MANAGEMENT OF ENDOCRINE DISEASE

Metabolic effects of bariatric surgery

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Abstract

Obesity is associated with an increased risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis, numerous cancers and increased mortality. It is estimated that at least 2.8 million adults die each year due to obesity-related cardiovascular disease. Increasing in parallel with the global obesity problem is metabolic syndrome, which has also reached epidemic levels. Numerous studies have demonstrated that bariatric surgery is associated with significant and durable weight loss with associated improvement of obesity-related comorbidities. This review aims to summarize the effects of bariatric surgery on the components of metabolic syndrome (hyperglycemia, hyperlipidemia and hypertension), weight loss, perioperative morbidity and mortality, and the long-term impact on cardiovascular risk and mortality.

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Introduction

Obesity is an epidemic on the rise. The World Health Organization projects that by 2015, ~2.3 billion adults will be overweight and more than 700 million will be obese (1). Obesity is associated with an increased risk of type 2 diabetes (T2DM), hypertension, dyslipidemia, cardiovascular disease, osteoarthritis, numerous cancers and increased mortality (2). It is estimated that at least 2.8 million adults die each year due to obesity-related cardiovascular disease (3). Increasing in parallel with the global obesity problem is metabolic syndrome, which has

also reached epidemic levels. The National Health and Nutrition Examination Survey reported that 34% of American adults have metabolic syndrome based on the National Cholesterol Education Program Adult Treatment Panel III criteria: waist circumference ≥ 102 cm (men) or ≥ 88 cm (women), triglycerides ≥ 150 mg/dl, HDL < 40 mg/dl (men) or < 50 mg/dl (women), hypertension $\geq 130/85$ mmHg and fasting glucose ≥ 100 mg/dl (4). Conventional treatments such as diet, lifestyle modification, exercise and pharmacotherapy have failed to

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achieve satisfactory sustained weight loss. In addition, the direct cost of obesity in the United States is extremely high, with an estimated \$190 billion spent in 2010 (5).

Numerous studies have demonstrated that bariatric surgery is associated with significant and durable weight loss and associated improvement of obesity-related comorbidities (6, 7, 8). Furthermore, the beneficial effects of bariatric surgery on mortality, overall disease-specific risk reduction and long-term quality of life are well documented (9, 10, 11, 12). The degree of the effect on obesity-related comorbid conditions depends on the bariatric surgical approach, typically classified based on its restrictive and/or malabsorptive effect. Current data from the International Federation for the Surgery of Obesity and Metabolic Diseases (IFSO) reports that the most commonly performed procedures are the Roux-en-Y gastric bypass (RYGB) (45%), sleeve gastrectomy (SG) (37%), adjustable gastric banding (AGB) (10%) and biliopancreatic diversion (BPD) with or without duodenal switch (DS) (2.5%) (13). This review aims to summarize the effects of bariatric surgery on the components of metabolic syndrome (hyperglycemia, hyperlipidemia and hypertension), weight loss, perioperative morbidity and mortality, and the long-term impact on cardiovascular risk and mortality.

Weight loss

Historically, the primary endpoint of bariatric surgical procedures has been weight loss and the reported weight loss achieved is generally sustained (14, 15). The overall percentage of excess weight loss (EWL) has been reported to be 47–70% in long-term series (16). Unfortunately, there is a relative lack of randomized controlled trials with long-term results addressing this primary endpoint. In the controlled Swedish Obesity Study (SOS), patients were prospectively followed over 20 years and those who underwent bariatric surgery retained 18% of weight loss compared to 1% in the non-surgical group. The mean 20-year weight reduction was 15% for AGB and 25% for RYGB patients (14). A systematic review conducted by O'Brien *et al.* (17) detected sustained EWL > 50% for AGB and RYGB at 8 and 10 years respectively.

