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LIFESTYLE MANAGEMENT TO REDUCE DIABETES/CARDIOVASCULAR RISK (B CONWAY AND H KEENAN, SECTION EDITORS)

The Role of Bariatric Surgery on Diabetes and Diabetic Care Compliance

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Abstract

Purpose of Review Bariatric surgery is a durable and long-term solution to treat both obesity and its associated comorbidities, specifically type 2 diabetes mellitus (T2DM). Many studies have demonstrated the benefits of bariatric surgery on T2DM, but weight recidivism along with recurrence of comorbidities can be seen following these procedures. Patient compliance post-bariatric surgery is linked to weight loss outcomes and comorbidity improvement/resolution. The role of compliance with respect to T2DM medication in bariatric patients specifically has not recently been examined. This article seeks to review the role of bariatric surgery on short- and long-term resolution of T2DM, recurrence, and compliance with T2DM medication following bariatric surgery.

Recent Findings Seven randomized control trials have examined metabolic surgery versus medical therapy in glycemic control in patients meeting criteria for severe obesity. Six out of seven studies demonstrate a significant advantage in the surgical arms with regards to glycemic control, as well as secondary endpoints such as weight loss, serum lipid levels, blood pressure, renal function, and other parameters. While patient compliance with lifestyle modifications post-bariatric surgery is linked to weight loss outcomes, there are no studies to date that directly evaluate the role of lifestyle modifications and T2DM medication adherence in the management of T2DM post-bariatric surgery.

Summary Bariatric surgery is an effective treatment option to achieve long-term weight loss and resolution of obesity-related medical comorbidities, specifically T2DM. Patient compliance to lifestyle modifications post-bariatric surgery is linked to weight loss outcomes and comorbidity resolution. The role of diabetic care compliance in bariatric patient outcomes, however, is poorly understood. Further studies are needed to elucidate the predictors and associated risk factors for non-compliance in this patient population.

Keywords Metabolic and bariatric surgery · Diabetes · Patient compliance

This article is part of the Topical Collection on *Lifestyle Management to Reduce Diabetes/Cardiovascular Risk*

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) parallels the global epidemic of obesity. Approximately 23% of patients with severe obesity have type 2 diabetes mellitus (T2DM) [1]. In 2016, the World Health Organization (WHO) estimated that over 650 million people had obesity and that nearly 9% of the adult population had T2DM [2, 3]. By 2030, it is estimated that the prevalence of obesity will increase by 33% and that the incidence of T2DM will increase by 2% [1, 4]. If obesity were to remain at current levels, savings in medical expenditures would be nearly $550 billion by 2030 [4].

Severe obesity represents a major risk factor for the development of T2DM. Due to the strong association between obesity and diabetes, the term "diabesity" was coined to describe the co-occurrence of these two conditions [5]. Obesity and being overweight confer a degree of insulin resistance to an individual, but diabetes only develops in those who lack sufficient insulin secretion to match their insulin resistance [5]. Obesity represents about 44% of the attributable risk of diabetes mellitus [5].

Obesity is not just a risk factor for T2DM. It is also associated with the development of cardiovascular disease, musculoskeletal disease, and many cancers [2]. In fact, the association between obesity and chronic medical conditions was integral to the National Institutes of Health 1991 Consensus Statement on the criteria for metabolic and bariatric surgery (MBS): a body mass index (BMI) $\geq$ 40 kg/m^2 or a BMI $\geq$ 35 kg/m^2 with associated comorbidities [6].

A durable and long-term solution to both obesity and its associated comorbidities is MBS [6]. The Roux-en Y Gastric Bypass (RYGB) and sleeve gastrectomy (SG) have become two of the most popular and efficient procedures used to achieve long-term weight loss and resolution of the medical comorbidities associated with obesity. In 1999, the first laparoscopic SG was performed as part of a duodenal switch (DS) procedure (the latter performed less commonly today) [7]. In 2000, the first laparoscopic SG was performed as a standalone procedure [8, 9]. Since that time, the SG has gained popularity over the laparoscopic RYGB and it is now the most commonly performed bariatric surgery in the USA in the pediatric and adult populations [7, 10].

