (2), Venezuela (1), Italy (1), Spain (1), India (2), Turkey (1), and Australia (1). One study did not specify which region their subjects came from (subjects were Caucasian).

Diabetes Remission

All studies reported the T2DM remission rate. This rate was defined differently in each study (Table 2). HbA1c alone or combined with other parameters was included in the definition of diabetes remission in 23 studies. The study carried out by García-Caballero [12] defined diabetes resolution as not taking any glucose-lowering medication, and the study by Cui et al. [22] and Wentworth et al. [20], as the combination of fasting blood glucose (FBG) and postprandial glucose. The most common definition was HbA1c < 6% without any glucose-lowering medications. The remission rate ranged from 0 to 90.2% for all types of surgery. The highest remission rate was observed in patients who had undergone LOAGB, and the lowest was observed in patients who had undergone DJB.

Our mixed-effects meta-analysis model for overall diabetes remission rate produced an estimate of 43% (95% IC 34–53%; $p < 0.001$) (Fig. 2).

Additionally, moderator effects of the variables race (Asian vs. non-Asian), preoperative HbA1c, BMI, months of follow-up, duration of diabetes, and age on diabetes remission were also assessed, with no significant effects being found in any of them (race: estimate = − 0.005, 95% CI (− 0.88, 0.89), HbA1c: estimate = − 0.17, 95% CI (− 0.79, 0.45); BMI: estimate = 0.086, 95% CI (− 0.17, 0.34); months follow-up: estimate = 0.01, 95% CI (− 0.03, 0.05); years with diabetes: estimate = 0.12, 95% CI (− 0.01, 0.26), age: estimate = 0.04, 95% CI (− 0.08, 0.15).

Change in BMI

Twenty-five studies of the meta-analysis included BMI prior to surgery. Mean BMI ranged from 23.1 to 29 kg/m^2 at baseline and ranged from 20.6 to 26.4 at follow-up.

The meta-analysis estimate of BMI before surgery was 26.05 (95% IC 25.24, 26.86; $p < 0.001$). The meta-analysis estimate of the 21 studies that included BMI after surgery was 22.48 (IC 95% 21.74, 23.22; $p < 0.001$) (Fig. 3). The change of BMI was − 3.57 kg/m^2. It was not possible to

