# Biological effects of bariatric surgery on obesity-related comorbidities

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The prevalence of obesity has increased so rapidly over the last few decades that it is now considered a global epidemic. Obesity, defined as a body mass index (BMI) of 30 or more, is associated with several comorbid conditions that decrease life expectancy and increase health care costs. Diet therapies have been reported to be ineffective in the long-term treatment of obesity, and guidelines for the surgical therapy of morbid obesity (BMI ≥ 40 or BMI ≥ 35 in the presence of substantial comorbidities) have since been established. Considering the number of bariatric surgical procedures has dramatically increased since these guidelines were established, we review the types of bariatric surgical procedures and their impact on diabetes, sleep apnea, dyslipidemia and hypertension — 4 major obesity-related comorbidities.

La prévalence de l'obésité a augmenté si rapidement au cours des quelques dernières décennies qu'on considère désormais qu'il s'agit d'une épidémie mondiale. L'obésité, définie par un indice de masse corporelle (IMC) de 30 ou plus, est associée à plusieurs comorbidités qui réduisent l'espérance de vie et font augmenter le coût des soins de santé. La diétothérapie serait inefficace pour le traitement à long terme de l'obésité et des lignes directrices concernant le traitement chirurgical de l'obésité morbide (IMC ≥ 40 ou IMC ≥ 35 en présence d'autres comorbidités importantes) ont donc été établies. Compte tenu du fait que le nombre de chirurgies bariatriques a considérablement augmenté depuis la parution de ces lignes directrices, nous passons en revue les différents types de chirurgies bariatriques et leur impact sur le diabète, l'apnée du sommeil, la dyslipidémie et l'hypertension, 4 importantes comorbidités liées à l'obésité.

Obesity is a serious public health problem associated with increased morbidity and mortality and decreased quality of life. According to the World Health Organization, in 2005 there were about 1.6 billion overweight adults (aged 15 years or older) and at least 400 million obese adults worldwide.[1] The prevalence of obesity has increased so rapidly over the last few decades that it is now considered a global epidemic.

The World Health Organization defines overweight as a body mass index (BMI) of 25 or more and obesity as a BMI of 30 or more.[1] Obese patients are further categorized into class I (BMI 30–34.9), class II (BMI 35–39.9) and class III (BMI 40 or more).[2,3] While these subcategories are relevant when analyzing trends in prevalence, evidence suggests that the risk of chronic disease increases progressively from a BMI as low as 21.[1] In addition, the risk of obesity-related comorbidities increases in individuals with a large waist circumference, even if they are categorized as healthy or overweight. Specifically, a waist circumference greater than 101.6 cm (40 inches) in men and greater than 89.9 cm (35 inches) in women predicts an increased risk of diabetes, dyslipidemia, hypertension and cardiovascular disease.

In the United States, the National Health and Nutrition Examination Surveys conducted by the Centers for Disease Control study the prevalence of obesity using directly measured heights and weights. Studies have reported that currently there are 72 million obese adults. Interestingly, while the prevalence in adults aged 20–74 years has more than doubled over the last 4 decades (13.4% in 1960–1962 v. 35.1% in 2005–2006),[4] it seems to have reached a plateau in the last 3 years.[5–7] However, when comparing the distribution of BMI in 1976–1980 with that in 2005–2006, it appears that the distribution among adults has shifted, reflecting a change in prevalence of superobesity

(BMI > 50), which increased from 0.9% in 1960–1962 to 6.2% in 2005–2006.[6]

In Canada, statistics from 2004 demonstrated that about 23% (5.5 million people) of adults were obese compared with 14% in the late 1970s.[2,8] The total direct cost of obesity in Canada has been estimated to be more than $1.8 billion, which corresponded to 2.4% of the total health care expenditures for all diseases in Canada in 1997.[9] When the cost of obesity-related comorbidities was taken into account, the 3 largest contributors were hypertension ($656.6 million), type 2 diabetes mellitus (T2DM; $423.2 million) and coronary artery disease ($346.0 million).[9]

Studies have indicated that obesity is responsible for more than 2.8 million deaths worldwide per year[10] owing to an increased prevalence of related comorbidities, including type 2 diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, heart disease, stroke, asthma, back and lower extremity weight-bearing degenerative problems, several forms of cancer and depression.[10–12] In addition, obesity is an independent risk factor for death. A study by Fontaine and colleagues[13] demonstrated that compared with an individual with a healthy weight, a 25-year-old morbidly obese man has a 22% reduction in life expectancy, representing about 12 years of life lost. A more recent study that examined 10-year mortality in more than 500 000 Americans aged 50–71 years demonstrated that in middle-aged men and women who were nonsmokers and had no pre-existing illnesses, there was a 20%–40% increase in mortality in those who were overweight and a 2- to 3-fold greater risk among those who were obese.[14]