One of the benefits of bariatric surgery is T2DM remission. Many studies, including randomized clinical trials, have demonstrated the benefits of MBS on T2DM [11–17]. Although lifestyle intervention and metformin can reduce the incidence of T2DM, MBS has been shown to be more effective than these measures in reducing the progression to T2DM in patients with obesity and without diabetes when compared with those who do not undergo MBS [18, 19]. Additionally, patients have had dramatic improvement or resolution of their comorbidities independent of weight loss following MBS [20, 21]. This finding has shed light on the important role of the GI tract in metabolic regulation and glucose homeostasis [20, 21].

Compliance (i.e., post-operative visits, medication adherence and exercise regimens) post-MBS is linked to weight loss outcomes and comorbidity improvement/resolution [22–25•]. However, the role of diabetic care compliance in MBS patients has not been examined recently.

This article will review the complications associated with T2DM, the role of MBS on short- and long-term resolution of T2DM, recurrence, and compliance with diabetic medication following MBS.

Diabetes-Associated Complications in Patients with Morbid Obesity

Complications of diabetes can be categorized as acute vs chronic, with further division of chronic complications as micro- or macrovascular. The acute complications include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) [26]. While DKA is often an initial manifestation of type 1 diabetes (T1DM), it may also occur in patients with T2DM, particularly when a stressor is present such as infection, infarction, surgery or nonadherence to medical therapy. DKA typically presents with abdominal pain, vomiting, Kussmaul respirations, a fruity odor on the breath, and an anion-gap metabolic acidosis. HHS can also develop under conditions of physiologic stress, but ketosis is not a presenting symptom. Instead, it is characterized by severe hyperglycemia, extreme dehydration, and hyperosmolality. Patients are weak, lethargic, and often have an altered mental state ranging from disorientation or confusion to coma [26, 27].

The long-term microvascular complications of diabetes are more prevalent than the macrovascular complications [28, 29]. Microvascular complications include neuropathy, nephropathy, and retinopathy. Diabetic foot syndrome is defined as the presence of foot ulcers associated with neuropathy, peripheral artery disease, and infection [30]. It is a major cause of lower limb amputation among those with diabetes. Chronic kidney disease (CKD) in diabetes can result in microalbuminuria initially and can progress to macroalbuminuria. Retinopathy generally precedes neuropathy and occurs after diabetes has been present for 3–5 years [26]. It is classified as background, pre-proliferative, or proliferative [31]. Retinopathy is characterized by changes to the blood supply of the retina that leads to microaneurysms and vessel proliferation. If left untreated, this will progress to blindness. Annual dilated ophthalmoscopic examinations are important for early diagnosis and effective treatment with laser or anti-VEGF therapy [26, 31].

Macrovascular complications of diabetes consist of cardiovascular disease, stroke and peripheral artery disease, and these complications are associated with an increased risk of myocardial infarction and stroke [26, 30]. As diabetes is considered a coronary artery disease (CAD) risk equivalent, intensive risk factor modification is recommended for all individuals with T2DM. This includes hypertension control (which also mitigates microvascular complications, particularly chronic kidney disease (CKD)), lipid optimization, smoking cessation, weight management, anti-platelet therapy, and increased physical activity [31].

Bariatric Surgery Anatomy Review and Impact on Glucose Metabolism

The laparoscopic (SG) and RYGB are the two most commonly performed procedures for weight loss surgery, and they will be the focus of our review article. As a review of the anatomy, the RYGB is performed when a surgical stapler is used to create a small gastric pouch, usually less than 30 ml in size and a gastrojejunostomy is created between the small pouch and the jejunum. Ingested food bypasses ~ 95% of the stomach, the entire duodenum, and a portion of the jejunum. Bile and nutrients mix in the distal jejunum and can be absorbed through the remaining portion of the small bowel [7]. The SG involves removal of approximately 75% of the stomach along a line roughly parallel to the greater curvature, resulting in a crescent shaped stomach lacking the majority of the ghrelin-rich fundus. The purported advantages of the SG over the RYGB include the technical ease of the procedure and the lower associated morbidity and mortality with effective comorbidity resolution. Additionally, there is no associated risk of marginal ulceration or internal hernia formation, and there are less nutritional deficiencies in comparison to the RYGB. Finally, the SG is able to be revised and converted to other bariatric procedures [8, 9].