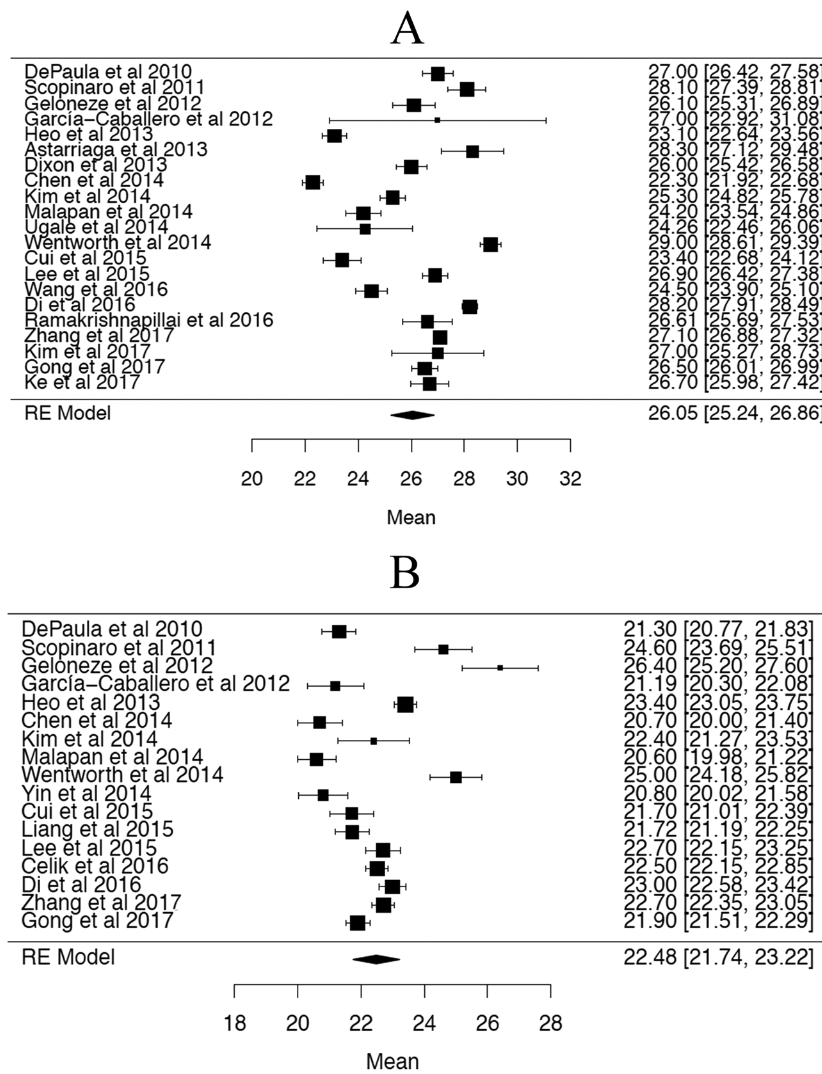

Fig. 3 **a** Meta-analysis of BMI before metabolic surgery in T2DM patients. **b** Meta-analysis of BMI after metabolic surgery in T2DM patients. CI confidence interval, BMI body mass index

produce an estimate of variability for this parameter with the data provided in the included studies; thus, only the point estimate is given, along with the estimates and their corresponding 95% confidence intervals for the pre- and post-surgery time points.

Change in FBG and HbA1C

Twenty studies included in the meta-analysis reported changes in FBG. FBG prior to the intervention was 179.12 (IC 95% 167.26, 190.98; $p < 0.001$). The meta-analysis of FBG after intervention was 123.19 (117.30, 129.08; $p < 0.001$) (Fig. 4). The reduction in FBG was − 55.93 mg/dL. As in the case of BMI, no estimate of variability was available for FBG reduction.

Twenty-five studies reported HbA1c prior to surgery and 24 after surgery. HbA1c ranged from 6.9 to 10 at baseline and ranged from 4.5 to 8 at follow-up. The study by Cui et al. [22] showed the greatest change in HbA1c from 9% prior to the intervention, to 4.5% after surgery. The result estimate of our meta-analysis for HbA1c before surgery was 8.69 (8.37, 9.01; $p < 0.001$) and after surgery it was 6.61 (IC 95% 6.27, 6.96; $p < 0.001$) (Fig. 5). The overall reduction in HbA1c was − 2.08%.

Insulin Profile

C-peptide, insulin, and HOMA-IR levels ranged from 1.3 to 5.08 ng/mL, from 4.9 to 40.3 μU/mL, and from 2 to 12.9, respectively, before surgery, and ranged from 0.97 to 2.3 ng/mL, from 2.9 to 12.97 μU/mL, and from 1.1 to 3.4, respectively, after intervention.

Nine studies reported a reduction in c-peptide and one study reported a slight increase after surgery. As well as that, insulin levels decreased in nine studies and increased in one study. HOMA-IR levels suffered a decrease in nine studies after intervention.