Malabsorptive procedures such as BPD and RYGB achieve a greater percentage of EWL and more durable weight loss when compared to purely restrictive operations. However, this benefit comes at a cost of higher complications rates. Specifically, BPD provides the greatest weight loss in most published series but also has higher complication rates than less aggressive bariatric

approaches. A retrospective review of the Bariatric Outcomes Longitudinal Database (BOLD) from 2007 to 2010 showed 79% EWL for BPD-DS compared with 67% EWL for RYGB at 2 years follow-up (18).

While O'Brien *et al.* (19) have recently reported 47% EWL in a cohort of 3227 patients followed over a 15-year span, AGB is still considered a purely restrictive procedure with the lowest durable weight loss. For instance, a recent meta-analysis by Chakravarty *et al.* (20) including five randomized controlled trials comparing AGB with other procedures concluded that AGB is associated with less weight loss. Since its introduction in 2007, SG case volumes have increased dramatically, with published weight loss results comparable to RYGB. SG is considered a restrictive procedure; however, it has been increasingly recognized to have metabolic effects similar to those observed after RYGB (21). A recent 5-year outcomes study has reported successful SG results, with an 86% average EWL (22). However, other studies have demonstrated more modest long-term weight loss results (especially in patients with BMI > 50 kg/m²), with many patients ultimately requiring revision surgery for inadequate weight loss or recidivism (23).

Complications of metabolic surgery

In their systematic review and meta-analysis (the most cited paper in bariatric surgery), Buchwald *et al.* (24) reported exceptionally low early and late mortality rates after bariatric operations (0.28 and 0.35% respectively). Mortality was higher in open and conversion cases (0.30 and 0.07% respectively), the male gender (male:female ratio of 4.7:01) and super obese subjects (range, 0.8–1.2%). Open cases were considered those undergoing bariatric surgery via laparotomy, while conversions were defined as conversion from a laparoscopic procedure to an open (conventional) surgery (24). Similarly, a prospective, multicenter, observational study of 30-day outcomes in 4776 consecutive patients undergoing bariatric surgical procedures reported a comparably low perioperative mortality rate of 0.3% (8).

After bariatric surgery, cardiopulmonary complications such as myocardial infarction and pulmonary embolism are the major causes of mortality, representing 70% of all deaths (25). The overall mortality rate for RYGB performed in centers of excellence is 0.4% (8). The most serious procedure-specific early complication after RYGB is anastomotic leakage, with an incidence ranging from 0.1 to 5.6%. Patients at higher risk are those with higher BMI, older age, males, with multiple comorbidities, smoking,

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or prior revision operations. AGB is a safe procedure with 0.3% or less mortality rate (26). However, late complications such as band slippage, erosion, migration, port infection and gastroesophageal perforations are well documented and occur in about 20% of patients (27). In addition, long-term weight loss failure rates of over 50% have been reported, and this has led to a significant increase in revisions of AGB to RYGB or SG (28).

Procedure-specific late complications presenting clinically as bowel obstruction after RYGB include internal hernias and gastrojejunal anastomotic stricture. Internal hernias are more common after laparoscopic cases and range from 0.5 to 9.0% (29). Abdominal pain with or without clinical signs of bowel obstruction is the most common presentation, and diagnostic laparoscopy is the method of choice due to high false negative rates associated with abdominal computerized tomography (CT) scans (30). The incidence of gastrojejunal anastomotic stricture is about 10% and possible mechanisms include ischemia, excessive scarring, recurrent marginal ulcer and technical considerations such as excessive tension or torsion of the anastomosis. Endoscopy is the preferred tool for both diagnosis and treatment of gastrojejunal stricture (31). Gastrointestinal bleeding after RYGB is another uncommon late complication, typically caused by marginal ulceration. Marginal ulcers occur in 2% of patients within the first postoperative year, and then in 0.5% for up to 5 years (32). However, a recent study has shown significantly higher marginal ulceration rates (34%) in 328 symptomatic patients who underwent endoscopic exploration after RYGB. Uni- and multi-variate analyses for associated risk factors identified tobacco as the most significant risk factor for marginal ulceration recurrence (33).

