Review Article

Review of Metabolic Surgery for Type 2 Diabetes in Patients with a BMI < 35 kg/m^2

Hideharu Shimizu, Poochong Timratana, Philip R. Schauer, and Tomasz Rogula

M61 Cleveland Clinic, Bariatric and Metabolic Institute, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Correspondence should be addressed to Tomasz Rogula, rogulat@ccf.org

Bariatric/metabolic surgery is considered an accepted treatment option for type 2 diabetes mellitus (T2DM) with body mass index (BMI) $\geqq$ 35 kg/m^2. Mounting evidence also shows that metabolic surgery is effective for T2DM with BMI < 35 kg/m^2. To evaluate current status of metabolic surgery, we reviewed the available clinical studies which described surgical treatment for T2DM with mean BMI < 35 kg/m^2. 18 studies with 477 patients were identified. 30% of the patients was insulin users. The follow-up period ranged from 6 to 216 months. The weight loss effect was reasonable, not excessive. Mean BMI decreased from 30.4 to 24.8 kg/m^2. Remission of T2DM was achieved in 64.7% of the patients with fasting plasma glucose and glycated hemoglobin approaching slightly above normal range. Clinical T2DM status was an important factor when selecting the eligible candidates for metabolic surgery. Postoperative complication rate of 10.3% with mortality of 0% in the studies has been acceptable. Even though it would be premature at this point to state that metabolic surgery is an accepted treatment option for T2DM with BMI < 35 kg/m^2, it is clear that a high proportion of T2DM patients will derive substantial benefit from metabolic surgery.

1. Introduction

Diabetes mellitus represents an expanding pandemic that contributes markedly to worldwide morbidity and mortality. The world prevalence of diabetes among adults (aged 20–79 years) will be 6.4%, affecting 285 million adults, in 2010 and will increase to 7.7% and 439 million adults by 2030 [1]. There is a strong relationship between obesity and type 2 diabetes mellitus (T2DM) [2]. In a large USA population study, the prevalence of diabetes increases with increasing weight classes according to body mass index (BMI). Approximately half of those diagnosed with T2DM are obese [3]. Weight control is the key to successful T2DM management. Weight loss achieved by lifestyle interventions has been shown to be effective in preventing and treating T2DM [4–7]. However, conventional treatment, such as, lifestyle modification and pharmacotherapy has produced small improvements in weight [7–10]. By contrast, bariatric surgery has been shown to effectively provide durable weight loss [11].

Currently, bariatric surgery is now considered appropriate for T2DM patient with BMI $\geqq$ 35 kg/m^2. Bariatric surgery leads to remission of T2DM in the majority of patients and improvement in the rest [12]. The American Society of Bariatric and Metabolic surgery estimates that the number of bariatric procedures increased from about 16,000 in the early 1990s to more than 103,000 in 2003 and 220,000 people in the United States had bariatric surgery in 2008. Growing evidence from clinical and animal studies indicates that bariatric/metabolic surgery may be beneficial for T2DM in nonseverely obese or even nonobese patients (BMI < 35 kg/m^2) [13, 14]. Recently, International Diabetes Federation has released its position statement [15]: surgery should be an accepted option in people who have T2DM and BMI of 35 more. Surgery should be considered as an alternative treatment option in persons with BMI 30 to 35 when diabetes cannot be adequately controlled by optimal medical regimen, especially in the presence of other major cardiovascular disease risk factors. The surgical approach is

now being extended to overweight and mild to moderate obese (BMI < 35 kg/m^2) patients with T2DM.

Herein, to evaluate current evidence of metabolic surgery for treatment of T2DM in patients with a BMI < 35 kg/m^2, we conducted a review to date of available clinical studies.

2. Materials and Methods

2.1. Search Strategy and Study Inclusion Criteria. We conducted a comprehensive review of all studies published containing data on weight loss and T2DM-related outcomes of patients treated with any form of bariatric/metabolic surgery where the mean study BMI was <35 kg/m^2. Only reports published in English were included for review. Studies whose inclusion criteria indicated bariatric or metabolic surgery for low BMI patients were excluded if their mean BMI was $\geq$35 kg/m^2, all participants were not T2DM patients, diabetic participants had gastric surgery with anatomical similarities to RYGB because of gastric cancer and ulcer, or they did not report diabetes-related outcomes such as fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and postoperative clinical status. Pubmed was searched from January 1, 1980, to November 1, 2011, for citations using the following keywords: "metabolic surgery", "bariatric surgery", "diabetes surgery", "T2DM", "type 2 diabetes", "obesity", "BMI < 35 kg/m^2", "mild to moderate obesity", and "low-BMI". To supplement the electronic search, manual reference checks were performed in the identified studies.

2.2. Data Reporting. Study authors, country, year of publication, surgical procedure, and study design were summarized. Characteristics of the study groups, BMI, FPG, and HbA1c were recorded. Diabetes-related clinical outcomes were collected as % meds resolved (the percentage of the patients who discontinued antidiabetic medication postoperatively) and remission rate (the percentage of the patients who had remission or resolution of T2DM according to the varied definition in the studies included). These two parameters were calculated using available values if not specifically stated. Then, the studies were divided into 2 groups according to mean duration of T2DM prior to surgery. The percentage of insulin using patients prior to surgery and T2DM remission rate was compared. Regarding safety of metabolic surgery, all major and minor complications were counted because they were variably reported. Mortality was also checked.

2.3. Statistical Analysis. Weighted means for ages and duration of T2DM were calculated. Pre- and Postoperative mean values (and corresponding 95% confidence intervals) for BMI, FPG, and HbA1c were summarized using a random effects model to account for the variability between the different studies. Only studies which provided both a pre- and post-measurement were included in the mean estimation for each of the parameters considered.

