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Bariatric surgery and type 2 diabetes: are there weight loss-independent therapeutic effects of upper gastrointestinal bypass?

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Abstract

Type 2 diabetes (T2D) is a major worldwide public health concern. Despite a large armamentarium of T2D medications, a large proportion of patients fail to achieve recommended treatment goals for glycemic control. Weight loss has profound beneficial effects on the metabolic abnormalities involved in the pathogenesis of T2D. Accordingly, bariatric surgery, which is the most effective available weight loss therapy, is also the most effective therapy for treating patients with T2D. Surgical procedures that bypass the upper gastrointestinal (UGI) tract are particularly effective in achieving partial and even complete remission of T2D, suggesting that UGI bypass has weight loss-independent effects on glycemic control. Although a number of hypotheses (e.g. a role for multi-organ insulin sensitivity, β-cell function, incretin response, the gut microbiome, bile acid metabolism, intestinal glucose metabolism, and browning of adipose tissue) have been proposed to explain the potential unique effects of UGI tract bypass surgery, none has yet been adequately evaluated to determine therapeutic importance in patients with T2D. Here, we review the efficacy of UGI bypass surgery in treating T2D and the mechanisms that have been proposed to explain its potential weight loss-independent therapeutic effects.

Introduction

Type 2 diabetes (T2D) is a major public health problem worldwide, because of its high and increasing prevalence and profound effects on health and quality of life [1]. Despite the large number and variety of medications available to treat T2D, ~50% of patients fail to achieve American Diabetes Association treatment goals [2]. Bariatric surgery is the most effective therapy for achieving glycemic control in patients with T2D. Data from a series of randomized clinical trials have demonstrated the superiority of bariatric surgery over intensive medical therapy in the management of T2D [3–11]. Surgical procedures that

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Conflict of interest statement

S.K. is a shareholder of Aspire Bariatrics and has served on scientific advisory boards for Takeda Pharmaceuticals and NovoNordisk.

bypass the upper gastrointestinal (UGI) tract are particularly effective in achieving partial and complete remission of T2D. This observation has led to the concept that UGI tract bypass surgery has therapeutic weight loss-independent effects on glucose homeostasis. The purpose of this review is to summarize current knowledge of: (i) the regulation of glucose metabolism and pathogenesis of T2D; (ii) the effectiveness of UGI tract bypass surgery in the treatment of T2D; and (iii) the potential mechanisms responsible for weight loss-independent effects of UGI tract bypass on glucose metabolism.

Pathophysiology and pathogenesis of T2D

The diagnosis of T2D is based on fasting plasma glucose concentration, plasma glucose after an oral glucose load, or glycosylated plasma hemoglobin A1c (HbA1c) [12]. Multiple tissues are responsible for maintaining blood glucose levels within a narrow range by regulating endogenous glucose production (via gluconeogenesis and/or glycogenolyis) and its removal from the circulation (via oxidative or non-oxidative glucose disposal).

During postabsorptive conditions, the liver and kidneys produce glucose, which is secreted into the circulation for delivery to other organs. In healthy lean adults, the total endogenous glucose production is ~2 mg/kg body weight/min, of which the kidneys account for 20% [13, 14]. About half of the glucose released into the circulation (~1 mg/kg body weight/min) is taken up by the brain [15, 16], while ~0.5 mg/kg body weight/min [13] (or ~1–1.5 μmol/100 g tissue/min [17, 18]) is taken up by the liver and gastrointestinal tract, ~0.4 mg/kg body weight/min by the kidneys [14], and ~1 μmol/100g tissue/min by skeletal muscle and adipose tissue [19]. During hyperinsulinemia, skeletal muscle is the major tissue responsible for glucose clearance (~5.5 mg/kg body weight/min [13] or 6 μmol/100 g tissue/min [19]), while insulin-stimulated glucose uptake is ~3 μmol/100 g small intestine/min [18], ~5 μmol/100 g brown adipose tissue (BAT)/min [19], and ~2.5 μmol/100 g white adipose tissue (WAT)/min [19].