Major nutritional complications are typically associated with the malabsorptive effect of bariatric procedures and are usually seen after BPD, RYGB and, less commonly, AGB. Anemia is extremely common after RYGB and iron deficiency ranges from 17 to 50%; the etiology is believed to be multifactorial in nature. Importantly, Love *et al.* (34) reported an iron deficiency incidence of up to 50% in premenopausal women. Deficiencies in other trace minerals (selenium, zinc and copper) and vitamins (B12, B1, A, E, D and K) are commonly observed after bariatric procedures (35), specifically after BPD with or without DS (50–69%). Severe calcium and vitamin D deficiencies have been described after BPD and very long limb RYGB, leading to decreased bone mineral density and osteoporosis. Protein malnutrition can also occur after these malabsorptive operations, and lifelong monitoring for

nutritional complications is mandatory following these procedures (23).

Metabolic outcomes of bariatric surgery

Effects on glycemic control

Substantial evidence from observational data indicates that bariatric surgery is very effective in controlling T2DM, with high remission rates and reductions in anti-diabetic drug usage. Yet, not all bariatric procedures have demonstrated the same impact on glucose homeostasis. In the first large meta-analysis ($n=22\,094$) published in 2004, Buchwald *et al.* found that bariatric surgery achieved complete diabetes resolution in 76.8% of subjects. The results differed dramatically by the type of surgery, ranging from 48% remission rates with AGB to 84% remission rates with RYGB and 99% remission with biliopancreatic procedures (16). The authors concluded that malabsorptive procedures were the most effective with respect to T2DM control. Data from the BOLD, a national database for the American Society for Metabolic and Bariatric Surgery (ASMBS) Center of Excellence Program ($n=23\,106$ patients), reported the highest 12-month diabetes remission rates for BPD-DS (74%), followed by RYGB (62%), SG (52%) and AGB (28%) (36).

Many observational studies have reported long-term diabetes remission rates (14, 37). A meta-analysis conducted by Buchwald *et al.* (38) including 621 studies with 135 246 patients (all types of bariatric surgery) reported that 78% of diabetic patients had complete resolution ($\text{HbA}_{1c} < 6.5\%$ and no anti-diabetic drugs) and 86.6% had diabetes improvement. Several factors have been reported to be predictors of T2DM remission, including shorter duration of diabetes, greater weight loss, previous treatment with lifestyle modification and former oral anti-diabetic agent usage. Conversely, longer duration of diabetes, decreased weight loss, severity of diabetes and insulin requirements are factors associated with inadequate glycemic control after surgery (23, 39, 40). In a study by Brethauer *et al.* (41) clinical outcomes of 217 patients with T2DM who underwent bariatric surgery between 2004 and 2007 and had at least 5-year follow-up were assessed (RYGB, $n=162$; AGB, $n=32$; SG, $n=23$). Complete remission was defined as $\text{HbA}_{1c} < 6\%$ and fasting blood glucose < 100 mg/dl off diabetic medications. The mean EWL was 55% and the mean HbA_{1c} level decreased from $7.5 \pm 1.5\%$ to $6.5 \pm 1.2\%$ ($P < 0.001$). Shorter duration of T2DM ($P < 0.001$) and higher long-term EWL ($P = 0.006$) predicted long-term remission.

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Recurrence of T2DM after initial remission occurred in 19% and was associated with longer duration of T2DM ($P=0.03$), less EWL ($P=0.02$), and weight regain ($P=0.015$). Of note, the number of years after bariatric surgery is another predictive factor of relapse of diabetes that has been reported in the literature (40).