Comparisons of 2 groups with a short (<8 years) and long history (>8 years) of diabetes with respect to insulin using patients and diabetes remission were performed by the chi-square test. The statistics was performed using the software package PASW, version 18.0, for Windows (SAS Institute, Cary, NC, USA).

3. Results

3.1. Study Characteristics. A total of 18 studies met inclusion criteria as identified by literature search and reference checks [16–33] Of the 18 studies, 17 (94%) were performed outside of the United States, in Brazil (7, 39%), Italy (4, 22%), Taiwan (4, 22%), Chile (1, 6%), and India (1, 6%). 13 studies (72%) have been published in the last 3 years from 2009 to 2011. The studies were performed prospectively (16, 89%) or retrospectively (2, 11%). Surgical procedures performed in this paper included Roux-en-Y gastric bypass (RYGB) in 6 (33%) studies, duodenal-jejunal bypass (DJB) in 4 (22%), biliopancreatic diversion (BPD) in 3 (17%), minigastric bypass (MGB) in 2 (11%), ileal interposition with sleeve or diverted sleeve gastrectomy (II-SG or II-DSG) in 2 (11%), sleeve gastrectomy (SG) in 1 (6%), and stomach- and pylorus-preserving BPD (BPD-SPP) in 1 (6%). The data are summarized in Table 1.

3.2. Patient Characteristics. Of the 18 studies, total 477 patients underwent metabolic/bariatric surgery. 16 studies reported the patient gender, and 53% of the total study population was female. The mean age of the patients ranged from 34 to 56 and its weighted mean was 47. The followup period ranged from 6 months to 18 years, and its weighted mean was 22 months. 2 studies reported the results of a longer than 5-year followup. The duration of diabetes prior to surgery ranged from 6 months to 28 years, and its weighted mean was 8.2 years. Majority of patients were taking oral antidiabetic medication and/or insulin. The percentage of Insulin using patients was 30.1% in 16 studies. The data are summarized in Table 1.

3.3. BMI. 14 studies were included in the mean estimation. The BMI decreased from 30.4 (95% CI 28.4–32.3) to 24.8 (95% CI 24.1–25.5) kg/m^2. There were only two studies reporting that one of the total 15 patients was in the mildly undernourished range (BMI 17–18.5 kg/m^2) after RYGB without any evidence of malnutrition [21] and 12 patients (17.4%) after II-DSG were underweight (BMI < 20 kg/m^2) without lowering serum albumin value [24]. Overall, the risk of excessive weight loss after metabolic surgery was 2.7% (13 patients). The data are summarized in Tables 2 and 3.

3.4. T2DM Outcomes. 12 studies were included in the mean estimation of FPG. It decreased from 203.5 (95% CI 187.4–219.6) to 112.5 (95% CI 103.9–121.1) mg/dL. 10 studies were included in the mean estimation of HbA1c. It decreased from 9.0 (95% CI 8.6–9.5) to 6.3 (95% CI 6.1–6.6) %. Regarding clinical outcomes of diabetes, 86.8% of the patients stopped taking antidiabetic medication after surgery (% meds off). The definition of resolution or remission of T2DM varied. When it is defined as FPG < 126 mg/dL and/or HbA1c < 6.5% without the use of antidiabetic medication at the time of evaluation, 64.7% of the patients met the criteria. The data are summarized in Tables 2 and 3.

TABLE 1: Baseline characteristics of T2DM patients with BMI < 35 kg/m^2.

	Author	Year	Procedure	N	Female/male	Mean age (range)	Mean followup (range)	Mean duration of diabetes	Insulin user
1	Lee	2011	MGB, RYGB	62	38/24	43.1	24 months	5.4 years	23% ($n = 14$)
2	Boza	2011	RYGB	30	17/13	48.0 (28–65)	24 months ($n = 20$)	4 years	3.3% ($n = 1$)
3	de Sa	2011	RYGB	27	—	50.3	20 (4–86) months	8.8 years	22% ($n = 6$)
4	Huang	2011	RYGB	22	20/2	47.4 (28–63)	12 months	6.6 years	18.2% ($n = 4$)
5	Scopinaro	2011	BPD	30	11/19	56.4 (43–69)	12 months	11.2 years	40% ($n = 12$)
6	Shah	2010	RYGB	15	7/8	45.6	9 months	8.7 years	80% ($n = 12$)
7	Lee	2010	SG	20	14/6	46.3	12 months	>6 months	20% ($n = 4$)
8	DePaula	2009	II-SG, II-DSG	58 (30,28)	18/40	51.4 (40–66)	19.2 (14–28) months	9.6 years	37.9% ($n = 22$)
9	DePaula	2009	II-DSG	69	22/47	51.4 (41–63)	21.7 (7–42) months	11 years	44% ($n = 30$)
10	Ramos	2009	DJB	20	9/11	43.0 (29–60)	6 months	5.3 years	0% ($n = 0$)
11	Ferzli	2009	DJB	7	—	43.3 (33–52)	12 months	10.7 years	85.7% ($n = 6$)
12	Geloneze	2009	DJB	12	3/9	50.0	6 months	9 years	100% ($n = 12$)
13	Chiellini	2009	BPD	5	2/3	48.0	18 months	3–15 years	—
14	Lee	2008	MGB	44	38/6	39.0	1–5 years	—	—
15	Scopinaro	2007	BPD	7	2/5	49.0 (39–60)	13 (10–18) years	4.1 years	0% ($n = 0$)
16	Cohen	2007	DJB	2	0/2	47.0 (43–51)	9 months	4.5 years	100% ($n = 2$)
17	Cohen	2006	RYGB	37	30/7	34.0 (28–45)	20 (6–48) months	—	0% ($n = 0$)
18	Noya	1998	BPD-SPP	10	5/5	52.1 (40–62)	7 (2–18) months	—	40% ($n = 4$)
	Total	—	—	477	236/207	—	—	—	30.1% (129/428)
	Weighted mean	—	—	—	—	47	22 months	8.2 years	—

RYGB: Roux-en-Y gastric bypass, MGB: mini-gastric bypass, BPD: biliopancreatic diversion, SG: sleeve gastrectomy, II-SG: ileal interposition with sleeve gastrectomy, II-DSG: ileal interposition with diverted sleeve gastrectomy, DJB: duodenal jejunal bypass, BPD-SPP: stomach- and pylorus-preserving BPD.