As evidenced by the existence of countless weight loss programs, most adults attempt to lose weight at some point in their lives.[15] However, diet therapy, with and without supports and pharmaceutical agents, is ineffective in the long-term treatment of obesity.[3] In 1991, the National Institutes of Health established guidelines for surgical therapy for morbid obesity (BMI ≥ 40 or BMI ≥ 35 in the presence of substantial comorbidities),[16,17] and since then the number of bariatric surgical procedures has dramatically increased. About 144 000 obese individuals received surgical treatment in 2004 compared with about 20 000 in 1999.[18] The dramatic increase is most likely related to the use of minimally invasive surgical techniques, increased media coverage and increased patient satisfaction. Of the various available weight-loss strategies, bariatric surgery is the only effective long-term weight-loss therapy for obese individuals.[19]

The present paper reviews the types of bariatric surgical procedures and their impact on diabetes, sleep apnea, dyslipidemia and hypertension; 4 major obesity-related comorbidities.

## Current surgical therapies for morbid obesity

Bariatric procedures are classified as restrictive and/or malabsorptive based on the presumed mechanism of weight loss[20] (Table 1).

### *Restrictive procedures*

Restrictive procedures limit the luminal diameter of the stomach, but do not reroute food through the gastrointestinal tract by exclusion of intestinal segments. Procedures may involve some form of foreign material or "band" (i.e., laparoscopic adjustable gastric band [LAGB]) and/or surgically resize the stomach with a stapler to create a small gastric pouch (i.e., vertical-banded gastroplasty [VBG] or sleeve gastrectomy [SG]).[21]

The LAGB is the second most common bariatric procedure, wherein an adjustable plastic and silicone ring is placed around the proximal stomach just beneath the gastroesophageal junction. A subcutaneous access port allows the degree of band constriction to be adjusted by the injection or withdrawal of saline. Although the risk of death and major morbidity is low, the amount of excess weight loss obtained is inferior than that achieved with the malabsorptive procedures.[22,23]

The laparoscopic SG is a relatively new surgical procedure for the management of obesity. The procedure involves resection of the greater curvature of the stomach by stapling it over a sizing tube 11–20 mm in diameter.[24] Originally developed as part of a biliopancreatic diversion with duodenal switch (BPD+DS),[25] it was subsequently used as the initial procedure of staged surgery for superobesity.[26,27] Currently, LSG is most commonly applied as a stand-alone procedure[28] and is being used with increasing frequency (i.e., LSG accounted for 7.8% of primary bariatric operations in 2010).[29] The effectiveness of LSG with respect to weight loss and resolution of comorbidities is less than that of Roux-en-Y gastric bypass (RYGB) but greater than that of LAGB. These results suggest that, at least in the short-term, LSG is an efficacious method of weight loss.

### *Primarily malabsorptive procedures with some restriction*

Malabsorptive procedures are designed to reduce the area of intestinal mucosa available for nutrient absorption. The jejunoileal bypass (JIB) involves bypassing most of the small intestine by anastomosing the proximal jejunum, past the ligament of Trietz, to the terminal ileum. While excellent weight loss is achieved, the blind jejunal-ileal limb leads to nutritional complications and hepatic cirrhosis secondary to bacterial overgrowth.[30–32] As such, this procedure was abandoned, and the BPD was devised to improve upon the JIB.

The BPD consists of a partial gastrectomy, resulting in a 200–500 mL proximal gastric pouch and creation of a distal Roux and proximal biliary limb by division of the

small bowel 250 cm proximal to the terminal ileum. The gastric pouch is then anastomosed to the end of the Roux limb, and the biliary limb is attached 50 cm proximal to the ileocecal valve, thereby creating a very short common channel.[21] The procedure was later modified, creating the BPD-DS. This entails creating a gastric sleeve with a maximum reservoir of 150–200 mL. The small bowel is then divided at 2 points: 4–5 cm distal to the pylorus and 250 cm proximal to the terminal ileum. The proximal duodenal end is reconnected to the last 250 cm of small intestine, and the biliary limb is anastomosed 100 cm proximal to the terminal ileum.[22,30,33] This procedure preserves the antrum, pylorus, a short segment of duodenum and vagal nerve integrity, thereby having a theoretical advantage of preserving a more physiologic digestive behaviour and diminishing the risk of dumping syndrome, ulcerogenicity and hypocalcaemia.[30]