The pathogenesis of T2D involves a constellation of metabolic derangements involving multiple organs that cause: (i) inadequate insulin secretion from pancreatic β-cells [20, 21]; (ii) increased glucose production by the liver because of impaired insulin-mediated suppression of hepatic glucose production [22, 23] and increased pancreatic α-cell glucagon secretion [24–27]; (iii) decreased plasma glucose clearance, because of impaired insulin-stimulated glucose disposal in many tissues, particularly skeletal muscle [22, 28]; and (iv) increased renal glucose reabsorption [29].

Bariatric surgery and remission of T2D

Bariatric surgery is an extraordinarily effective therapy for patients with T2D. Data from a series of randomized controlled clinical trials have demonstrated that bariatric surgery results in better glycemic control and greater rates of T2D remission than intensive medical/lifestyle therapy [3–11]. The remission rate reported in different studies varies from 20% to 100%, depending on the patient population, type of surgical procedure, duration of follow-up, and the amount of weight loss achieved. The criteria used to define remission are also a critical determinant of reported remission rates and confound the interpretation of results

among studies [30–32]. In 2009, an expert panel developed criteria to determine ‘partial’ and ‘complete’ remission of T2D [33]. Partial remission was defined as HbA1c <6.5%, fasting glucose 100–125 mg/dL (5.6–6.9 mmol/L) of at least 1 year’s duration in the absence of active pharmacological therapy, or ongoing procedures; complete remission was defined as HbA1c in the normal range, fasting glucose <100 mg/dL (5.6 mmol/L) of at least 1 year’s duration in the absence of active pharmacological therapy, or ongoing procedures. However, these criteria have not been universally accepted, and the definition of T2D remission after bariatric surgery continues to vary between studies [4, 8].

Several factors, which reflect the severity of T2D, have been identified that are associated with failure to achieve complete remission of T2D after bariatric surgery, including: (i) poor baseline glycemic control [34–38]; (ii) long duration of T2D [36–39]; and (iii) poor β-cell function [35, 40, 41]. In addition, percent weight loss is associated with remission after surgery, and those who lose more weight are more likely to achieve remission than those who lose less weight [11, 35, 38, 42, 43]. In general, ~50% of patients who achieve remission of T2D will relapse within 5–10 years [4, 44–47]. The most important predictor of relapse is weight regain [44, 46–48]. Preoperative factors associated with relapse include age, poor glycemic control, insulin use, and long duration of T2D [44, 46, 48].

The rate of remission of T2D after bariatric surgery differs among surgical procedures. Data from prospective randomized and non-randomized clinical trials support the notion that bypass of the UGI tract has weight loss-independent therapeutic effects on remission of T2D, and that the length of the bypass influences outcome [3, 7, 10, 49, 50]. The results of randomized controlled trials that evaluated the effect of UGI tract bypass surgery on inducing remission of T2D are presented in Table 1. The results from two randomized clinical trials showed that, at similar relative amounts of weight loss, patients who had Roux-en Y gastric bypass (RYGB) tended to have better glycemic control than those who had sleeve gastrectomy at 1 [7] and 3 years [3] after surgery, and those who had biliopancreatic diversion (BPD) had significantly greater diabetes remission rates than those who had RYGB at 2 [51] and 5 years [4] after surgery. However, it is not known whether all predictors, particularly β-cell function, were the same among groups, which could have influenced the outcomes.