3.5. Clinical Outcomes of Diabetes According to Duration of T2DM prior to Surgery. When the studies were stratified by mean duration of T2DM (5 studies, $\leqq 8$ years, and 7 studies, >8 years), the percentage of insulin-using patients prior to surgery was 18.2% and 45.9% ($P < 0.01$). Remission of T2DM was achieved in 66.0% of the patients with a short history ($\leqq 8$ years) of T2DM and 52.9% of those with a long history (>8 years) of T2DM ($P = 0.03$). The data are shown in Figure 1.

3.6. Complications and Mortality. Overall, complication rate was 10.3% (range 4.5–33.3%) in 16 studies. The types of complication varied and were dependent on follow-up period and surgical procedures. Therefore, we included all major and minor complications. The mortality rate was 0% in 17 studies. The data are summarized in Table 2.

4. Discussion

The concept of metabolic surgery was defined by Buchwald and Varco in 1978 in their book "*Metabolic Surgery* as the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain" [34]. Now, metabolic surgery is defined as any modification of the gastrointestinal (GI) tract, where rerouting the food passage seems to improve T2DM, based on mechanisms that are weight loss independent. This new frontier of bariatric/metabolic surgery includes the application of conventional bariatric procedures (RYGB, BPD, SG, MGB) and the introduction of new procedures (DJB, II-SG, II-DSG, BPD-SPP) designed with the specific aim of having metabolic effects irrespective of causing massive weight loss.

There is strong evidence that bariatric surgery for severely obese patients (BMI $\geq$ 35 kg/m^2) provides exceptional sustained weight loss and 50–85% remission of T2DM [35]. In view of growing enthusiasm for surgical interventions to treat T2DM, the 1st diabetes surgery summit was held in Rome in March 2007 to develop guidelines for the use of GI surgery to treat T2DM. The recommendations were made by a multidisciplinary group of 50 voting delegates [36]. Accordingly, the "Standards of Medical Care in Diabetes" published yearly by the American Diabetes Association, for the first time, mentions surgical therapy in 2009 [37]. Recently, International Diabetes Federation has released its position statement [20]. These statements

Table 2: Outcomes of metabolic surgery: changes in BMI, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c), clinical outcomes of diabetes (% meds resolved and remission rate), and safety of metabolic surgery (complication and mortality).

		BMI		Fasting plasma glucose		HbA1c (%)					
	Author	Mean preop (range)	Mean postop (range)	Mean preop (range)	Mean postop (range)	Mean preop (range)	Mean postop (range)	% meds resolved	Remission	Complications	Mortality
1	Lee	30.1 kg/m²	23 kg/m²	195.8 mg/dL	106.3 mg/dL	9.7%	5.9%	90% (n = 18/20)	55% (n = 11/20)	11.3% (n = 7)	0 %
2	Boza	33.7 (30.4–35) kg/m²	23.9 kg/m²	145 mg/dL	109.9 mg/dL	8.1%	6.5%	—	83.3% (n = 25/30)	33.3% (n = 10)	0 %
3	de Sa	33.6 kg/m²	25.7 kg/m²	176.1 mg/dL	93.9 mg/dL	8.4%	6.0%	74.1% (n = 20/27)	48.1% (n = 13/27)	25.9% (n = 7)	0 %
4	Huang	30.8 (25.0–34.8) kg/m²	23.7 kg/m²	204.2 mg/dL	103.5 mg/dL	9.2%	5.9%	90.9% (n = 20/22)	63.6% (n = 14/22)	9.1% (n = 2)	0 %
5	Scopinaro	30.6 (25.3–34.9) kg/m²	25.3 kg/m²	220 mg/dL	149 mg/dL	9.3 (7.5–12.9) %	6.5%	83.3% (n = 25/30)	30% (n = 9/30)	16.7% (n = 5)	0 %
6	Shah	28.9 kg/m²	23 kg/m²	233 mg/dL	89.2 mg/dL	10.1%	6.1%	100% (n = 15/15)	100% (n = 15/15)	0% (n = 0)	0 %
7	Lee	31 kg/m²	24.6 kg/m²	240.1 mg/dL	132.9 mg/dL	10.1%	7.1%	—	50% (n = 10/20)	0% (n = 0)	0 %
8	DePauLa	28.2 (20–34.8) kg/m²	—	215.3 mg/dL	105.4 mg/dL	8.9 (7.5–12.8) %	—	91.2% (n = 53/58)	63.7% (n = 37/58)	10.3% (n = 6)	0 %
9	DePaula	25.7 kg/m²	21.8 (17.7–25.8) kg/m²	218.1 (90–334) mg/dL	102.0 (73–161) mg/dL	8.7 (7.5–13.7) %	5.9 (4.8–8.5) %	95.7% (n = 66/69)	65.2% (n = 45/69)	7.3% (n = 5)	0 %
10	Ramos	27.1 (25–30) kg/m²	24.4 (20.2–28.3) kg/m²	171.3 (127.0–242.0) mg/dL	96.3 (78.0–118.0) mg/dL	8.8 (7.5–10.2) %	6.8 (5.8–7.9) %	90% (n = 18/20)	—	0% (n = 0)	0 %
11	Ferzli	27.5 (21.7–33.0) kg/m²	27.3 (23–33) kg/m²	208.9 (112.0–286.0) mg/dL	154.9 (63.0–315.0) mg/dL	9.4 (6.6–11.8) %	8.5 (6.3–12) %	14% (n = 1/7)	14 % (n = 1/7)	0% (n = 0)	0 %
12	Geloneze	26.1 (1.7) kg/m²	25.6 (1.2) kg/m²	183.8 mg/dL	156.8 mg/dL	8.9%	7.8%	0% (n = 0/12)	0% (n = 0/12)	16.7% (n = 2)	0 %
13	Chiellini	30.9 kg/m²	25.1 kg/m²	—	—	8.5%	5.7%	100% (n = 5/5)	—	—	0%
14	Lee	31.7 kg/m²	23.2 kg/m²	168.7 mg/dL	88.6 mg/dL	7.3%	5.6%	—	89.5% (n = 40/44)	4.5% (n = 2)	0%