Laparoscopic adjustable gastric banding (AGB) and biliopancreatic diversion (BPD) are two additional bariatric procedures that have decreased in popularity due to poor weight loss outcomes and poorly tolerated side effect profiles, respectively. The AGB procedure involves an inflatable band that is placed around the upper portion of the stomach, creating a small stomach pouch above the band. This procedure has fallen out of favor due to a large percentage of patients failing to lose at least 50% of excess body weight compared to the RGB and SG [7–9].

BPD involves gastric resection (typically a SG) and a long intestinal bypass that results in a mixture of bile and other nutrients in a short 50-cm common channel proximal to the ileocecal valve. Concerns regarding the higher likelihood of protein deficiencies and long-term vitamin and mineral deficiencies have diminished the popularity of this procedure, and it is now performed much less commonly than the RYGB and SG [7, 9].

In terms of the physiologic mechanisms for the improvements in glucose metabolism following MBS, the significantly decreased caloric intake in the immediate post-operative period has been hypothesized to put less stress on the insulin–glucose axis by requiring less insulin production to control the blood glucose levels [32]. Additionally, weight loss improves insulin resistance in the peripheral tissues, allowing relatively lower insulin production in these patients to control blood glucose. Clinical observations of rapid improvement in glucose control prior to significant weight loss have led researchers to investigate other etiologies, independent of weight that could impact glucose homeostasis. Based on this observation, Hickey and colleagues introduced what is known as the “proximal” bowel hypothesis. This hypothesis suggests that the antrum, duodenum, and proximal jejunum have dynamic endocrine activity and that bypassing these areas is the cause of improvement or resolution of T2DM following RYGB, rather than total weight lost [33].

Changes in hormone levels of glucagon-like-peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY), and ghrelin have all been described following MBS, specifically RYGB and SG [34–45]. With respect to the RYGB and BPD, exclusion of the proximal intestine (primarily the duodenum) from nutrient flow has also been proposed by Rubino and colleagues to exert an anti-diabetic effect by downregulating one or more unidentified anti-incretin factors [46]. Bile acid alterations, gut microbiome alterations, and taste alterations are other hypothesized weight independent anti-diabetic mechanisms [47].

Outcomes of Bariatric Surgery vs Medical Therapy in Diabetes Remission

The clinician must consider both safety and efficacy when initiating therapy for diabetes and obesity. Medical therapy including lifestyle intervention with diet and increased physical activity is first-line therapy for patients due to minimal risk and low cost of implementation. However, studies show modest weight loss in patients with obesity (< 10% total body weight (TBW)) with weight regain commonly occurring in the following months [48]. The largest medical trial studying intensive lifestyle intervention (ILI) versus standard diabetes support and education in patients with obesity and diabetes was the Look AHEAD (Action for Health in Diabetes) randomized study. This trial examined the effect of these two interventions of cardiovascular mortality and weight loss over an 8-year period. ILI included weekly group or individual sessions, as well as structured meal plans with meal replacements that were provided free of charge in the first 4 months of the study. The Look AHEAD study found no difference in cardiovascular mortality between treatment groups [49]. In the ILI group, although there was significantly more weight loss at the end of year 1 (8.5%

TBW), half of all patients who lost 5% of their body weight after the first year regained weight by year 8 with mean weight loss by the end of the study at 4.7% TBW. It was concerning that over 25% of subjects gained weight above their baseline at the end of the study period.