The beneficial long-term effects of bariatric surgery are not limited to remission of T2D. Data from the Swedish Obese Subjects study, which included more than 4000 patients who were followed for up to 20 years, demonstrated that bariatric surgery improves long-term survival, and decreases the incidence ofT2D, myocardial infarction, stroke, and cancer [52]. Nonetheless, bariatric surgery is also associated with complications. Most complications are those that occur with any gastrointestinal surgical procedure, including death, pneumonia, deep vein thrombosis, pulmonary embolism, anastomotic leak with peritonitis, wound infection, gastrointestinal bleeding, and incisional hernias, whereas other complications, such as dumping syndrome, hypoglycemia, and nutritional deficiencies, are related to specific bariatric surgical procedures [4, 52].

Potential weight loss-independent effects of RYGB

It has been proposed that anatomical bypass of the UGI tract and functional remodeling of the intestine has therapeutic weight loss-independent effects on glycemic control by a number of potential mechanisms (Fig. 1), which can interact with each other, including: (i) insulin sensitivity; (ii) first-phase insulin secretion and incretin effects; (iii) intestinal glucose metabolism; (iv) bile acid (BA) physiology; (v) the gut microbiome; and (vi) browning of adipose tissue.

Insulin sensitivity

Resistance to the action of insulin is a major component of the pathogenesis of T2D [53]. Acute caloric restriction (negative energy balance) rapidly improves hepatic insulin sensitivity [54] due to reduced hepatic glycogen content and glucose production rate [54, 55], whereas a moderate 5% weight loss improves insulin sensitivity in liver, adipose tissue, and skeletal muscle in obese individuals without T2D [56]. The profound effects of calorie restriction and weight loss on insulin sensitivity make it difficult to determine whether UGI tract bypass surgery has weight loss-independent effects on insulin action, because this evaluation requires matching energy intake and weight loss in the comparator group with values in the intestinal bypass group. In addition, differences in the amount of weight loss achieved and the method used to assess insulin sensitivity can affect the results and confound the interpretation of results between studies. Data from most studies do not support a weight loss-independent effect of RYGB on insulin sensitivity. The early improvement in insulin sensitivity, assessed using the homeostasis model assessment of insulin resistance [57] or the intravenous glucose tolerance test [58], after 2–8% weight loss within the first 21 days after RYGB surgery was the same in subjects who had surgery as in control subjects matched on calorie intake and weight loss [59, 60]. In addition, the improvement in insulin sensitivity, assessed using the hyperinsulinemic-euglycemic clamp procedure [61], was the same after ~20% weight loss in subjects who had laparoscopic adjustable gastric banding (LAGB) as in those who had RYGB surgery [10, 62–65]. By contrast, BPD seems to have unique effects on insulin sensitivity, manifested by rapid improvement in insulin sensitivity, assessed using the hyperinsulinemic-euglycemic clamp procedure, after <10% weight loss [66].

First-phase insulin secretion and incretin effect

The ingestion of glucose induces a biphasic secretion of insulin: a rapid first phase followed by a sustained second phase. The first phase of insulin secretion represents the rapid release of insulin from a ‘readily releasable pool’ present in secretory granules within the β-cell and occurs within the first 10 min of glucose ingestion; this phase limits the increase in postprandial glucose concentrations by promoting the systemic clearance of the prandial load and suppressing hepatic glucose production. In addition, oral glucose ingestion causes a much greater increase in plasma insulin concentration than a matched increase in plasma glucose induced by an intravenous glucose infusion [67]. This phenomenon is known as the ‘incretin effect’ because it is believed to be caused by the secretion of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotopic polypeptide, released from entero-endocrine L and K cells, respectively [68, 69]. Both the first-phase insulin

response and the incretin effect are reduced or absent in individuals with T2D and contribute to postprandial hyperglycemia [70, 71].