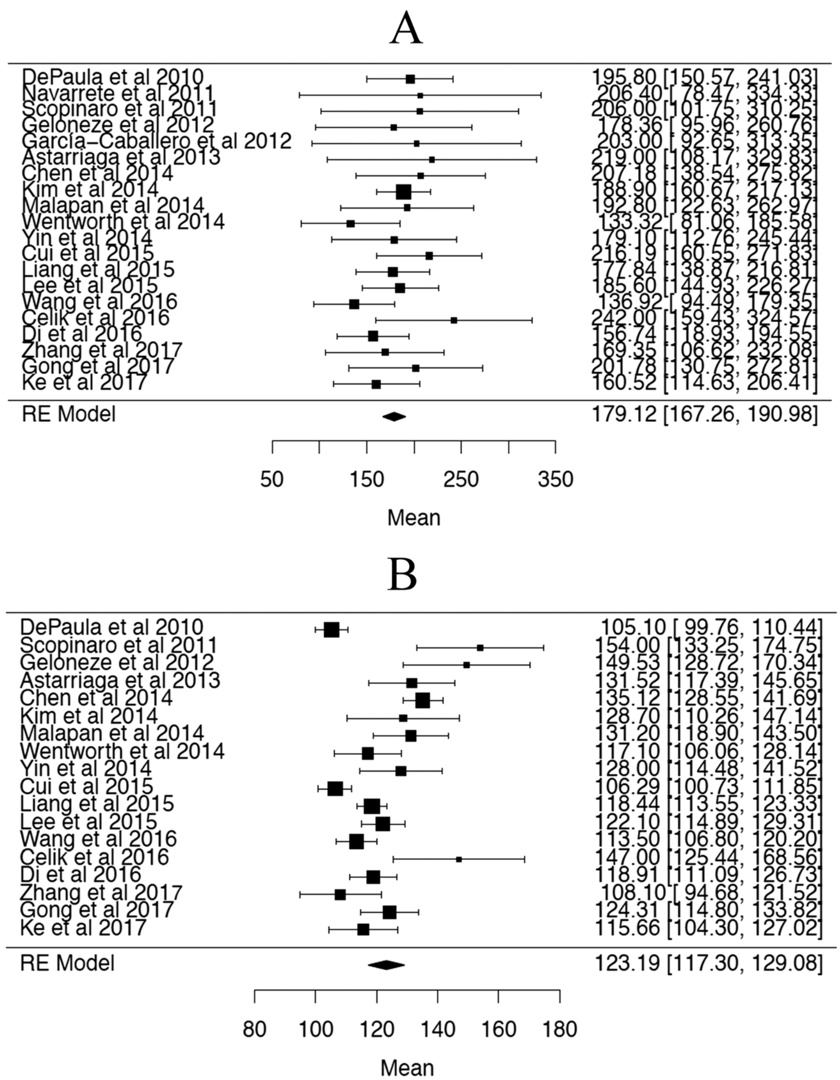

Fig. 4 **a** Meta-analysis of FBG before metabolic surgery in T2DM patients. **b** Meta-analysis of FBG after metabolic surgery in T2DM patients. CI confidence interval, FBG fasting blood glucose

Publication Bias

We assessed the possibility of publication bias using a funnel plot representing the results of all the included studies for diabetes remission. As seen in Fig. 6, the funnel plot is fairly symmetrical, with no obvious bias neither for negative nor for positive results. Thus, no evidence for publication bias was found in the papers included in the meta-analysis.

Consistency I^2

Consistency was measured by estimating the degree of inconsistency in the results of the studies [34]. Inconsistency was high in all performed meta-analyses, ranging from 86.53 to 97.97%, with the exception of FGB prior to surgery which was 0.17%.

Discussion

This systematic review and meta-analysis focuses on the effects on glycemic control of ≥ 6 months of several procedures of metabolic surgery on patients with T2DM and BMI < 30 kg/m^2.

T2DM is often not adequately controlled despite lifestyle changes and optimal medical therapy. Bariatric surgery has shown to be effective in the resolution of obesity comorbidities. The American Diabetes Association (ADA) [35] and other international diabetes organizations proposed a BMI threshold of 30 kg/m^2 (27.5 in Asian patients) for considering metabolic surgery in patients with T2DM with uncontrolled hyperglycemia. However, several weight loss-independent mechanisms are involved in glycemic improvement such as changes in gut hormones (GLP-1 and ghrelin), bile acid signaling, intestinal nutrient sensing, and alterations in the gut microbiota. These changes lead to increased tissue glucose

