Curr Cardiol Rep (2014) 16:444
DOI 10.1007/s11886-013-0444-5

DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Role of Bariatric Surgery in Diabetes

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Published online: 10 January 2014

Abstract Obesity and diabetes are chronic diseases frequently linked together. Durable weight loss is uncommon with medical/behavioral approaches. For severe obesity, bariatric surgery is the only treatment resulting in sustained weight loss. Bariatric surgery may be considered for adults with BMI≥35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. Bariatric surgery reduces the incidence of diabetes in overweight insulin-resistant subjects and is associated with remission of diabetes in a large proportion of patients. In considering the usefulness of bariatric surgery, it is also important to recognize that long-term follow-up is required before assigning a beneficial therapeutic effect in patients with diabetes because of the potential for weight regain that has been observed. As diabetes is a lifelong disease, it is important to emphasize that a certain percentage of patients will suffer from relapse of their diabetes.

Keywords Type 2 diabetes · Obesity · Weight loss · Bariatric surgery · Non-surgical duodenal exclusion · Diabetes remission

Introduction

Obesity is associated with an increased metabolic burden such as hypertension, dyslipidemia and diabetes. These cardiovascular risk factors translate into elevated rates of cardiovascular disease and heart failure. Thus, obese patients do have increased mortality but less so if patients are stratified based of the presence or absence of risk factors such as diabetes and hypertension. Indeed, life span may be only minimally reduced when these risk factors are absent [1]. The medical costs for a type 2 diabetes patient are two to four times greater than the costs for a patient without diabetes. Estimated yearly costs of managing a diabetes patient ($13,243) are more than five times that of a patient without diabetes ($2560) [2]. The largest components of costs are hospital inpatient care (50 %), medication and supplies (12 %), retail prescriptions to treat complications (11 %), and physician office visits (9 %) [2]. Non pharmacological approaches such as diet and exercise always play a role in obesity and diabetes management, but lifestyles interventions alone do not achieve durable weight loss inducing beneficial clinical outcomes in the majority of obese patients with diabetes [3]. This was the case in the Look Ahead study where the primary outcome, defined as the composite of first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for angina, occurred in 403 patients in the intervention group and in 418 patients in the control group (1.83 and 1.92 events per 100 person-years, P=0.51) [4].

Hence major, durable weight loss is uncommon with medical and/or behavioral approaches, and adequate glycemic control often remains elusive [5••]. Since only a small proportion of obese individuals are able to maintain long-term weight loss, there has been a considerable focus on the role of adjunctive therapy such as pharmacotherapy for long-term weight maintenance. Since the beginning, the quest for weight loss drugs has encountered warnings from regulatory agencies with withdrawal from the market of efficient but unsafe medications with unacceptable pulmonary and cardiac adverse effects. For severe obesity, bariatric surgery is the only

This article is part of the Topical Collection on *Diabetes and Cardiovascular Disease*

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treatment resulting in significant and sustained weight loss. Nevertheless, only a very small fraction of the eligible candidates undergo surgery [6]. It has been noticed by clinicians that bariatric operations can dramatically resolve type 2 diabetes, often before and out of proportion to postoperative weight loss. Indeed, bariatric operations, especially intestinal-bypass variants, exert powerful antidiabetes effects [7, 8]. Not all patients who underwent bariatric suffer from diabetes. In a recent systematic review regarding bariatric surgery involving 19,543 subjects, the baseline prevalence of diabetes was 24 % [9].

Indication for Bariatric Surgery

The American Diabetes Association [10], the International Diabetes Federation [11] as well as other organizations [12••, 13], recommend bariatric surgery for adults with type 2 diabetes and body mass index (BMI)≥35 kg/m^2. Bariatric surgery may be considered for adults with BMI≥35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring (level of evidence B) [10]. Patients selected for bariatric surgery should be carefully screened before this treatment alternative and also made aware of the potential complications of the procedure. With the widespread use of the laparoscopic approach and the continued improvement in both surgical techniques and devices, bariatric surgery can now be performed with minimal morbidity and mortality of less than 1 % [14].

Type of Bariatric Surgery

Nowadays, five bariatric surgical procedures are considered acceptable therapy for appropriate patients: 1- roux-en-Y gastric bypass (RYGB), 2- laparoscopic adjustable gastric banding (LAGB), 3- laparoscopic sleeve gastrectomy (LSG), 4- biliopancreatic diversion (BPD), and 5- BPD with duodenal switch. Weight loss after RYGB, LAGB, and LSG procedures is primarily due to a decrease in energy intake because there is little or no malabsorption after these procedures, and weight loss after BPD with or without duodenal switch is due to a combination of decreased energy intake and nutrient malabsorption.