There are currently four FDA-approved monotherapy medications and two combination medications for weight loss approved for chronic use. One of these medications, liraglutide, a GLP-1 receptor agonist, may also be used to treat diabetes [50, 51]. It is prescribed in two different dosages (1.8 mg daily and 3.0 mg daily) for diabetes and obesity, respectively, but the lower dose use of liraglutide for glycemic control has also been noted to result in weight loss, in part due to delayed gastric emptying and increased satiety [52]. Other approved medications include phentermine, orlistat, lorcaserin, phentermine–topiramate, and bupropion–naltrexone, all with different mechanisms of action; long-term use of these medications may be limited due to adverse effects, high cost of medications, concerns about safety profile, and low utilization [51, 53].

Seven randomized control trials have examined MBS versus medical therapy in glycemic control which have included patients with BMI ≥ 35 kg/m^2 (class 2, moderate obesity) (Table 1). Surgical interventions in these trials include laparoscopic adjustable gastric banding (LAGB), laparoscopic Roux-en-Y gastric bypass (LRYGB), laparoscopic sleeve gastrectomy (LSG), and biliopancreatic diversion (BPD) versus best medical therapy (standard practice) or intensive multidisciplinary medical therapy or medications. Only one study showed surgery to be equivalent to medical therapy [54], but this compared medical therapy to Laparoscopic AGB which is associated with less weight loss and anti-diabetic effect compared to other surgical interventions for weight regulation, and the follow-up is relatively short at 12 months. The remaining 6 studies showed a significant advantage in the surgical arms with regards to glycemic control, as well as secondary endpoints such as weight loss, serum lipid levels, blood pressure, renal function, and other parameters [1, 13, 55–57, 58••, 59–64].

Table 1 Randomized control trials of metabolic surgery versus medical therapy for patients with obesity and diabetes

	Intervention	Number	Duration of follow-up	Results
Dixon 2008 [54]	LAGB vs BMT	60	2 years	73% remission of DM in surgical arm vs 12% in medical arm ($P < 0.001$)
Liang 2013 [55]	LRYGB vs exenatide vs BMT	108	12 months	90% remission of DM in surgical arm vs no remission in either medical arm.
Courcoulas 2014 [59]	LRYGB vs LAGB vs LWLI	69	12 months	LRYGB: 50% partial, 17% total remission DM LAGB: 27% partial, 23% total remission DM LWLI: no remission
Halperin 2014 [60]	LRYGB vs IMT	38	12 months	58% remission of DM in surgical arm vs 16% remission in medical arm ($P < 0.03$)
Ding 2015 [53]	LAGB vs IMWM	55	12 months	33% remission of DM in surgical arm vs 23% in medical arm ($P = 0.457$)
Mingrone 2012, 2015 [55, 62]	LRYGB vs BPD vs BMT	60	5 years	At 5 years: • LRYGB: 37% remission of DM • BPD: 63% remission of DM • BMT: no remission at 2 or 5 years ($P < 0.001$)
Cummings 2016 [1]	LRYGB vs ILMI	32	12 months	60% HbA1c < 6% in surgical arm vs 5.9% HbA1c < 6% in medical arm ($P = 0.002$)
Schauer 2012, 2014, 2017 [13, 56, 63]	LRYGB vs LSGvs IMT	150	5 years	At 5 years: • LRYGB: 29% HbA1c < 6% • LSG: 23% HbA1c < 6% • IMT: 5% HbA1c < 6% ($P < 0.03$)
Ikramuddin 2015, 2018 [57, 58]	LRYGB vs lifestyle	120	5 years	At 5 years: • LRYGB: 55% HbA1c < 7% • Lifestyle: 14% HbA1c < 7% ($P = 0.002$)

LAGB laparoscopic adjustable gastric banding, *BMT* best medical therapy, *DM* diabetes mellitus, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *ILMI* intensive lifestyle and medical intervention, *HbA1c* glycated hemoglobin, *IMT* intensive medical therapy, *IMWM* intensive medical diabetes and weight management, *LWLI* intensive lifestyle weight loss intervention, *LSG* laparoscopic sleeve gastrectomy, lifestyle lifestyle-intensive medical intervention

For example, Schauer and colleagues conducted a randomized trial looking at 5-year outcomes of medical therapy alone versus medical therapy with bariatric surgery (RYGBP and SG) in patients with diabetes who had a BMI of 27–43 [58••]. The primary outcome was a glycated hemoglobin level of 6.0% or less with or without the use of diabetes medications.