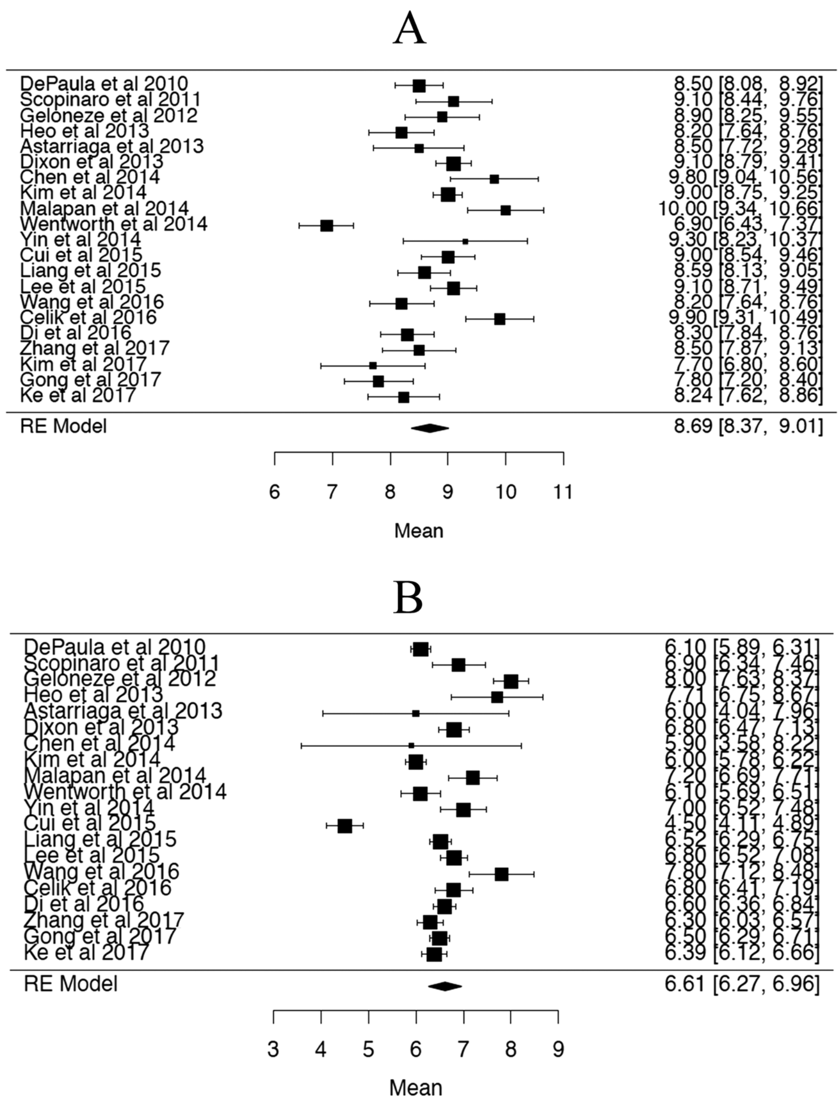

Fig. 5 **a** Meta-analysis of HbA1c before metabolic surgery in T2DM patients. **b** Meta-analysis of HbA1c after metabolic surgery in T2DM patients. CI confidence interval

uptake, reduced hepatic glucose production, improved insulin sensitivity and β-cell function [36, 37], suggesting that BMI at baseline does not predict the glycemic effects after surgery.

A meta-analysis of the 11 published randomized clinical trials directly comparing bariatric/metabolic surgery vs. medical/lifestyle interventions for T2DM provides evidence

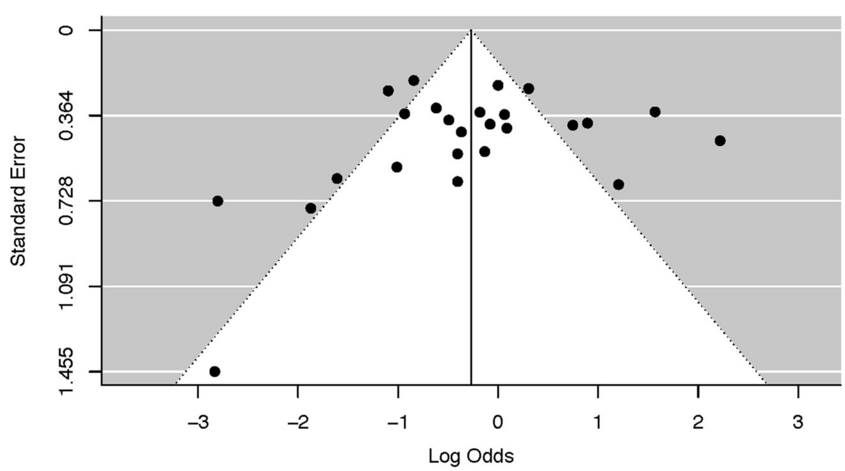

Fig. 6 Funnel plot representing the results of all the included studies for diabetes remission