The rapid delivery of nutrients into the upper intestine after RYGB surgery causes an early and pronounced increase in plasma glucose, insulin, and GLP-1 concentrations after ingestion of a mixed meal or glucose [65, 72–77]. Moreover, RYGB causes a large increase in the in cretin effect of an oral glucose load [78]. Both the increase in plasma glucose and increase in GLP-1 contribute to the early and high plasma insulin concentrations observed after consumption of a meal or glucose in patients who have had RYGB surgery [79, 80]. Although it seems logical that the improved first-phase insulin response and incretin effect would contribute to achieving remission of T2D after RYGB, this hypothesis has not yet been proven in patients. Pharmacological GLP-1 receptor blockade with exendin (9–39) in patients with T2D who had sleeve gastrectomy resulted in impaired insulin secretion without a deterioration in oral glucose tolerance [81], which underscores the need for similar studies in patients who have had RYGB and who have experienced remission, no remission, relapse, or no relapse of T2D.

Intestinal glucose metabolism

The intestine takes up glucose during both basal conditions and hyperinsulinemia [13, 17, 18]. Data from studies conducted in rodent models have shown that RYGB induces villus hyperplasia and increases villus height in the Roux limb [82–84], and increases intestinal glucose uptake from plasma [85]. In humans, RYGB surgery causes a small decrease in the total amount of glucose delivered to the systemic circulation after ingestion of a mixed meal, but the magnitude of intestinal glucose retention is small and does not cause an improvement in postprandial glycemic control [86]. It was recently found that insulin-stimulated jejunal glucose uptake, assessed using [(18)F]fluoro-2-deoxyglucose positron emission tomography-computed tomography in conjunction with the hyperinsulinemic-euglycemic clamp procedure, increased 6 months after RYGB compared with preoperative baseline values in patients with and without T2D [18]. However, this study did not include a matched diet-induced weight loss group, so it is uncertain whether these results are attributable to weight loss or UGI tract bypass *per se*.

BA physiology

BAs are synthesized from cholesterol in the liver and are then secreted into the gallbladder, where they are stored. After ingestion of a meal, contraction of the gallbladder results in secretion of BAs into the duodenum, which are subsequently absorbed primarily in the terminal ileum and transported back to the liver via the portal vein, while small amounts are delivered to the colon and excreted in feces [87]. This enterohepatic circulation of BAs occurs many times a day and is important for tightly regulating the BA pool with a minimal amount of *de novo* synthesis. The primary BAs are those synthesized by the liver and include cholic acid and chenodeoxycholic acid, which can be conjugated to either taurine (taurocholic acid and taurochenodeoxycholic acid) or glycine (glycocholic acid and glycochenodeoxycholic acid) to form BA salts [88, 89]. Primary BAs are dehydroxylated by gut bacteria into secondary BAs (e.g. deoxycholic acid from cholic acid and lithocholic acid from chenodeoxycholic acid).

Although BAs have canonical roles in dietary lipid absorption and in regulating cholesterol metabolism, they also act as hormones by binding to the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 5 (TGR5), which are highly expressed in hepatocytes and enterocytes and affect glucose, lipid, and energy metabolism [90–92]. BAs can regulate glucose metabolism through FXR-mediated pathways that increase glycolysis, decrease gluconeogenesis, stimulate hepatic glycogen synthesis, and increase insulin sensitivity and glucose disposal [93, 94]. BAs can also activate TGR5 in L cells to stimulate GLP-1 secretion [95]. The effect of BAs on metabolic function is extraordinarily complex, because of the large number of different BAs and differences in their ability to activate FXR and TGR5 receptors [96–98]. Therefore, in order to understand the potential metabolic effect of alterations of BAs induced by bariatric surgery it is important to understand the changes in individual BAs, not simply alterations in total serum BA concentration.