While many non-controlled studies have reported excellent improvements in glycemic control after bariatric surgery, direct comparisons with intense medical treatment are scarce. The results of the SOS study, a non-randomized trial comparing medical therapy with bariatric surgery, demonstrated higher rates of diabetes resolution at 2, 10 and 20 years follow-up in the bariatric surgery cohorts (14). The SOS study also reported significant benefits in the surgical arms with regards to long-term complications, major cardiovascular events and mortality of any cause. However, the SOS study investigators have recently reported a decline in T2DM remission rates at 15 years follow-up from 72.3 to 30.4% (42).

Five short-term (1–2 years follow-up) randomized controlled trials comparing bariatric surgery with medical treatment have been published (42, 43, 44, 45, 46, 47). The first randomized controlled trial by Dixon *et al.* in 2008 evaluated laparoscopic AGB vs pharmacotherapy and lifestyle intervention ($n=60$, obese patients with T2DM). The surgical group achieved T2DM remission in 73% compared to 13% in the nonsurgical group (2 years follow-up). Of note, weight loss was significantly higher in the surgical group (20.7% vs 1.7%) (42). Mingrone *et al.* randomly assigned 60 obese T2DM patients to receive conventional medical therapy or undergo either RYGB or BPD. Subjects included in the trial had diabetes for at least 5 years, BMI ≥ 35 kg/m², and HbA1c of 7.0% or greater. The major endpoint was the rate of remission (defined as HbA1c level $<6.5\%$). At 2 years, the remission rate was 0% for medical treatment, 75% for the RYGB group and 95% in the BPD group ($P<0.001$ for both comparisons) (44).

At the Cleveland Clinic, we randomized 150 patients with T2DM to conventional medical therapy, RYGB or SG. The primary endpoint of the 'Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently' (STAMPEDE) study was the proportion of patients achieving HbA1c of 6.0% or less 12 months after treatment. A total of 42% in the RYGB arm, 37% in the SG arm and 12% in the medical group achieved remission at 1 year. The mean HbA1c level was $7.5 \pm 1.8\%$ in the medical therapy group, $6.6 \pm 1.0\%$ in the SG group, and $6.4 \pm 0.9\%$ in the RYGB group. Mean weight loss was 5.4 kg in the medically treated group vs 25.1 and 29.4 kg in the SG and RYGB groups, respectively. Complications were higher in the

RYGB cohort and least in the conventional medical therapy group (45). The Diabetes Surgery Study was a 12-month non-blinded randomized trial involving 120 participants (T2DM for at least 6 months, HbA1c level of 8.0% or higher and BMI 30–40 kg/m²) at four teaching hospitals in the United States and Taiwan (43). In this study, intensive lifestyle modification and medical intervention was compared to RYGB. The primary endpoint (HbA1c level below 7%) was reached by 48.5% of the RYGB cohort and 19% of the medical therapy group. However, patients in the surgical arm had 50% more serious adverse events than the medical treatment-only group. Liang *et al.* compared three treatment arms in 108 obese T2DM patients with hypertension: conventional medical therapy, conventional medical therapy plus Exenatide (glucagon-like peptide-1 agonist) and surgical intervention (RYGB). At 12 months follow-up, diabetes remission had occurred in neither of the medical therapy groups vs 90% in the metabolic surgery arm. There was a significant decrease in antihypertensive drug requirements in the surgical group compared with medical groups ($P<0.05$) (47).

We recently published the STAMPEDE 3-year outcomes (randomization of 150 patients with uncontrolled T2DM to intensive medical therapy alone or intensive medical therapy plus RYGB or SG) with 91% of patients completing follow-up. At 36 months, the primary endpoint (HbA1c level $\leq 6\%$) was achieved by 5% of patients in the medical group compared with 38% in the RYGB arm and 24% in the SG arm ($P=0.01$) (46). Furthermore, the use of anti-diabetic medications (including insulin) was lower in both surgical groups when compared to the medical therapy cohort. The surgically treated patients had improved glycemic control at 3 years and more than 90% of patients had glycemic control without the use of insulin. Weight loss and shorter duration of diabetes were the main predictors of HbA1c level $\leq 6\%$ after surgery (46). The results of our study suggest that bariatric surgery is superior to intensive medical therapy alone in glycemic control after 3 years of randomization.