that surgery is superior for T2DM remission, glycemic control, and HbA1c lowering, equally true for patients whose baseline BMI is below or above 35 kg/m^2. Moreover, T2DM remission rates following bariatric/metabolic surgery are comparable above and below the 35 kg/m^2 BMI threshold [5]. Another meta-analysis performed by Rao et al. [38] published a diabetes remission rate (BMI < 35) ranging from 65 to 93% and the systematic review by Panuzi et al. [39] reported a rate of 72%. Diabetes remission was achieved in 58–64% of patients in some studies performed in Asian subjects [40, 41]. A diabetes remission rate between 13.3 and 90.2% was reported in a recent systematic review with diabetic patients with BMI < 30 kg/m^2 [42], which is similar to our findings (between 0 and 90.2%). The best diabetes remission rate was reported by Kim et al. 2014 [17]. The loss of follow-up in this study is remarkable (> 50% at the end of the study), so that it could influence the result of its diabetes remission rate. The diabetes remission rate reported by Wenthworth et al. [20] could be affected by HbA1c at baseline. The patients underwent AGB and they had a reduction of BMI similar to the rest of studies, nevertheless, the HbA1c at baseline was lower. Mean HbA1c was 6.9% before intervention and 6.3% at the end of the study. This fact might contribute patients reached more easily the diabetes remission. The diversity in the definition of diabetes remission could also explain the heterogeneity in rates of different publications. A diabetes remission rate of 42.4% (defined as the achievement of HbA1c < 6%) was published in a meta-analysis conducted by Baskota et al. [43]. Our results are similar to data published previously (rate estimate of 43% (95% IC 34–53%, $p < 0.001$)) but our meta-analysis was conducted using the definition of diabetes remission provided by each study.

Our systematic review found several studies in overweight patients that suggested that surgery provided potential benefits in treating T2DM (Gong et al. [32], García-Caballero et al. [12], Cui et al. [22], Kim et al. 2014 [17]), whereas others reported low remissions (Geloneze et al. [11], Heo et al. [13], Chen et al. [16], Kim et al. 2017 [31]). Kim et al. 2017 [31] reported a diabetes remission of 0%, which can be explained by either the small sample included in the study (eight patients) or, as the authors mentioned, LDJB not being an effective procedure for controlling T2DM. It was observed that DJB was also the procedure used in studies with low diabetes remission rates [11, 13].

Our results also suggested an improvement in glycemic parameters (HbA1c, c-peptide, insulin, HOMA-IR) and BMI after surgery. A reduction of − 2.08% of HbA1c was observed after surgery. This finding is similar to data reported in randomized clinical trials with patients with diabetes and BMI < or > 35 kg/m^2 (a median HbA1c reduction of − 2%) [3], and the HbA1c reduction of − 1.88% reported in the meta-analysis of Baskota et al. [43] (BMI < 30 kg/m^2). As well as that, a similar BMI reduction was observed in our study (− 3.57 kg/m^2) and the study of Baskota et al. [43] (− 2.79 kg/m^2). However, BMI reduction was higher in the meta-analysis preformed with patients with higher BMI (− 7.42 to − 13.5 kg/m^2) [4, 44].

Moderator effects of the variables race (Asian vs. non-Asian), preoperative HbA1c and BMI, months of follow-up of the study, duration of diabetes, and age of patients on diabetes remission were also assessed, with no significant effects being found. Nevertheless, a longer follow-up period and shorter duration of diabetes were found to be two factors benefiting more from bariatric surgery in the meta-analysis by Baskota et al. [43].

This meta-analysis has some limitations:

1) Most studies included in the meta-analysis were not randomized and not compared with a non-exposed cohort.
2) There are many different definitions of diabetes remission, according to the studies, as well as many different bariatric procedures, thus providing a high inconsistency in the meta-analysis.
3) Most studies included in the meta-analysis have a short follow-up, and the long-term effect of surgery is unknown. Some studies have a small sample size.

Conclusions

Based on the current meta-analysis, metabolic surgery could be effective in the achievement of type 2 diabetes remission in BMI < 30 kg/m^2 patients, and improving glycemic parameters. However, additional randomized studies, with a larger sample size and long-term follow-up should be carried out. To establish a single definition of diabetes, remission should be a priority in order to appreciate the real effect of bariatric surgery in T2DM.

Compliance with Ethical Standards

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

Ethical Approval Statement For this type of study, formal consent is not required.

Informed Consent Statement Informed consent statement does not apply.