Table 2: Continued.

Author	BMI		Fasting plasma glucose		HbA1c (%)		% meds resolved	Remission	Complications	Mortality
	Mean preop (range)	Mean postop (range)	Mean preop (range)	Mean postop (range)	Mean preop (range)	Mean postop (range)				
15 Scopinaro	33.4 (32.0–34.6) kg/m²	27.1 (22.0–31.2) kg/m²	252.7 (131–400) mg/dL	121.0 (68–146) mg/dL	—	—	100% (n = 7/7)	—	—	0 %
16 Cohen	29.6 (29.0–30.3) kg/m²	28.3 (27–29.5) kg/m²	—	83.0 (77–89) mg/dL	—	5.4 (5.0–5.7) %	100% (n = 2/2)	100% (n = 2/2)	0% (n = 0)	0 %
17 Cohen	32.5 (32.0–34.90 kg/m²	—	146.0 (126–242) mg/dL	88.0 (60–94) mg/dL	—	<6.0%	100% (n = 37/37)	100% (n = 37/37)	0% (n = 0)	0 %
18 Noya	33.2 (24.0–38.9) kg/m²	27.6 (20.46–32.4) kg/m²	—	—	—	—	90% (n = 9/10)	90% (n = 9/10)	20% (n = 2)	0 %

TABLE 3: Mean estimation of BMI, FPG, and HbA1c before and after metabolic surgery. Combined data from 18 existing bariatric studies.

Variable (# studies)	Pre Means ± SE	95% CI	Post Means ± SE	95% CI
BMI ($n = 14$), kg/m^2	30.4 ± 0.98	(28.4, 32.3)	24.8 ± 0.33	(24.1, 25.5)
FPG ($n = 12$), mg/dL	203.5 ± 8.2	(187.4, 219.6)	112.5 ± 4.4	(103.9, 121.1)
HbA1c ($n = 10$), %	9.01 ± 0.22	(8.6, 9.5)	6.3 ± 0.14	(6.1, 6.6)

SE: standard error.

have mentioned that bariatric surgery for T2DM patients with a BMI $\geqq 35$ kg/m^2 is considered an accepted option as with standard medical therapy and metabolic surgery might, moreover, be considered a reasonable therapeutic alternative for low BMI (<35 kg/m^2) patients with T2DM who do not respond to standard medical therapy. The aim of this paper was to explore the current evidence with a view to evaluate the potential of metabolic surgery for T2DM with a BMI < 35 kg/m^2.

Metabolic surgery to treat T2DM in patients with low BMI provided desirable results regarding weight loss. The estimated mean BMI categorized as class I obesity prior to surgery reached normal weight range after surgery. Importantly, only 13 patients (2.7%) following RYGB or II-DSG in 2 studies reported excessive weight loss, and they did not show any evidence of malnutrition [21, 24]. Even the procedures that typically produce the greatest reduction in BMI and excess weight in morbidly obese patients did not affect a similarly dramatic BMI reduction in the low-BMI patients [38]. Scopinaro and so forth reported that BPD does not entail risk of excessive or undue weight loss because there is a maximum energy absorption capacity after the operation, which corresponds to a weight of stabilization of low BMI patients [39]. The similar homeostatic mechanism may explain weight stabilization without causing undesirable weight loss after surgical procedures including intestinal bypass.

In this paper, diabetic status was significantly improved after metabolic surgery in the majority of studies. Discontinuation of antidiabetic medication and remission of T2DM after metabolic surgery were achieved in 86.8% and 64.7% of the patients with FPG and HbA1c approaching slightly above normal range. Moreover, metabolic surgery provided adequate glycemic control for 30.1% of the patients using insulin prior to surgery. It has been described that malabsorptive bariatric procedures have higher diabetes remission rates than restrictive ones [12, 40]. T2DM typically resolves within a few days to weeks following malabsorptive procedures such as RYGB and BPD before significant weight loss is achieved. Although the exact mechanism is not yet fully understood, growing evidence shows that malabsorptive procedures involving rerouting of food might improve T2DM by enhancing insulin sensitivity and/or by improving β-cell function that is additive to weight loss and reduced caloric intake [16, 41, 42]. The recent studies have described that acute insulin response to intravenous glucose and early phase insulin response to oral glucose load improved significantly within a month following GI bypass surgery [16, 20]. The mechanism for these changes could be due to a dramatic decrease of insulin resistance and an increase in
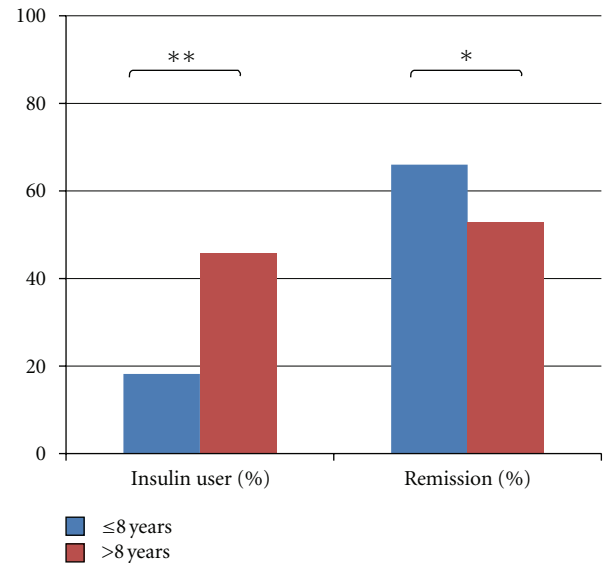