Diabetes Remission Following Bariatric Surgery

According to the 2009 Cochrane review, percentage remission of diabetes can be related to the procedure, ranging from 57 % for banding to up to 95 % for the biliopancreatic diversion [15]. In a recent systematic review, post-operative resolution/improvement of diabetes occurred in 73 % [9]. Definition of remission did not in most of the series follow exactly that what is recommended by the American Diabetes Association (HbA1c≤6.0 %, normal fasting glucose while off-diabetes medication for at least 1 year). Several studies showed that surgical intervention in patients with recently diagnosed type 2 diabetes have higher rates of resolution of type 2 diabetes than patients with longer duration of the disease [16]. Having either type 2 diabetes for more than 10 years or more advanced forms of the disease (according to the type of anti-diabetic treatment) is associated with less weight loss after bariatric surgery, smaller improvements in glycemic control and less frequent resolution of type 2 diabetes. Also, resolution of diabetes is more frequent in patients undergoing gastric bypass than in those undergoing gastric banding [17]. The rapidity of the appearance of remission of diabetes after bariatric surgery, sometimes occurring within days after surgery before major weight loss has been achieved, suggests surgery-specific, weight independent effects on glucose homeostasis.

Recently, the therapeutic superiority of bariatric surgery over medical therapy has been shown in three 1-year or 2-year prospective randomized controlled trials [18, 19••, 20••]. In one study, 73 % of patients who underwent LAGB surgery but only 13 % in the medical and lifestyle therapy group achieved remission of type 2 diabetes [18]. Two randomized controlled trials comparing bariatric operations with medical therapy to treat type 2 diabetes, including patients below the usual BMI threshold for surgery, report that surgery yields better glycemic control, diabetes remission and reduction of other cardiovascular risk factors, with seemingly acceptable complications, for 1–2 years [19••, 20••]. Mingrone et al. [20••] examined RYGB and BPD, whereas Schauer et al. [19••] studied RYGB and sleeve gastrectomy, all of which were compared with medical and lifestyle therapy in patients with type 2 diabetes. Both studies showed better results after surgery for diabetes remission, improved glycemic control and reductions in other cardiovascular risk factors, including dyslipidemia and hypertension. In the first trial, postsurgical diabetes remission rates were dramatic; 75 % after RYGB, 95 % after BPD, and 0 % with medical therapy alone [20••]. Results seemed less striking in the second study 42 %, 37 %, and 12 % diabetes control after RYGB, sleeve gastrectomy and medical therapy, respectively [19••]. This between-trial heterogeneity probably arises from differences in the primary endpoint, which in the study by Mingrone et al. was a glycated hemoglobin value<6.5 % in patients off all diabetes medications, as opposed to≤6.0 % (with or without medications) in the study by Schauer et al. Although fewer patients achieved the latter study's more stringent endpoint, glycated hemoglobin reduction after surgery was noteworthy from ~9.4 to ~6.5 % with important decreases in glucose-lowering medication usage.

Early remission does not necessarily translate to long-term success, and relapse can occur but short-to-moderate-term diabetes remission rates are 80–85 % after RYGB and even higher after BPD [21].

An important confounding factor in interpreting the efficacy of bariatric surgery in treating type 2 diabetes is the absence of a uniform definition of diabetes "remission" or "resolution," and different criteria have been used in different studies. Remission has most often been defined as the withdrawal of all diabetes medications, in conjunction with a "normal" fasting plasma glucose concentration (ranging from<100 to <126 mg/dl) and/or a "normal" HbA1c (ranging from<6 % to <7 %) [8]. Obviously, differences in the definition of remission among studies will lead to differences in estimated remission rates. Consequently, the remission rate of type 2 diabetes is not the same among surgical procedures. The results from a meta-analysis involving ~8000 patients with type 2 diabetes found that the rate of diabetes resolution was much greater in patients who had surgical procedures that involved anatomic diversion of the upper gastrointestinal tract (BPD and RYGB: 95 % and 80 % resolution rates, respectively) than those that simply restricted the stomach (LAGB: 57 % resolution rate) [17, 21].