References

1. NCD Risk Factor Collaboration (NCD RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387:1513–30.

2. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357:753–61.
3. Rubino F, Nathan DM, Eckel RH, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care. 2016;39:861–77.
4. Cohen R, Le Roux CW, Junqueira S, et al. Roux-en-Y gastric bypass in type 2 diabetes patients with mild obesity: a systematic review and meta-analysis. Obes Surg. 2017;27:2733–9.
5. Cummings DE, Cohen RV. Bariatric/metabolic surgery to treat type 2 diabetes in patients with BMI <35 kg/m^2. Diabetes Care. 2016;39: 924–33.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100.
7. The Otawa Hospital Research Institute [Internet]. Canada, The Otawa Hospital; [Cited 2018, July 16]. Avaliable from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
8. DePaula AL, Stival AR, DePaula CC, et al. Impact on dyslipidemia of the laparoscopic ileal interposition associated to sleeve gastrectomy in type 2 diabetic patients. J Gastrointest Surg. 2010;14:1319–25.
9. Navarrete SA, Leyba JL, Llopis SN. Laparoscopic sleeve gastrectomy with duodenojejunal bypass for the treatment of type 2 diabetes in non-obese patients. Obes Surg. 2011;21:663–7.
10. Scopinaro N, Adami GF, Papadia FS, et al. The effects of biliopancreatic diversion on type 2 diabetes mellitus in patients with mild obesity (BMI 30-35 kg/m^2) and simple overweight (BMI 25-30 kg/m2): a prospective controlled study. Obes Surg. 2011;21:880–8.
11. Geloneze B, Geloneze SR, Chaim E, et al. Metabolic surgery for non-obese type 2 diabetes: incretins, adipocytokines, and insulin secretion/resistance changes in a 1-year interventional clinical controlled study. Ann Surg. 2012;256:72–8.
12. García-Caballero M, Valle M, Martínez-Moreno JM, et al. Resolution of diabetes mellitus and metabolic syndrome in normal weight 24-29 BMI patients with one anastomosis gastric bypass. Nutr Hosp. 2012;27:623–31.
13. Heo Y, Ahn JH, Shin SH, et al. The effect of duodenojejunal bypass for type 2 diabetes mellitus patients below body mass index 25 kg/m2: one year follow-up. J Korean Surg Soc. 2013;85:109–15.
14. Astiarraga B, Gastaldelli A, Muscelli E, et al. Biliopancreatic diversion in nonobese patients with type 2 diabetes: impact and mechanisms. J Clin Endocrinol Metab. 2013;98:2765–73.
15. Dixon JB, Hur KY, Lee WJ, et al. Gastric bypass in type 2 diabetes with BMI < 30: weight and weight loss have a major influence on outcomes. Diabet Med. 2013;30:e127–34.
16. Chen W, Yan Z, Liu S, et al. The better effect of Roux-en-Y gastrointestinal reconstruction on blood glucose of nonobese type 2 diabetes mellitus patients. Am J Surg. 2014;207:877–81.
17. Kim MJ, Hur KY. Short-term outcomes of laparoscopic single anastomosis gastric bypass (LSAGB) for the treatment of type 2 diabetes in lower BMI (<30 kg/m^2) patients. Obes Surg. 2014;24:1044–51.
18. Malapan K, Goel R, Tai CM, et al. Laparoscopic Roux-en-Y gastric bypass for nonobese type II diabetes mellitus in Asian patients. Surg Obes Relat Dis. 2014;10:834–40.
19. Ugale S, Gupta N, Modi KD, et al. Prediction of remission after metabolic surgery using a novel scoring system in type 2 diabetes - a retrospective cohort study. J Diabetes Metab Disord. 2014;13:89.
20. Wentworth JM, Playfair J, Laurie C, et al. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. Lancet Diabetes Endocrinol. 2014;2: 545–52.
21. Yin J, Xu L, Mao Z, et al. Laparoscopic Roux-en-Y gastric bypass for type 2 diabetes mellitus in nonobese Chinese patients. Surg Laparosc Endosc Percutan Tech. 2014;24:e200–6.
22. Cui JF, Chen T, Shi L, et al. Gastric bypass surgery in non-obese patients with type 2 diabetes mellitus: a 1-year follow-up of 58 cases in Chinese. Int J Clin Exp Med. 2015;8:4393–8.