Weight loss induced by RYGB surgery increases both fasting and postprandial serum BA levels [89, 99–103]. Although this observation has led to the hypothesis that increased circulating levels of BAs contribute to the beneficial effects of RYGB surgery on β-cell function and hepatic and muscle insulin sensitivity, there is no direct evidence demonstrating a causal relationship between BAs and improved metabolic function in patients who have had RYGB surgery. Moreover, the relationship between serum BAs and glucose control after RYGB is unclear because of conflicting data from different studies, with some studies demonstrating a dissociation between an increase in serum BAs and an improvement in metabolic outcomes [101, 104, 105]. For example, the results from one study showed a direct correlation between the change in postprandial serum BAs and peak GLP-1 concentrations after matched weight loss induced by either LAGB or RYGB surgery, but improvement in β-cell function and insulin sensitivity was the same in both groups even though basal and postprandial serum BA concentrations decreased after LAGB but increased after RYGB surgery [103]. In two other studies that evaluated subjects before and at 1 week, 3 months, and 1 year after RYGB surgery it was found that the increase in postprandial GLP-1 concentration and improvements in β-cell function, oral glucose tolerance and insulin sensitivity occurred before there was an increase in postprandial BA concentration [101, 104]. The complexity of the relationship between BAs and metabolic function makes it difficult to attribute changes in plasma BA concentrations and composition to changes in metabolic function.

Gut microbiome

Alterations in the composition and diversity of the gut microbiome are associated with obesity and T2D in humans [106–108]. The potential causal relationship between the gut microbiome and metabolic function is supported by data from studies demonstrating that transplantation of fecal microbiota from metabolically abnormal individuals can transmit the abnormal phenotype to gnotobiotic mice [109] and transplantation of fecal microbiota from healthy lean donors to those with metabolic syndrome improves their insulin sensitivity [109].

Few studies have evaluated the effect of RYGB surgery on the human gut microbiome. The available data demonstrate that weight loss induced by RYGB is associated with an increase

in the microbial diversity/richness (number of different types of bacteria). There is also a change in the relative amounts of specific bacterial phyla and species, but these changes are not consistent among studies [110–113]. The mechanism responsible for the change in gut bacteria after RYGB is not known, but is likely to involve a combination of factors, such as changes in body weight, dietary intake, nutrient flow through the intestine, gut motility, intraluminal pH, and bile flow [114–117]. Although it has been proposed that bypass of the UGI tract causes unique changes in the gut microbiome that contribute to the beneficial metabolic effects of RYGB, similar changes in gut microbiome are also found after vertical banded gastroplasty [118]. Moreover, it is not known whether the changes in the microbiome are simply associated with, or contribute to, the metabolic benefits of surgery. Transfer of the fecal microbiota from patients who had RYGB or vertical banded gastroplasty to germ-free mice resulted in reduced accumulation of body fat in recipient mice, but the weight-independent effects on metabolic function were not evaluated [118]. Together, data from studies conducted in humans demonstrate that profound alterations in the gut microbiome are caused by bariatric surgery-induced weight loss. Additional studies are needed to determine whether these changes are specific to surgery itself or diet-related weight loss, and whether they confer weight loss-independent therapeutic effects on glucose homeostasis.

Browning of subcutaneous WAT

BAT is primarily located in the supraclavicular adipose tissue depot in adults [119–121]. Brown adipocytes contain high numbers of mitochondria, rich in uncoupling protein 1, which uncouples oxidative phosphorylation from ATP production leading to heat generation [122]. When activated (by cold, insulin, or other stimuli), brown adipocytes can increase their glucose uptake 12-fold [19], suggesting they might be important in whole-body glucose homeostasis [123]. In fact, there is evidence that BAT increases whole-body insulin sensitivity with respect to glucose metabolism [123, 124]. A low amount of BAT in individuals is associated with excess adiposity and T2D [119, 125], whereas weight loss induced by a very low-calorie diet [126], gastric banding [127], or RYGB [128] increases BAT activity. Although RYGB surgery causes an increase in plasma concentrations of BAs and GLP-1, which can increase BAT metabolic activity and cause browning of WAT [129–131], it is not known whether RYGB-induced weight loss causes a greater increase in BAT than calorie restriction alone.