The mechanism of diabetes control/remission following bariatric surgery is complex, is partly due to weight loss but the degree of improvement does not always correlate with the amount of weight loss. Currently this field of study continues to evolve since it is very difficult to draw conclusions about the endocrine mechanisms related to bariatric surgery, given that most studies have not directly examined this question or have found inconsistent relationships. Potential mechanisms underlying the direct antidiabetic impact of RYGB include enhanced nutrient stimulation of incretin hormones (e.g., glucagon-like peptide-1) (foregut hypothesis), altered physiology from excluding ingested nutrients from the upper intestine (hindgut hypothesis), compromised ghrelin secretion, and improved hepatic insulin sensitivity partly because of energy restriction and later on also improved peripheral insulin sensitivity because of weight loss [7, 22–24]. Functions of ghrelin include food intake regulation, gastrointestinal (GI) motility, and acid secretion by the GI tract. Also, changes in the rate of eating, gastric emptying, intestinal transit time, nutrient absorption and sensing, as well as bile acid metabolism, may also be implicated [25]. Recently, reduced intestinal gluconeogenesis has also been suggested to be involved in the amelioration of glucose homeostasis following RYGB [26].

Outcomes after Bariatric Surgery

Few studies have examined the mid- to long-term outcomes of bariatric surgery in patients with diabetes. In a large, population-based, retrospective cohort study (from 1996 to 2009) of adult obese patients with type 2 diabetes, the authors assessed the outcomes major cardiovascular or microvascular events in patients undergoing bariatric surgery (n=2580) compared with nonbariatric surgery controls (n=13 371) (Table 1). Bariatric surgery was associated with a 65 % reduction in major macrovascular and microvascular events in moderately and severely obese patients with type 2 diabetes (Fig. 1) [27]. Bariatric surgery was associated with favorable 5-year event-free survival estimates for the primary study outcomes (any major macro- or microvascular events: 95±1 vs. 81±1 % ($p<0.001$ as well as each secondary outcomes (macrovascular events: 95±1 % vs. 84±1 % $p<0.001$; microvascular events: 99±0 % vs. 96±0 %, $p<0.001$; and other vascular events: 96±1 % vs. 75±1 %, $p<0.001$) compared with controls [27]. The event rate was much higher than the one reported in a subgroup analysis of patients with diabetes in the Swedish Obese Subjects (SOS) study where bariatric surgery was associated with a 47 % reduction in the risk of cardiovascular events [28]. Bariatric surgery was associated with a reduced myocardial infarction incidence (38 events among the 345 subjects in the bariatric surgery vs. 43 events among the 262 subjects in the control group; $p=0.025$). No effect of bariatric surgery was observed on stroke incidence. Mean follow-up was 13.3 years [28]. Thus, the annualized myocardial event rate was 0.83 % in the surgery group vs. 1.23 % in the control group. Also, the risk factor-treatment interaction analysis showed that the effect of surgery on myocardial infarction was greater in participants with higher total cholesterol and triglycerides levels, possibly suggesting that, in obese patients with type 2 diabetes, those with dyslipidemia should be prioritized.

Table 1 Details of primary and secondary study outcomes in a large, population-based, retrospective cohort study of adult obese patients with type 2 diabetes in patients undergoing bariatric surgery (n=2580) compared with nonbariatric surgery controls (n=13 371)

Primary outcomes
Major macrovascular events
-acute myocardial infarction
-stroke
-all-cause death
Major microvascular event
-new diagnosis of blindness
-laser eye or retinal surgery
-nontraumatic amputation
-creation of a permanent arteriovenous access for dialysis
Secondary outcomes
-revascularization of coronary, carotid or lower extremity arteries
-new diagnosis of congestive heart failure
-new diagnosis of angina