23. Liang H, Guan W, Yang Y, et al. Roux-en-Y gastric bypass for Chinese type 2 diabetes mellitus patients with a BMI < 28 kg/m^2: a multi-institutional study. J Biomed Res. 2015;29:112–7.
24. Lee WJ, Almulaifi A, Chong K, et al. The effect and predictive score of gastric bypass and sleeve gastrectomy on type 2 diabetes mellitus patients with BMI < 30 kg/m^2. Obes Surg. 2015;25:1772–8.
25. Kwon O, Lee YJ, Yu JH, et al. The recovery of beta-cell function is critical for antidiabetic outcomes of gastric bypass in Asian subjects with type 2 diabetes and a body mass index below 30. Obes Surg. 2017;27:541–4.
26. Wang G, Zhu L, Li W, et al. Can low BMI Chinese patients with type 2 diabetes benefit from laparoscopic Roux-en-Y gastric bypass surgery? Surg Obes Relat Dis. 2016;12:1890–5.
27. Celik A, Cagiltay E, Ugale S, et al. Diverted sleeve gastrectomy with ileal transposition in overweight, obese, and morbidly obese patients with type 2 diabetes: results of 1-year follow-up. Surg Obes Relat Dis. 2016;12:541–9.
28. Di J, Zhang H, Yu H, et al. Effect of Roux-en-Y gastric bypass on the remission of type 2 diabetes: a 3-year study in Chinese patients with a BMI <30 kg/m^2. Surg Obes Relat Dis. 2016;12:1357–63.
29. Ramakrishnapillai P, Pai M, Shams F, et al. Effectiveness of minimally invasive hybrid surgery for ileal interposition (MIHSII) for the resolution of type 2 diabetes. Surg Innov. 2016;23:42–51.
30. Zhang H, Han X, Yu H, et al. Effect of Roux-en-Y gastric bypass on remission of T2D: medium-term follow-up in Chinese patients with different BMI obesity class. Obes Surg. 2017;27:134–42.
31. Kim DJ, Paik KY, Kim MK, et al. Three-year result of efficacy for type 2 diabetes mellitus control between laparoscopic duodenojejunal bypass compared with laparoscopic Roux-en-Y gastric bypass. Ann Surg Treat Res. 2017;93:260–5.
32. Gong K, Li K, Zhang N, et al. Gastric bypass procedure for type 2 diabetes patients with BMI <28 kg/m^2. Surg Endosc. 2017;31: 1172–9.
33. Ke Z, Li F, Chen J, et al. Effects of laparoscopic Roux-en-Y gastric bypass for type 2 diabetes mellitus: comparison of BMI > 30 and < 30 kg/m2. Obes Surg. 2017;27:3040–7.
34. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
35. American Diabetes Association. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S65–72.
36. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care. 2016;39:893–901.
37. Cummings DE, Rubino F. Metabolic surgery for treatment of type 2 diabetes in obese individuals. Diabetologia. 2018;61:257–64.
38. Rao WS, Shan CX, Zhang W, et al. A meta-analysis of short-term outcomes of patients with type 2 diabetes mellitus and BMI ≤ 35 kg/m2 undergoing Roux-en-Y gastric bypass. World J Surg. 2015;39: 223–30.
39. Panunzi S, De Gaetano A, Carnicelli A, et al. Predictors of remission of diabetes mellitus in severely obese individuals undergoing bariatric surgery: do BMI or procedure choice matter? A meta-analysis. Ann Surg. 2015;261:459–67.
40. Lakdawala M, Shaikh S, Bandukwala S, et al. Roux-en-Y gastric bypass stands the test of time: 5-year results in low body mass index (30-35 kg/m^2) Indian patients with type 2 diabetes mellitus. Surg Obes Relat Dis. 2013;9:370–8.

41. Hsu CC, Almulaifi A, Chen JC, et al. Effect of bariatric surgery vs medical treatment on type 2 diabetes in patients with body mass index lower than 35: five-year outcomes. JAMA Surg. 2015;150: 1117–24.
42. Huang ZP, Guo Y, Liu CQ, et al. The effect of metabolic surgery on nonobese patients (BMI<30 kg/m^2) with type 2 diabetes: a systematic review. Surg Obes Relat Dis. 2018;14:810–20.
43. Baskota A, Li S, Dhakal N, et al. Bariatric surgery for type 2 diabetes mellitus in patients with BMI <30 kg/m2: a systematic review and meta-analysis. PLoS One. 2015;10:e0132335.
44. Kang JH, Le QA. Effectiveness of bariatric surgical procedures: a systematic review and network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96: e8632.