### *Primarily restrictive procedure with some malabsorption*

The RYGB is considered the "gold standard" for bariatric surgery and is the most commonly performed operation.[20,30] Technically, the procedure involves creating a gastric pouch, Roux limb and biliary limb. Using surgical staplers, a small, vertically oriented gastric pouch with a volume of less than 30 $cm^3$ is formed. The Roux and biliary limbs are created by dividing the small bowel 30–40 cm from the ligament of Trietz. Restoration of continuity occurs by connecting the distal end of the divided bowel (Roux limb) to the pouch, creating a gastrojejunostomy, and anastomosing the biliary limb about 100–150 cm distal to the gastrojejunostomy. After an RYGB, the size of the pouch restricts the volume of ingested food, and approximately 95% of the stomach, the entire duodenum and a portion of the jejunum are effectively bypassed.[30]

**Table 1. Comparison of bariatric procedures**

| Measure | LAGB | VBG | SG | JIB | BPD | BPD with or without DS | RYGB |
|---|---|---|---|---|---|---|---|
| Mechanism of action | Restriction | Restriction | Restriction | Malabsorption > restriction | Malabsorption > restriction | Malabsorption > restriction | Restriction > malabsorption |
| Procedure | Involves placing an adjustable plastic and silicone ring around the stomach below the gastroesophageal junction. A subcutaneous access port allows adjustment of the band by injection or withdrawal of saline. | Involves partitioning the stomach using surgical staples to create a vertical pouch and horizontal segment at the top edge of the stomach. A polypropylene band is used around the lower end of the vertical pouch to prevent stretching.[21] | Involves dividing the greater curve of the stomach, starting 6 cm proximal to the pylorus and continuing to the angle of His, by stapling it over a sizing tube ranging from 32 F to 48 F.[24] | Involves bypassing a majority of small intestine by anastomosing the proximal jejunum, past the ligament of Trietz, to the terminal ileum, leaving a blind jejunal-ileal limb. | Involves forming a gastric pouch (horizontal gastrectomy) anastomosed to the distal 250 cm of small intestine (Roux limb). The biliary limb is connected to the Roux limb 50 cm proximal to the ileocecal valve.[21] | Modification of BPD. Involves creating an SG and dividing the small bowl 4–5 cm distal to the pylorus and 250 cm proximal to the terminal ileum. The proximal duodenum/stomach is connected to the distal 250 cm of small intestine, and the biliary limb is connected to the Roux limb 100 cm from the ileocecal valve.[33] | Involves creating a small, vertically oriented gastric pouch (~30 mL) that is connected to a Roux limb formed by division of the jejunum about 40–60 cm from the ligament of Trietz. The biliary limb is reconnected to the Roux limb 150 cm from the gastrojejunostomy.[21] |
| Excess weight loss | 47.5% 2 yr postop[19] | 68.2% 2 yr postop[19] | 33%–83% 1 yr postop[106,107] | 34%–36% 2 yr postop[31,32] | 63.2%–77.8% 10 yr postop[108] | 74%[33] | 61.6%[19] |
| Early complications ≤ 30 d postop | Gastric or esophageal perforation, port/wound infection, stoma obstruction, hemorrhage[109] | Staple line leak, stenosis, ulcer, wound infection, staple line disruption, pouch dilation and band erosion[21] | Staple line leak, abscess, bleeding, stricture, wound infection, splenic injury[107] | Diarrhea, electrolyte abnormalities (B12, folate)[110] | Wound infection, dehiscence, anastomotic leak[21,111] | Gastric staple line leak[23] | Anastomotic leaks, bowel obstruction, bleeding, wound infection, deep vein thrombosis/pulmonary embolism[21] |
| Late complications > 30 d postop | Band slippage, access-port infection, port and tubing problems, band erosion[109] | 30% revision rate, anastomotic stricture, incisional hernia, marginal ulcer, nutritional deficiencies, bowel obstruction[21] | Staple line leak, stricture, choledocholithiasis and bile duct stricture[112] | Diarrhea, electrolyte abnormality, nephrolithiasis, cholecystitis, cirrhosis[110] | Incisional hernia, protein malnutrition, gastric ulcer, hypoalbuminaemia, anemia[21,111] | Protein malnutrition, incisional hernia[33] | Anastomotic stricture, bowel obstruction, incisional hernia, marginal ulceration, nutritional deficiencies[21] |
| Mortality < 30 d:> 30 d | 0.06%:0%[35] | 0.21%:0%[35] | 0.46%:0.15[113] | 0.9%:3%–4%[31,32] | 1.3%:NA[111] | 1.11%:NA[35] | 0.16%:0.09%[35] |