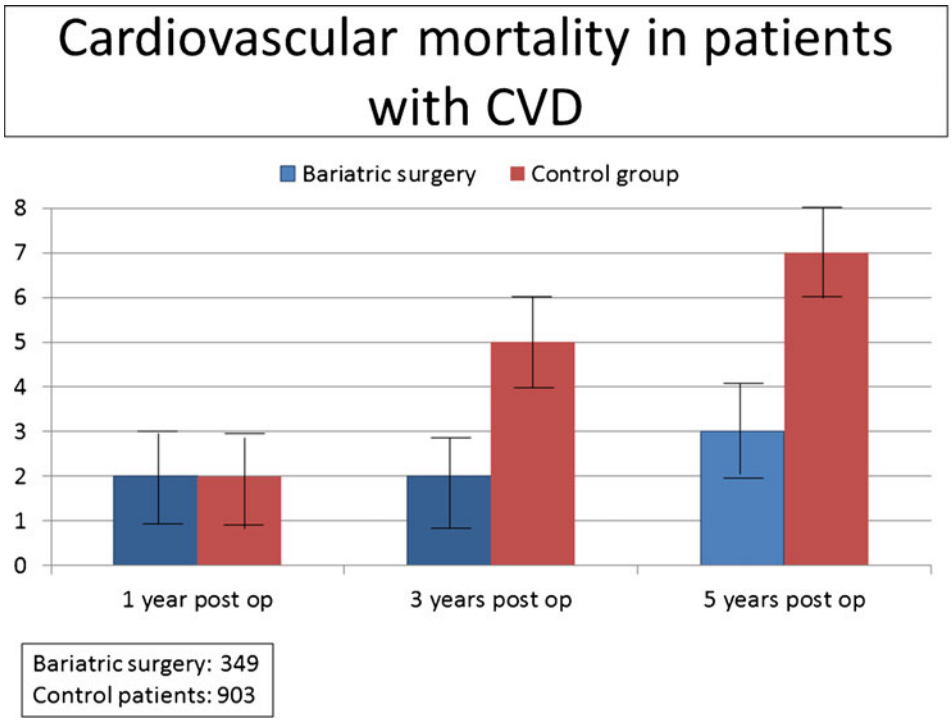

Fig. 1 Cardiovascular mortality in patients with cardiovascular disease. (Adapted from: Johnson RJ, Johnson BL, Blackhurst DW: Bariatric surgery is associated with a reduced risk of mortality in morbidly obese patients with a history of major cardiovascular events. Am Surg. 2012 Jun;78(6):685–92) [37]

Diabetes Relapse Following Bariatric Surgery

The long-term data of bariatric surgery on diabetes remission shows that there is some relapse. Data from the Swedish Obese Subjects long-term observational study, which evaluated the effect of bariatric surgery in 4047 patients with type 2 diabetes, found that 72 % of patients recovered from diabetes at year 2 after surgery, but after 10 years this was reduced to 36 % of patients [29]. Seventy-two percent of subjects who achieved remission at 2 years after surgery remained in remission at 10 years [29]. The precise reasons for recurrence of diabetes are not known but are likely related to recidivism of weight loss because relapse or worsening of type 2 diabetes is associated with weight regain. In another study, among 88 patients with diabetes at baseline, 66 (75 %) were in remission at 2 years after surgery. By 6 years, this had decreased to 62 %, for a 18 % relapse rate [30]. Arterburn et al. reported that 68 % of 4434 patients with diabetes had complete diabetes resolution at 5 years following surgery, but 35 % of these patients redeveloped diabetes at 6 years after surgery [31]. This gradual recurrence of diabetes over time raises questions and concerns about the durability of the effects.

Bariatric Surgery in Patients with a BMI between 30 and 35 kg/m^2

The appreciation that bariatric surgery in patients with type 2 diabetes and a BMI of at least 35 kg/m^2 resulted in remission or improvement of diabetes in the vast majority of patients and the fact that diabetes remission is not always linked to the timing and degree of weight loss substantiate that surgical procedures, such as gastric bypass, may be considered as a valuable approach for diabetes control and remission in patients with a BMI between 30 and 35 kg/m^2. There are limited data from randomized clinical trials to directly address the clinically important question of whether bariatric surgery is associated with greater weight loss and better glycemic control that nonsurgical therapy in patients with diabetes and a BMI of 30 to 35 kg/m^2. A systematic review suggests that bariatric surgery, when compared with nonsurgical treatments, is associated with more short-term weight loss and better intermediate glucose outcomes in patients with diabetes and BMI of 30 to 35 kg/m^2 [32]. However, data on long-term benefits and risks are unknown. However, considering the direct few data from clinical trials in patients with a BMI of 30 to 35 kg/m^2, data from clinical trials of patient with higher BMI, and the nonsurgical therapies all consistently find that weight loss and short-term glucose control are better in patients treated with bariatric surgery. Data also indicate these improvements are greater in patients treated with gastric bypass than with gastric banding [32].

Non-surgical Duodenal Exclusion

Some operations engage weight-independent antidiabetes mechanisms [7, 8]. These benefits result in part from

mechanisms beyond reduced food intake and body weight as glycemic improvements preceded substantial weight loss. In Mingrone et al. [20••], all surgical subjects achieved glycemic control without diabetes medications within only 15 days after surgery. In Schauer et al. [19••], diabetes medication use decreased postoperatively, long before maximum weight loss. Thus, the new studies corroborate a growing body of evidence showing that weight-independent mechanisms contribute to diabetes remission after some bariatric operations [8, 33]. This notion is based primarily on: 1- the early postoperative effects of RYGB surgery on glycemic control, 2- the long-term efficacy of different surgical procedures on resolution of type 2 diabetes, 3- the effect of duodenal-jejunal bypass (DJB) surgery, which bypasses the upper gastrointestinal tract but causes minimal weight loss, 4- the hormonal response to glucose or mixed meal ingestion, and 5- upper gastrointestinal tract bypass in rodent models. Operations that reroute chyme such that the duodenum and proximal jejunum are bypassed, resulting in chyme delivery directly to the jejunum, may be a promising pathophysiological avenue in the management of diabetes. In fact, an alternative approach would be to duplicate the effects of the gastric bypass/BPD by diverting chyme from the proximal small intestine.