Conclusion

Bariatric surgery is currently the most effective therapy for T2D and results in remission in many patients. Bypass of the UGI tract has profound effects on the metabolic response to ingestion of glucose or a mixed meal and on BA physiology. The greater rate of complete remission of T2D after RYGB than after similar weight loss induced by sleeve gastrectomy, and the greater rate of remission after BPD than after similar weight loss induced by RYGB, suggest that bypass of the UGI tract and the length of the bypass have weight loss-independent effects on glycemic control. Although several hypotheses have been proposed to try to explain the potential unique effects of RYGB surgery in achieving remission of T2D, none has yet been adequately evaluated in studies conducted in patients.

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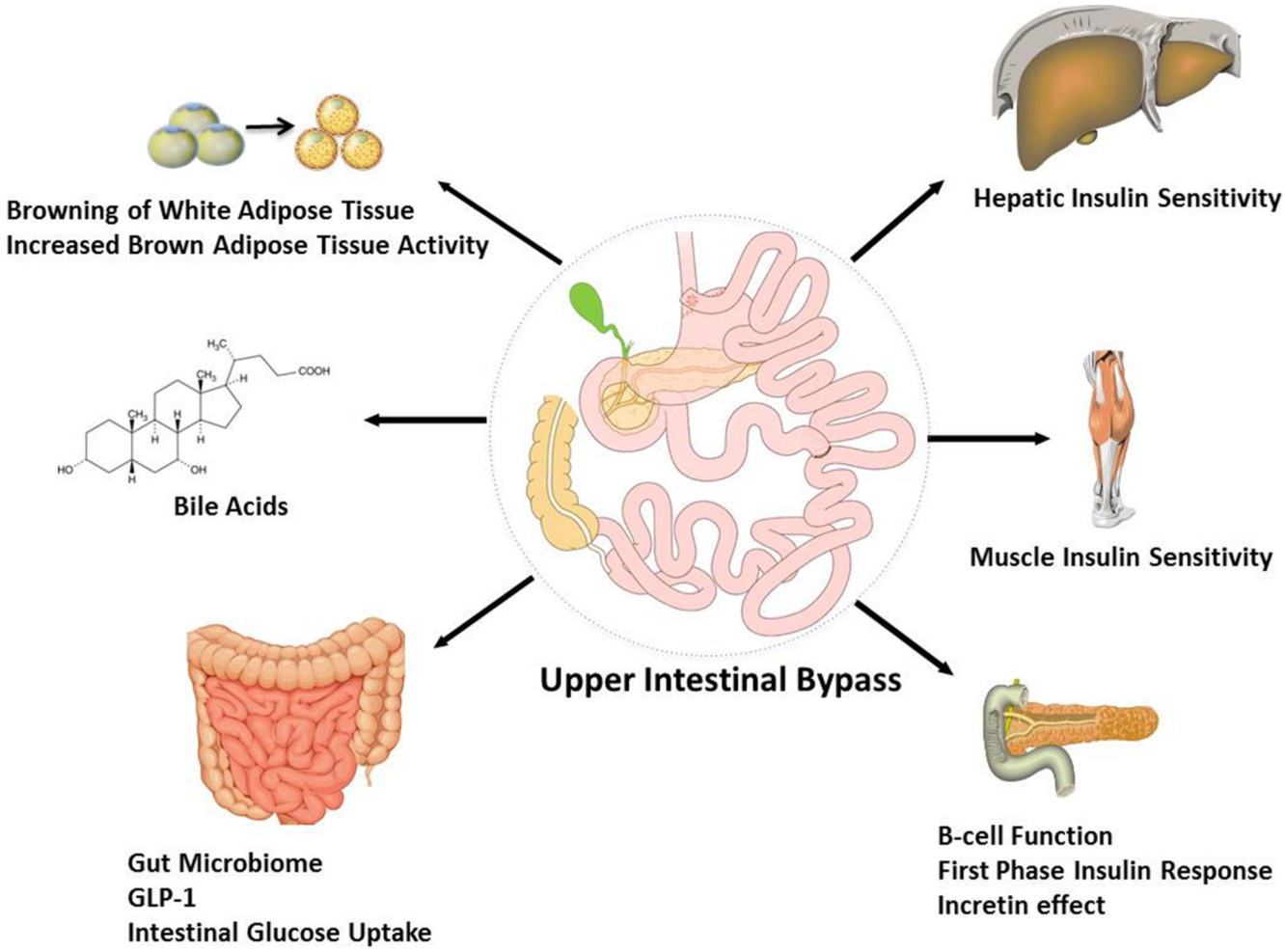