FIGURE 1: Clinical outcomes of diabetes according to duration of T2DM prior to surgery. $^{**}P < 0.01$, $^{*}P < 0.05$.

postprandial plasma levels of glucagon-like peptide-1 (GLP-1) early after surgery. Currently, two hypotheses (hindgut and foregut theory) have been proposed to explain T2DM remission after metabolic surgery in addition to decreased calorie intake after surgery and surgical-induced weight loss which might contribute to improving insulin sensitivity. The former states that surgical rerouting of nutrients to the distal part of the small intestine results in increased secretion and concomitant glucose-lowering effects of GLP-1, and the latter emphasizes that surgical bypass of the foregut prevents the release of a hitherto unidentified nutrient-induced diabetogenic signal in susceptible individuals [43]. The novel surgical procedures such as DJB, BPD-SPP, II-SG, and II-DG were designed to apply hindgut or/and foregut hypotheses without massive weight loss and achieved 56% of T2DM remission and 84% of diabetes meds off in this paper. The weight loss effect of metabolic surgery on T2DM in low BMI patients might be lower than that of bariatric surgery on T2DM in high BMI patients. Understanding and enhancing the abovementioned mechanism are the key to success in metabolic surgery.

There is no strong evidence describing the durability of metabolic surgery in long-term followup. In this paper, 2 studies showed durable diabetes remission of T2DM during 5–18 years period after MGB and BPD [29, 30]. By contrast, the recent studies of bariatric surgery for T2DM patients with

severe obesity showed that 24%–43% of the patients with initial remission or improvement of their T2DM subsequently developed T2DM recurrence or worsening during the mid- to long-term followup period [44, 45]. A low preoperative BMI and severe T2DM status were associated with failure of consistent durable remission of diabetes. The common causes for failure of diabetes remission after bariatric surgery are known as inadequate weight loss or regain of weight, longstanding poorly controlled or aggressive T2DM, lower preoperative BMI, and latent autoimmune diabetes in adults (LADA) [46]. LADA comprises 10% of diabetic age 30–55 and is more prevalent in low BMI individuals [47, 48].

Most clinical guidelines and statements have followed the BMI-based criteria established by 1991 National Institutes of Health Consensus Conference Guidelines [49]. Although BMI is convenient to classify the grade of obesity, it does not seem to be appropriate in selecting the suitable T2DM candidates for metabolic surgery. For instance, the risk of diabetes and/or metabolic syndrome is determined by ethnicity, waist circumference, fat distribution, body composition, and intrahepatic fat [50, 51]. South Asian and Chinese individuals have distributions of elevated glucose and lipid levels similar to Europeans at significantly lower BMI values [52]. The natural history of type 2 diabetes is also important to consider in determining the timing of intervention. As the diabetes state progresses, there is continued beta-cell deterioration together with a decline in insulin secretion within 6–10 years of T2DM diagnosis [53, 54]. Schauer et al. showed that a shorter history of diabetes and milder disease according to preoperative medication status were associated with an increased likelihood of remission after RYGB [55]. Dixon and O'Brien reported that a shorter history of diabetes and greater weight loss were positive predictive factors for remission [56]. This paper was consistent with this. A shorter history of diabetes with less number of insulin using patients prior to metabolic surgery resulted in greater remission rate of diabetes. Metabolic surgery should be considered early in the diabetic stage before irreparable beta-cell damage occurs. BMI alone is not an adequate measure to define the overall risk of morbidity and mortality in patients with established diabetes [50]. The clinical status of T2DM should be taken into account to select the suitable candidates for metabolic surgery.

The goals of treatment of T2DM are not only glycemic control but also prevention of diabetes-related complications such as macro- and microvascular diseases. The target blood pressure of <130/80 mmHg, the target cholesterol level of <200 mg/dL, and HbA1C level <7% should be achieved in diabetic patients. It has been reported that only 7.3% of adults with diabetes achieved all three recommended goals with conventional medical treatment [57]. In contrast, bariatric surgery improved hyperlipidemia in 70% or more of patients and resolved or improved hypertension in 78.5% of patients [58]. A systematic review to evaluate the effect of bariatric surgery on cardiovascular risk profile demonstrated that on average, hypertension, diabetes, and dyslipidemia resolved in 68%, 75%, and 71% and a 40% relative risk reduction for 10-year coronary heart disease risk was observed after bariatric surgery, as determined by the Framingham risk score [59]. In this paper, Shah et al. reported that RYGB for T2DM in low BMI patients reduced the predicted 10-year cardiovascular disease risk substantially for fatal and nonfatal coronary heart disease and stroke [21].

The mortality rates from bariatric operations (0.28–0.35%) [60] are compared favorably with those of other commonly performed operations, including laparoscopic cholecystectomy, whose mortality in USA ranges between 0.35 and 0.60% [61]. In this paper, no mortality was observed. Major and minor complication rate was also low (10.3%). Huang et al., and so forth reported that the operating time and duration of hospitalization of LRYGB for low BMI patients were lower than those for morbidly obese patients because of lower BMI [19]. T2DM-related additional risk should be counted, but safety of metabolic surgery for low BMI patients seems to be higher or at least similar, compared to bariatric surgery for severe obesity.