Mechanisms underlying glycemic control

There are many theories with regard to the mechanisms underlying the beneficial metabolic effects of bariatric surgery. Several studies have reported early resolution of T2DM 1 month after RYGB, with metabolic improvements greater than expected for the magnitude of weight lost (48). These data suggest a weight loss-independent effect of RYGB on glucose homeostasis control. Conversely,

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glycemic improvement following AGB appears to be related to the amount of weight loss. Thus, AGB appears to lack weight-independent effects on metabolic disease since remission of diabetes occurs gradually and in parallel with weight loss (42).

The mechanisms by which RYGB improves metabolic profiles have been thoroughly studied. In addition to the restriction related to the gastric pouch and the malabsorption associated with bypassing the proximal small bowel, there are two accepted theories on the benefits of RYGB on T2DM control (49). The 'foregut hypothesis' is based on the importance of duodenal exclusion and is supported by rat studies where the duodenal-jejunal bypass leads to glycemic improvement. Interestingly, this beneficial effect is not sustained when the gastro-jejunal nutrient transit is restored (50). Novel devices like the EndoBarrier Endoluminal Sleeve (GI Dynamics Inc., Lexington, MA, USA) try to mimic the anti-diabetic effect of RYGB by excluding the duodenum and proximal jejunum from nutrient transit (based on the 'foregut hypothesis') (51). In contrast, the 'hindgut hypothesis' is supported by the observation that rapid delivery of nutrients to the distal small bowel results in exaggerated gut hormone secretion, in particular GLP-1. This hypothesis is best illustrated in animal studies where rats undergo ileal interposition surgery (interposition of a segment of ileum to a segment of proximal small bowel) that has shown similar effects to those observed via RYGB (52).

GLP-1 has numerous metabolic effects but probably the most important is its ability to enhance B-cell function (53). The rapid entry and absorption of nutrients in the distal small bowel induces GLP-1 increases (up to threefold), which is secreted by L-cells from the gut and improves beta cell function and insulin sensitivity (54). The important role of GLP-1 has been demonstrated in studies using GLP-1 receptor antagonists that eliminate beneficial glycemic effects after RYGB (55). Postprandial levels of GLP-1 are observed to be enhanced after both SG and RYGB in human and rodent models, suggesting that alterations in intestinal hormone secretion are of significant importance with respect to the metabolic benefit of these procedures (56, 57, 58). Changes in GLP-1 levels were studied in T2DM obese patients (T2DM for <5 years) before and 1 month after RYGB. Interestingly, oral glucose-stimulated GLP-1 (AUC) and gastric inhibitory peptide (GIP) peak levels increased significantly, compared to controls (59). Despite this, some authors have suggested that GLP-1 is likely not involved in diabetes improvement after bariatric surgery (60). Functional studies designed to assess the influence of GLP-1 signaling have obtained mixed results (57, 58, 61).

The results of pharmacological blockade of the action of GLP-1 on its receptor (promoting prandial insulin release inhibition) tend to argue against GLP-1 being critical in diabetes remission after SG or RYGB. Several studies have shown modest impairment in glycemic control after GLP-1 receptor blockade, indicating that the contribution of endogenous GLP-1 after bariatric surgery to pancreatic beta cell function may only be minor (62).

The SG operation (no gastrointestinal rearrangements) has also been shown to have metabolic effects. Many studies have shown incretin upregulation after SG (63) and some reports suggest that RYGB and SG are associated with comparable remission rates of T2DM (64).

Numerous other factors have been implicated as potential contributors in the metabolic improvement observed after bariatric surgery including other intestinal gut hormones (GLP-2, PYY), ghrelin (anorexic hormone secreted by the gastric fundus), adipokines, the increased energy expenditure following surgery, changes in the gut microbiome and bile acid (BA) metabolism (49).