Of the randomized patients at 5 years, the primary end point was met by 2 of 38 patients (5%) who received medical therapy alone, as compared with 14 of 49 patients (29%) who underwent gastric bypass and 11 of 47 patients (23%) who underwent sleeve gastrectomy. Patients who had bariatric surgery had a greater mean percentage reduction from baseline in glycated hemoglobin level than did patients who received medical therapy alone (2.1% vs 0.3%). At 5 years, changes from baseline observed in the gastric bypass and sleeve gastrectomy groups were superior to the changes seen in the medical therapy group with respect to body weight (− 23%, − 19%, and − 5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups, respectively), triglyceride level (− 40%, − 29%, and − 8%), high-density lipoprotein cholesterol level (32%, 30%, and 7%), use of insulin (− 35%, − 34%, and − 13%), and quality-of-life measures (general health score increases of 17, 16, and 0.3). No major late surgical complications were reported except for one reoperation [58••].

Meta-analyses of these abovementioned trials confirm the superiority of surgical therapy with partial and complete remission of diabetes, as well as weight loss [65, 66]. In addition, comorbid conditions that co-exist with both diabetes and obesity such as hypertension and hyperlipidemia were also found to be significantly improved after surgical intervention compared to medical therapy. The most commonly reported adverse events reported in the surgical intervention groups are nutritional deficiencies, specifically iron deficiency anemia [63].

Diabetes Recurrence and the Role of Medical Therapy

MBS is the most effective treatment with respect to weight loss and comorbidity resolution for persons with moderate (BMI 35–39.9) and severe obesity (BMI > 40) to date [47, 67, 68]. Patients in this demographic typically experience complete resolution or significant improvement of obesity-related comorbidities [69]. Unfortunately, inadequate weight loss or weight recidivism can occur following bariatric surgery. Inadequate weight loss is generally defined as an initial loss of less than 50% of excess weight and more recently, less than 20% total weight loss (TWL) [70, 71]. Weight regain is typically multifactorial and can be linked to patient or operation specific factors [72–81]. With weight regain, comorbidities that initially improved after bariatric surgery can reemerge [82, 83].

There are several reasons why diabetes may recur or fail to resolve after bariatric surgery. Among these are inadequate weight loss, over-indulgence in high-calorie foods, lack of adherence to proper diet and exercise, long-standing poor glycemic control, lower pre-operative BMI, surgical technique, T1DM, endocrine/metabolic alterations, mental health issues, and adherence to recommended medication treatment protocols [84–86]. After RYGB, failure of diabetes resolution has been reported in at least 10% of patients, and in greater numbers after operations where weight loss expectation is lower, such as the SG [6].

Immediately following MBS, diabetes medications are typically significantly reduced and sometimes completely withdrawn due to immediate effects of surgical intervention on glucose regulation. However, as time progresses and due to many of the factors stated above, diabetes control is reduced often due to weight regain and on-going beta cell failure [87]. If patients are unable to maintain long-term weight loss, the resulting weight gain can lead to an increase in A1C values [82]. This will necessitate intensification of anti-diabetes medical therapy. Although the A1C target may vary depending on the patient's condition and length of diabetes duration, the generally accepted goal as per the American Diabetic Association (ADA) is A1C < 7% [87].