Metabolic surgery for T2DM, although not the current standard care for the disease, may be coming closer to the mainstream. The ponderable statement has suggested that metabolic surgery might be considered a reasonable therapeutic alternative for low BMI ($<35 \, \text{kg/m}^2$) patients with T2DM who do not respond to standard medical therapy. The data from the studies included in this paper are encouraging. Although large randomized clinical trials against best medical care and assessment of the long-term efficacy and safety should be prioritized to define the role of metabolic surgery, it is clear that a high proportion of low BMI patients with T2DM will derive substantial benefit from metabolic surgery.

5. Conclusions

In this paper, including 18 studies and 477 patients, T2DM patients with a BMI $< 35 \, \text{kg/m}^2$ derived benefit from metabolic surgery. The weight loss effect was reasonable without any serious excessive weight loss. The antidiabetic effect was also considered excellent. Remission of T2DM and % meds off were achieved in 64.7% and 86.8% of the patients. T2DM clinical status is important to select the eligible candidates for metabolic surgery besides current BMI criteria for bariatric surgery. Metabolic surgery can be performed safely with acceptably low complication rate and mortality. Although several concerns need to be addressed, metabolic surgery for low BMI patients is coming closer to the mainstream of diabetes treatment.

Conflict of Interests

The authors declare that they have no relevant competing interests.

Acknowledgment

References

[1] J. E. Shaw, R. A. Sicree, and P. Z. Zimmet, "Global estimates of the prevalence of Diabetes for 2010 and 2030," *Diabetes Research and Clinical Practice*, vol. 87, no. 1, pp. 4–14, 2010.

[2] D. M. Nathan, J. B. Buse, M. B. Davidson et al., "Medical management of hyperglycaemia in type 2 Diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes," *Diabetologia*, vol. 52, no. 1, pp. 17–30, 2009.

[3] C. L. Leibson, D. F. Williamson, L. J. Melton III et al., "Temporal trends in BMI among adults with Diabetes," *Diabetes Care*, vol. 24, no. 9, pp. 1584–1589, 2001.

[4] D. F. Williamson, T. J. Thompson, M. Thun, D. Flanders, E. Pamuk, and T. Byers, "Intentional weight loss and mortality among overweight individuals with Diabetes," *Diabetes Care*, vol. 23, no. 10, pp. 1499–1504, 2000.

[5] W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., "Reduction in the incidence of type 2 Diabetes with lifestyle intervention or metformin," *The New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.

[6] J. Tuomilehto, J. Lindström, J. G. Eriksson et al., "Prevention of type 2 Diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance," *The New England Journal of Medicine*, vol. 344, no. 18, pp. 1343–1350, 2001.

[7] S. L. Norris, X. Zhang, A. Avenell et al., "Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 Diabetes: a meta-analysis," *The American Journal of Medicine*, vol. 117, no. 10, pp. 762–774, 2004.

[8] M. A. Khan, J. V. S. Peter, G. A. Breen, G. G. Hartley, and J. T. Vessey, "Diabetes disease stage predicts weight loss outcomes with long-term appetite suppressants," *Obesity Research*, vol. 8, no. 1, pp. 43–48, 2000.

[9] P. Zimmet, J. Shaw, and K. G. Alberti, "Preventing type 2 Diabetes and the dysmetabolic syndrome in the real world: a realistic view," *Diabetic Medicine*, vol. 20, no. 9, pp. 693–702, 2003.

[10] R. R. Wing, M. D. Marcus, L. H. Epstein, and R. Salata, "Type II diabetic subjects lose less weight than their overweight nondiabetic spouses," *Diabetes Care*, vol. 10, no. 5, pp. 563–566, 1987.

[11] L. Sjöström, K. Narbro, C. D. Sjöström et al., "Effects of bariatric surgery on mortality in Swedish obese subjects," *The New England Journal of Medicine*, vol. 357, no. 8, pp. 741–752, 2007.

[12] H. Buchwald, R. Estok, K. Fahrbach et al., "Weight and type 2 Diabetes after bariatric surgery: systematic review and meta-analysis," *The American Journal of Medicine*, vol. 122, no. 3, pp. 248–256, 2009.

[13] F. Rubino, A. Forgione, D. E. Cummings et al., "The mechanism of Diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 Diabetes," *Annals of Surgery*, vol. 244, no. 5, pp. 741–749, 2006.

[14] F. Rubino, P. R. Schauer, L. M. Kaplan, and D. E. Cummings, "Metabolic surgery to treat type 2 Diabetes: clinical outcomes and mechanisms of action," *Annual Review of Medicine*, vol. 61, pp. 393–411, 2010.

[15] J. B. Dixon, P. Zimmet, K. G. Alberti, and F. Rubino, "Bariatric surgery: an IDF statement for obese type 2 Diabetes," *Diabetic Medicine*, vol. 28, no. 6, pp. 628–642, 2011.

[16] W. J. Lee, K. Chong, C. Y. Chen et al., "Diabetes remission and insulin secretion after gastric bypass in patients with body mass index < 35 kg/m^2," *Obesity Surgery*, vol. 21, no. 7, pp. 889–895, 2011.

[17] C. Boza, R. Muñoz, J. Salinas et al., "Safety and efficacy of Roux-en-Y gastric bypass to treat type 2 Diabetes mellitus in non-severely obese patients," *Obesity Surgery*, vol. 21, no. 9, pp. 1330–1336, 2011.

[18] V. C. de Sa, A. A. Ferraz, J. M. Campos, A. C. Ramos, J. G. Araujo Jr., and E. M. Ferraz, "Gastric bypass in the treatment of type 2 Diabetes in patients with a BMI of 30 to 35 kg/m^2," *Obesity Surgery*, vol. 21, no. 3, pp. 283–287, 2011.