BA are increasingly recognized as molecules with endocrine functions, and a link between BA and glycemic control has been suggested. Human studies and animal models support that RYGB promotes a rise in BA concentrations (65). Plasma BA bind to the G-protein-coupled receptor (TGR5) that is present in enteroendocrine cells, liver, skeletal muscle and brown adipose tissue. The activation of TGR5 increases GLP-1 release, which can improve insulin secretion and insulin sensitivity (66). BA are also involved in the regulation of hepatic glucose metabolism by the nuclear receptor *Farnesoid X Receptor* (FXR) pathways. The FXR is highly expressed in the liver and intestine, but also in adipose tissue, the pancreas and the adrenal glands. BA can also improve the glucose profile indirectly via FXR-mediated induction of the fibroblast growth factor 19 (FGF19) in the intestine (67, 68, 69). A recent animal study conducted by Kohli *et al.* (70) has demonstrated the metabolic effect of diverting bile to the distal gut. The investigators placed a catheter into the common bile duct of obese rats to drain bile to the distal part of the jejunum. The results highlighted the role of BA in glucose homeostasis control. Unfortunately, only a few human studies have addressed the role of BA in diabetes control after bariatric surgery (71). Patti *et al.* (71) performed a cross-sectional analysis of fasting and post-meal serum BA and metabolic variable composition in three groups of subjects; post-RYGB group ($n=9$), non-RYGB group matched to preoperative BMI ($n=5$), and non-RYGB group matched to current BMI ($n=10$). Total serum BA concentrations were significantly higher in the RYGB

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group compared to the other two groups. Total BA were also inversely correlated with 2-h post-meal glucose and fasting triglycerides and positively correlated with adiponectin and peak GLP-1 (follow-up study at 24–48 months).

One target of FXR signaling is the gut bacterial flora (72). Recent findings suggest that intestinal bacteria have an impact on host metabolism, obesity and diabetes (73). It has been observed that gastrointestinal rearrangements after RYGB promote substantial changes on the gut microbiota (74). Studies in mice surrounding fecal transplants from RYGB-treated animals have shown substantial weight loss in comparison with mice containing fecal transplants from sham-treated mice, thus suggesting that changes in gut bacteria after RYGB can modulate body weight of the host organism (75).

Cardiovascular risk

Bariatric surgery has been shown to resolve or improve cardiovascular risk factors such as diabetes, hypertension and dyslipidemia (38, 41, 48, 76). For instance, Sugerman *et al.* (76) studied 521 hypertensive patients undergoing RYGB and reported hypertension resolution rates at 1 and 5–7 years after surgery of 66 and 69%, respectively, with superior outcomes in subjects achieving more EWL. Similar effects were reported in Buchwald's meta-analysis, which demonstrated a hypertension resolution rate of 62% and improvement in 17% of patients (16). The retrospective cohort study by Adams *et al.* (77) also showed sustained decreases in blood pressure during a 10-year period after surgery. However, the SOS study investigators suggest that hypertension seems to reappear in the context of weight regain, even with an overall weight reduction (14).

Weight loss surgery promotes substantial decreases in triglycerides levels as well as improvements in cholesterol profiles (16, 78). Zlabek *et al.* (78) showed a 41% reduction in serum triglycerides 1 year after RYGB, an elevation in HDL cholesterol by 23% and lowering of LDL cholesterol by 19%, with sustained beneficial effects on cholesterol profiles up to 2 years follow-up. A long-term follow-up study of morbidly obese patients with T2DM ($n=219$) reported a 40% decrease in triglyceride levels and 20% increase in HDL-C levels (79). These improvements were maintained 2–4 years after surgery.