Medical therapy for recurrent diabetes following bariatric surgery includes both nutrition therapy and pharmacologic therapy [82]. Medical nutrition therapy (MNT) provided by registered dietitians and nutritionists is shown to be not only cost-effective, but it also improves medical outcomes and quality of life [69, 88]. A systematic review from the Academy of Nutrition and Dietetics found that 2 to 12 visits (60-min initial visit and 20- to 45-min follow-ups) were associated with improved weight (− 0.5 to − 9.0 kg), body mass index (− 0.2 to − 7.8), waist circumference (− 2.0 to − 14 cm), fasting blood glucose (− 5.2 mg to − 9.5 mg/dL), total cholesterol (− 4.3 mg to − 59 mg/dL), low-density lipoprotein cholesterol (− 15 mg to − 47 mg/dL), high-density lipoprotein cholesterol (+ 2.0 mg to + 11 mg/dL), and triglycerides (− 12 mg to − 60 mg/dL). Indeed, the Diabetes Prevention Programs (DPPs) showed lifestyle changes improved clinical outcomes more than medication. Finally, in adults with T2DM, MNT significantly lowered HbA1c by 0.3 to 2.0% at 3 months and, with ongoing MNT, decreases were maintained or improved for more than 12 months [88].

Regarding pharmacological therapy after bariatric surgery, there are distinctions between immediate post-operative therapy and long-term therapy. In the acute post-operative phase, metformin can be instituted as a stand-alone therapy in those with a HbA1c < 9%. If the HbA1c is > 9%, a second agent may be added to help facilitate additional weight loss and/or cardiovascular risk reduction. At later post-operative intervals, the long-term approach to pharmacologic management shifts to coupling metformin with agents that confer cardiovascular risk reduction, weight loss, and renal protection. Three agents that fulfill these criteria are the sodium-glucose cotransporter-2 (SGL2) inhibitors canagliflozin and empagliflozin and the glucagon-like peptide 1 (GLP-1) analogue liraglutide [88]. Liraglutide may also have beneficial effects on bone metabolism- particularly relevant given the diminished skeletal health in patients following MBS [89]. The other two agents have neutral effects on bone metabolism. Given that the positive effects of metabolic surgery can subside with time, an SGL2 inhibitor or GLP-1 analogue may extend the durability of the positive outcomes by fostering weight loss and cardiovascular risk reduction in this population [87]. However, it is important to note that weight loss pharmacotherapy has demonstrated success in patients with inadequate weight loss and weight regain after MBS, and weight loss medications may have a role in improving weight status and glycemic control in the post-operative course [89–91, 92•, 93].

Diabetes Care Compliance following Bariatric Surgery

Patient compliance is fundamental to medical and surgical outcomes. A common definition of "compliance" is the extent to which a patient's behavior with regards to taking medication, following diets, or implementing lifestyle changes coincides with medical or health advice [94]. Non-compliance can be defined as when patients fail to have medication dispensed, take medication as directed, reject the physician treatment plan, or exhibit unintentional non-compliance related to social, demographic, clinical, and psychological variables [25•].

Following MBS, compliance with post-operative visits, medication, and exercise regimens has been shown to be linked to patient outcomes with respect to weight loss and resolution of comorbidities [24, 25•, 95–97]. There is literature suggesting that patients with diabetes who still require medication, following MBS, require less insulin and fewer oral medications to achieve control than prior to MBS [97–100]. That said, there are no studies that examine the medication needs in patients with longer time intervals post-MBS (greater than 6 months) and there are no current studies that directly examine patient compliance with medication regimens for diabetes following MBS. Reasons for this could be the lack of a standard definition for compliance in clinical practice and that it may be difficult to reliably identify the social/psychological variables that impact medication compliance. More specific research is needed to establish a standardized compliance definition and to more clearly elucidate the role of medication compliance in resolution/control of morbidities in the post-MBS patient.

Conclusion

Obesity is a major risk factor for the development of T2DM. MBS is an effective treatment option to achieve long-term weight loss and resolution of obesity-related medical comorbidities, specifically diabetes. Patient compliance post-bariatric surgery is linked to weight loss outcomes and comorbidity resolution. The role of diabetic care compliance in bariatric patient outcomes, however, is poorly understood. Further studies are needed to elucidate the predictors and associated risk factors for non-compliance in this patient population.

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Compliance with Ethical Standards

Conflict of Interest Hope T. Jackson, Chika Anekwe, Julietta Chang, and Ivy N. Haskins declare that they have no conflict of interest.

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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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•• Of major importance

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