[19] C. K. Huang, A. Shabbir, C. H. Lo, C. M. Tai, Y. S. Chen, and J. Y. Houng, "Laparoscopic Roux-en-Y gastric bypass for the treatment of type II Diabetes mellitus in Chinese patients with body mass index of 25–35," *Obesity Surgery*, vol. 21, no. 9, pp. 1344–1349, 2011.

[20] N. Scopinaro, G. F. Adami, F. S. Papadia et al., "Effects of biliopancreatic diversion on type 2 Diabetes in patients with BMI 25 to 35," *Annals of Surgery*, vol. 253, no. 4, pp. 699–703, 2011.

[21] S. S. Shah, J. S. Todkar, P. S. Shah, and D. E. Cummings, "Diabetes remission and reduced cardiovascular risk after gastric bypass in Asian Indians with body mass index < 35 kg/m^2," *Surgery for Obesity and Related Diseases*, vol. 6, no. 4, pp. 332–338, 2010.

[22] W. J. Lee, K. H. Ser, K. Chong et al., "Laparoscopic sleeve gastrectomy for Diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion," *Surgery*, vol. 147, no. 5, pp. 664–669, 2010.

[23] A. L. Depaula, A. L. MacEdo, V. Schraibman, B. R. Mota, and S. Vencio, "Hormonal evaluation following laparoscopic treatment of type 2 Diabetes mellitus patients with BMI 20–34," *Surgical Endoscopy and Other Interventional Techniques*, vol. 23, no. 8, pp. 1724–1732, 2009.

[24] A. L. DePaula, A. L. Macedo, B. R. Mota, and V. Schraibman, "Laparoscopic ileal interposition associated to a diverted sleeve gastrectomy is an effective operation for the treatment of type 2 Diabetes mellitus patients with BMI 21–29," *Surgical Endoscopy and Other Interventional Techniques*, vol. 23, no. 6, pp. 1313–1320, 2009.

[25] A. C. Ramos, M. P. G. Neto, Y. M. de Souza et al., "Laparoscopic duodenal-jejunal exclusion in the treatment of type 2 Diabetes mellitus in patients with BMI <30 kg/m^2 (LBMI)," *Obesity Surgery*, vol. 19, no. 3, pp. 307–312, 2009.

[26] G. S. Ferzli, E. Dominique, M. Ciaglia, M. H. Bluth, A. Gonzalez, and A. Fingerhut, "Clinical improvement after duodenojejunal bypass for nonobese type 2 Diabetes despite minimal improvement in glycemic homeostasis," *World Journal of Surgery*, vol. 33, no. 5, pp. 972–979, 2009.

[27] B. Geloneze, S. R. Geloneze, C. Fiori et al., "Surgery for nonobese type 2 diabetic patients: an interventional study with duodenal-jejunal exclusion," *Obesity Surgery*, vol. 19, no. 8, pp. 1077–1083, 2009.

[28] C. Chiellini, F. Rubino, M. Castagneto, G. Nanni, and G. Mingrone, "The effect of bilio-pancreatic diversion on type 2 Diabetes in patients with BMI < 35 kg/m^2," *Diabetologia*, vol. 52, no. 6, pp. 1027–1030, 2009.

[29] W. J. Lee, W. Wang, Y. C. Lee, M. T. Huang, K. H. Ser, and J. C. Chen, "Effect of laparoscopic mini-gastric bypass for type 2 Diabetes mellitus: comparison of BMI > 35 and < 35 kg/m^2," *Journal of Gastrointestinal Surgery*, vol. 12, no. 5, pp. 945–952, 2008.

[30] N. Scopinaro, F. Papadia, G. Marinari, G. Camerini, and G. Adami, "Long-term control of type 2 Diabetes mellitus and

the other major components of the metabolic syndrome after biliopancreatic diversion in patients with BMI < 35 kg/m^2," *Obesity Surgery*, vol. 17, no. 2, pp. 185–192, 2007.

[31] R. V. Cohen, C. A. Schiavon, J. S. Pinheiro, J. L. Correa, and F. Rubino, "Duodenal-jejunal bypass for the treatment of type 2 Diabetes in patients with body mass index of 22–34 kg/m^2: a report of 2 cases," *Surgery for Obesity and Related Diseases*, vol. 3, no. 2, pp. 195–197, 2007.

[32] R. Cohen, J. S. Pinheiro, J. L. Correa, and C. A. Schiavon, "Laparoscopic Roux-en-Y gastric bypass for BMI < 35 kg/m^2: a tailored approach," *Surgery for Obesity and Related Diseases*, vol. 2, no. 3, pp. 401–404, 2006.

[33] G. Noya, M. L. Cossu, M. Coppola et al., "Biliopancreatic diversion preserving the stomach and pylorus in the treatment of hypercholesterolemia and Diabetes type II: results in the first 10 cases," *Obesity Surgery*, vol. 8, no. 1, pp. 67–72, 1998.

[34] H. Buchwald and R. L. Varco, Eds., *Metabolic Surgery*, Grune and Stratton, New York, NY, USA, 1978.

[35] J. B. Dixon, W. J. Pories, P. E. O'Brien, P. R. Schauer, and P. Zimmet, "Surgery as an effective early intervention for diabesity: why the reluctance?" *Diabetes Care*, vol. 28, no. 2, pp. 472–474, 2005.

[36] F. Rubino, L. M. Kaplan, P. R. Schauer, and D. E. Cummings, "The Diabetes surgery summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 Diabetes mellitus," *Annals of Surgery*, vol. 251, no. 3, pp. 399–405, 2010.

[37] American Diabetes Association, "Standards of medical care in Diabetes—2009," *Diabetes Care*, vol. 32, supplement 1, pp. S13–S61, 2009.