Very little is known about the effect of bariatric surgery on reducing the vascular complications of T2DM. Observational studies have suggested that bariatric surgery may reduce long-term renal impairment associated with diabetes (41, 80). A recent study conducted by

our institution evaluated diabetic nephropathy changes after bariatric surgery (81). We followed patients over a 5-year period measuring urinary albumin excretion serially. Preoperatively, 37.8% of patients had microalbuminuria or macroalbuminuria. After a mean follow-up of 5.5 years, the abnormal albuminuria resolved in 58.3% of patients after surgery (81). Another non-randomized study of the effects of BPD vs medical treatment on diabetic complications ($n=110$) studied long-term renal function after both treatments. Fifty patients completed the 10-year study. Renal function was preserved over 10 years in the BPD group and decreased in the medically treated group (glomerular filtration rate +13.6% vs –45.7%) (80). Furthermore, the STAMPEDE STUDY showed improvement of albuminuria in both surgical groups. The urinary albumin-to-creatinine ratio (milligrams of albumin to grams of creatinine) decreased from a median of 9–6 in the RYGB group ($P=0.08$) and from 12 to 7 in the SG group ($P<0.001$), as compared with the decrease from 6.5 to 5.5 in the medical arm ($P=0.77$) (46).

Weight loss surgery has also been shown to improve cardiac function and reverse remodeling of the heart up to 3 years postoperatively (82). Surgery can improve all phases of obesity-related cardiomyopathy, and can improve left ventricular systolic function in patients with severe heart failure who are awaiting heart transplantation (83). However, long-term microvascular and macrovascular benefits after bariatric surgery will require large multicenter clinical trials.

Mortality

The major goal of bariatric surgery is to decrease mortality. A meta-analysis including 44 022 participants from eight trials (mean follow-up of 7.5 years) showed reduced risk of global mortality (OR=0.55, CI 0.49–0.63) and cardiovascular mortality (OR=0.58, CI 0.46–0.73) after bariatric surgery compared with controls (no surgery) (84). Actually, weight loss surgery can reduce mortality by 30% (85). In the SOS trial, over a period of up to 10 years, mortality was significantly lower in the surgical group (5.0%) than in the control group (6.3%), representing a hazard ratio (HR) of 0.76 (95% CI 0.59–0.99, $P=0.004$). It should be noted that while the SOS study was not sufficiently powered to establish specific causes of death, the most common were attributable to cardiovascular-related causes (68). A retrospective cohort study by Adams *et al.* (77) compared long-term mortality in patients who underwent RYGB ($n=7925$) with obese control patients matched for age, sex and BMI ($n=7925$). During a mean follow-up of 7 years, all-cause

mortality rates were 40% lower in the surgical group compared with controls (HR, 0.60; 95% CI 0.45–0.67, $P < 0.001$). Another large study conducted in Canada comparing surgical vs non-surgical treatment for morbid obesity showed a reduction of the relative risk of death of 89% in the surgery group (9). The mortality in the surgical cohort was 0.68% compared with 6.17% for controls (relative risk 0.11, 95% CI 0.04–0.27) (9).

Conclusion

We are currently witnessing the exciting metamorphosis of bariatric surgery into a specialty concerned with metabolic disease and the damaging effects it imparts on obese individuals. Herein, we have presented several key studies that have advanced our understanding of the safety and efficacy of the various contemporary bariatric surgical procedures and the effect they have on obesity-related comorbid conditions. Bariatric and metabolic surgery has become one of the most studied fields in medicine, with an ever-growing abundance of new studies surfacing every year. As more comparative data emerges, the long-term risks and benefits of the various bariatric procedures will help aid patient and procedural selection for generations of bariatric surgeons to come. Even more intriguing is the current opinion that the indications for metabolic surgery may change in the near future to include broader, more metabolic indications and gradually move away from stricter weight-based criteria, like the National Institute of Health Guidelines. Studies addressing metabolic outcomes after bariatric surgery in type 2 diabetic patients with BMI < 35 are beginning to surface, and studies like this likely represent future directions in this dynamic specialty.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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