Fig. 1.

Purported mechanisms involved in the remission of type 2 diabetes in patients who have had upper gastrointestinal bypass surgery. GLP-1, glucagon-like peptide-1.

Table 1

Randomized controlled trials that evaluated the effect of upper gastrointestinal bypass surgery in inducing remission of type 2 diabetes

Author	Follow-up	Intervention	Weight loss (%)	Remission criteria	Remission (%)
Ikramuddin *et al.* 2013 [5]	1 year	RYGB: *n* = 60 MLT: *n* = 60	RYGB: 26. MLT: 7.9	HbA1c ≤6.0%	RYGB: 44 MLT: 9
Courcoulas *et al.* 2014 [6]	1 year	RYGB: *n* = 20 LAGB: *n* = 21 MLT: *n* = 20	RYGB: 27.0 LAGB: 17.3 MLT: 10.2	HbA1c <6.5% FPG <126 mg/dL No T2D medication	RYGB: 50 LAGB: 27 MLT: 0
Schauer *et al.* 2012 [7]	1 year	RYGB: *n* = 50 SG: *n* = 50 MLT: *n* = 50	RYGB: 27.5 SG: 25.0 MLT: 5.2	HbA1c ≤6.0% No T2D medication	RYGB: 42 SG: 27 MLT: 0
Halperin *et al.* 2014 [8]	1 year	RYGB: *n* = 19 MLT: *n* = 19	BMI decrease[a]: RYGB: ~9.5 kg/m^2 MLT: ~2.2 kg/m^2	HbA1c <6% FPG <100 mg/dL	RYGB: 32 MLT: 0
Schauer *et al.* 2014 [3]	3 years	RYGB: *n* = 48 SG: *n* = 49 MLT: *n* = 40	RYGB: 24.5 SG: 21.1 MLT: 4.2	HbA1c ≤6.0% No T2D medication	RYGB: 35 SG: 20 MLT: 0
Kehagias *et al.* 2011 [132]	3 years	RYGB: *n* = 30, T2D: *n* = 5 SG: *n* = 30, T2D *n* = 5	EWL[a]: RYGB: 62 SG: 68	FPG <126 mg/dL 2-h OGTT <200 mg/dL No T2D medication	RYGB: 80 SG: 80
Risstad *et al.* 2015 [133]	5 years	RYGB: *n* = 31, T2D *n* = 5 BPD-DS: *n* = 29, T2D n = 5	RYGB: 25.6 BPD-DS: 40.6	FPG <100 mg/dL No T2D medication	RYGB: 80 BPD-DS: 100
Mingrone *et al.* 2015 [4]	5 years	RYGB: *n* = 20 BPD: *n* = 20 MLT: *n* = 20	RYGB: 28.4 BPD: 31.1 MLT: 7.0	HbA1c <6.5% FPG <100 mg/dL No T2D medication	RYGB: 37 BPD: 63 MLT: 0

BMI, body mass index; BPD, biliopancreatic diversion; BPD-DS, biliopancreatic diversion with duodenal switch; EWL, excess weight loss; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; LAGB. laparoscopic adjustable gastric banding; MLT, medical and/or lifestyle therapy; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; T2D, type 2 diabetes.

[a]Alternative measures of weight loss documented in the original manuscripts.