[38] M. Fried, G. Ribaric, J. N. Buchwald, S. Svacina, K. Dolezalova, and N. Scopinaro, "Metabolic surgery for the treatment of type 2 Diabetes in patients with BMI < 35 kg/m^2: an integrative review of early studies," *Obesity Surgery*, vol. 20, no. 6, pp. 776–790, 2010.

[39] N. Scopinaro, G. M. Marinari, F. Pretolesi et al., "Energy and nitrogen absorption after biliopancreatic diversion," *Obesity Surgery*, vol. 10, no. 5, pp. 436–441, 2000.

[40] M. M. Hutter, B. D. Schirmer, D. B. Jones et al., "First report from the American College of Surgeons Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass," *Annals of Surgery*, vol. 254, no. 3, pp. 410–422, 2011.

[41] A. Mari, M. Manco, C. Guidone et al., "Restoration of normal glucose tolerance in severely obese patients after biliopancreatic diversion: role of insulin sensitivity and beta cell function," *Diabetologia*, vol. 49, no. 9, pp. 2136–2143, 2006.

[42] E. V. Polyzogopoulou, F. Kalfarentzos, A. G. Vagenakis, and T. K. Alexandrides, "Restoration of euglycemia and normal acute insulin response to glucose in obese subjects with type 2 Diabetes following bariatric surgery," *Diabetes*, vol. 52, no. 5, pp. 1098–1103, 2003.

[43] F. K. Knop, "Resolution of type 2 Diabetes following gastric bypass surgery: involvement of gut-derived glucagon and glucagonotropic signalling?" *Diabetologia*, vol. 52, no. 11, pp. 2270–2276, 2009.

[44] M. DiGiorgi, D. J. Rosen, J. J. Choi et al., "Re-emergence of Diabetes after gastric bypass in patients with mid- to long-term follow-up," *Surgery for Obesity and Related Diseases*, vol. 6, no. 3, pp. 249–253, 2010.

[45] S. M. Chikunguwo, L. G. Wolfe, P. Dodson et al., "Analysis of factors associated with durable remission of Diabetes after Roux-en-Y gastric bypass," *Surgery for Obesity and Related Diseases*, vol. 6, no. 3, pp. 254–259, 2010.

[46] M. Deitel, "Update: why Diabetes does not resolve in some patients after bariatric surgery," *Obesity Surgery*, vol. 21, no. 6, pp. 794–796, 2011.

[47] P. Zimmet, R. Turner, D. McCarty, M. Rowley, and I. Mackay, "Crucial points at diagnosis: type 2 Diabetes or slow type 1 Diabetes," *Diabetes Care*, vol. 22, supplement 2, pp. B59–B64, 1999.

[48] M. Deitel, "Surgery for Diabetes at lower BMI: some caution," *Obesity Surgery*, vol. 18, no. 10, pp. 1211–1214, 2008.

[49] "Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement," *The American Journal of Clinical Nutrition*, vol. 55, supplement 2, pp. 615S–619S, 1992.

[50] A. P. Schulman, F. del Genio, N. Sinha, and F. Rubino, ""Metabolic" surgery for treatment of type 2 Diabetes mellitus," *Endocrine Practice*, vol. 15, no. 6, pp. 624–631, 2009.

[51] E. Fabbrini, F. Magkos, B. S. Mohammed et al., "Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 36, pp. 15430–15435, 2009.

[52] F. Razak, S. S. Anand, H. Shannon et al., "Defining obesity cut points in a multiethnic population," *Circulation*, vol. 115, no. 16, pp. 2111–2118, 2007.

[53] G. C. Weir and S. Bonner-Weir, "Five of stages of evolving β-cell dysfunction during progression to Diabetes," *Diabetes*, vol. 53, no. 3, pp. S16–S21, 2004.

[54] R. S. Mazze, E. Strock, G. D. Simonson, and R. M. Bergenstal, *Staged Diabetes Management: Prevention, Detection and Treatment of Diabetes in Adults Quick Guide*, Matrex, Minneapolis, Minn, USA, 4th edition, 2005.

[55] P. R. Schauer, B. Burguera, S. Ikramuddin et al., "Effect of laparoscopic Roux-En Y gastric bypass on type 2 Diabetes mellitus," *Annals of Surgery*, vol. 238, no. 4, pp. 467–484, 2003.

[56] J. B. Dixon and P. E. O'Brien, "Health outcomes of severely obese type 2 diabetic subjects 1 year after laparoscopic adjustable gastric banding," *Diabetes Care*, vol. 25, no. 2, pp. 358–363, 2002.

[57] S. H. Saydah, J. Fradkin, and C. C. Cowie, "Poor control of risk factors for vascular disease among adults with previously diagnosed Diabetes," *The Journal of the American Medical Association*, vol. 291, no. 3, pp. 335–342, 2004.

[58] H. Buchwald, Y. Avidor, E. Braunwald et al., "Bariatric surgery: a systematic review and meta-analysis," *The Journal of the American Medical Association*, vol. 292, no. 14, pp. 1724–1737, 2004.

[59] H. M. Heneghan, S. Meron-Eldar, S. A. Brethauer, P. R. Schauer, and J. B. Young, "Effect of bariatric surgery on cardiovascular risk profile," *The American Journal of Cardiology*, vol. 108, no. 10, pp. 1499–1507, 2011.

[60] H. Buchwald, R. Estok, K. Fahrbach, D. Banel, and I. Sledge, "Trends in mortality in bariatric surgery: a systematic review and meta-analysis," *Surgery*, vol. 142, no. 4, pp. 621–635, 2007.

[61] S. F. Khuri, S. F. Najjar, J. Daley et al., "Comparison of surgical outcomes between teaching and nonteaching hospitals in the Department of Veterans Affairs," *Annals of Surgery*, vol. 234, no. 3, pp. 370–383, 2001.