The duodenal-jejunal bypass liner (DJBL) is an endoscopically placed and removable intestinal liner developed to achieve this goal by achieving duodenal exclusion and promoting significant weight loss beyond a minimal sham. The DJBL is a 60 cm impermeable fluoropolymer device, which, after endoscopic deployment in the proximal duodenum, functions to prevent partially digested food from contacting the proximal intestine, similar to RYGB but without gastric restriction. Bile and pancreatic secretions pass along the outer wall of the liner and mix with the chyme existing distal to the liner in the jejunum. Mean weight loss averaged ~10 kg after 12 weeks with diabetes remission in several patients [34–36]. There seems to be a procedural learning curve of five to seven procedures [36]. The majority of DJBL-related adverse events are mild or moderate in the implantation subjects. Many of the adverse events occurring within the first 2 weeks likely reflect adaptation to the DJBL. Mild bleeding is an expected adverse event associated with the anchoring of the device.

Conclusion

Management of obesity is pivotal in patients with diabetes. Although bariatric surgery is not a front-line treatment for all patients with type 2 diabetes, neither should it be viewed as a last resort approach. Bariatric surgery should be considered a safe method of weight loss, as there was little mortality associated with laparoscopic and open procedures among a low risk young population. Operative (30-day) mortality for bariatric surgery ranges from 0.1 % to 2 %. Mortality rates depend on several factors: complexity of the operation, patient comorbidities, patient body habitus, and experience of the surgeon and the center. Gastric banding typically has the lowest mortality rate of 0.1 %. Gastric bypass and sleeve gastrectomy mortality is 0.5 %, and malabsorptive operations tend to carry a higher average mortality rate of 1 %. More recent data reported a 30-day mortality rate not exceeding 0.3 %. The severely obese patient is at risk of developing several general complications. They include thromboembolism (1 %), pulmonary or respiratory insufficiency (<1 %), hemorrhage (1 %), peritonitis (1 %), and wound infection (2 %). Laparoscopy has been instrumental in decreasing these rates. The improvements gained with bariatric surgery far outweigh the small risk of mortality associated with the procedure. Overall, the most important goal in the management of patients with type 2 diabetes should be the attainment of treatment targets according to guidelines and the institution of therapies that have been proven to reduce cardiovascular morbidity and mortality.

Bariatric surgery with its substantial weight loss reduces the incidence of diabetes in overweight insulin-resistant subjects and is associated with remission of diabetes in a large percentage of patients. Although bariatric surgery appears to be an effective means for preventing and/or reversing type 2 diabetes, it cannot be considered today as a practical response to the worldwide epidemic of diabetes. In addition, bariatric surgery is associated with the potential for both immediate and long-term adverse metabolic consequences. In considering the usefulness of bariatric surgery, it is also important to recognize that long-term follow-up is required before assigning a beneficial therapeutic effect in patients with diabetes because of the potential for regain of weight that has been observed after some surgical procedures. As diabetes is a lifelong disease, it is important to emphasize that a certain percentage of patients with suffer from relapse of their diabetes which is clearly clinically important.

Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, there is currently insufficient evidence to generally recommend surgery in patients with BMI<35 kg/m^2 outside of a research protocol.

Consensus should be obtained on the definition of diabetes remission, durability of the beneficial effects should be investigated, safety and efficacy of different surgical techniques should be evaluated in randomized clinical trials, and cost effectiveness should be explored. The long-term benefits, cost-effectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed controlled trials with optimal medical and lifestyle therapy as the comparator. When such studies would be available, they would be an excellent evidence-based guide to develop recommendations that are tailored to manage overweight patients with type 2 diabetes and establish the place of metabolic

surgery in diabetes treatment algorithms. Recently, the laparoscopic adjustable gastric banding (LAGB) procedure was recommended to be approved for mildly obese individuals (BMI 30–35 kg/m^2) by the Food and Drug Administration. This is a well-tolerated and potentially reversible procedure, but the efficacy of this procedure is lower than that of RYGB.

Acknowledgment Paul Poirier has received grant support from the Canadian Institute Health Research (CHIR). Audrey Auclair is recipient of a studentship from the Canadian Institute of Health Research.

Compliance with Ethics Guidelines

Conflict of Interest Paul Poirier and Audrey Auclair declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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