BPD = biliopancreatic diversion; DS = duodenal switch; JIB = jejunal-ileal bypass; LAGB = laparoscopic adjustable gastric band; NA = not available; postop = postoperatively; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; VBG = vertical-banded gastroplasty.

## Effect of bariatric surgery on weight loss and operative mortality

The Swedish Obesity Study is the largest, longest running prospective, nonrandomized, interventional trial that examined the effects of bariatric surgery (i.e., LAGB, VBG, RYGB) on 4047 obese patients with contemporaneously matched conventionally treated controls.[34] Results demonstrated that in the surgical group there was a 23.4% decrease in weight at 2 years and a 16.1% decrease at 10 years. Conversely, there was an increase in weight in the control group at both time points (0.1% at 2 years and 1.6% at 10 years). In addition, Buchwald and colleagues[19] conducted a meta-analysis on the effects of bariatric surgery on weight loss and obesity-related comorbidities. Their study demonstrated that, 2 years postoperatively, the percentage of excess weight loss was 47.5% for gastric banding, 61.6% for RYGB, 68.2% for VBG and 70.1% for BPD with or without DS (BPD±DS). The overall excess weight loss for 10 172 patients was 61.2%.

The risks of bariatric surgery were summarized in a meta-analysis that reviewed early and late mortality in 85 048 patients who underwent surgery from 478 treatment groups in 361 studies published bewteen Jan. 1, 1990, and Apr. 30, 2006.[35] The results demonstrated that early mortality (i.e., ≤ 30 d) was 0.28% (95% confidence interval [CI] 0.22–0.34) in 475 treatment arms ($n$ = 84 931); and total mortality from 30 days to 2 years was 0.35% (95% CI 0.12–0.58) in 140 treatment arms ($n$ = 19 928).

## Effect of bariatric surgery on obesity-related comorbidities

### *Diabetes*

The idea that bariatric surgery may "cure" diabetes has been recognized for more than 2 decades. A landmark paper by Pories and colleagues[36] demonstrated that of 141 patients with diabetes or impaired glucose tolerance (IGT), all but 2 became euglycemic within 10 days after RYGB. Longer follow-up demonstrated that over 8 years, 83% of patients with preoperative T2DM and 99% of those with IGT were able to maintain normal levels of plasma glucose, $HgA1_C$ and insulin.[22,37] The Swedish Obesity Study demonstrated that 2 years after surgery, 72% of patients had complete resolution of T2DM compared with 21% of control patients. Follow-up for 8 years demonstrated that the prevalence of diabetes in the surgical group remained relatively stable, whereas incidence in the control group increased from 7.8% to 24.9%.[38] In an analysis of incidence,[34] 767 obese patients who underwent surgery were compared with 712 matched, conventionally treated controls. Results indicated that the incidence was significantly lower in the surgical group than in the control group at 2 years (0.2% v. 6.3%) and 10 years postoperatively (7% v. 24.9%).[34]

Meta-analysis of bariatric surgical outcomes[19] demonstrated that, of studies reporting resolution of diabetes, 1417 of 1846 (76.8%) patients experienced complete resolution. Of those who reported both resolution and improvement or only improvement, 414 of 485 (85.4%) patients experienced resolution or improvement. Procedure-specific subanalysis demonstrated that the degree of diabetes resolution depended on the procedure performed. Specifically, complete resolution was observed in 98.9% of patients who underwent BPD±DS, 83.7% who underwent RYGB, 71.6% who underwent VBG and 47.9% who underwent an adjustable gastric band. However, subanalysis of studies that described both resolution and improvement did not demonstrate a similar trend, probably owing to the small sample size ($n$ = 485).

Interestingly, the clinical resolution of diabetes via RYGB and BPD+DS, the most effective procedures, was associated with the duration and severity of the disease. Specifically, improvement of diabetes was most pronounced in patients with a milder form and shorter duration of the disease, or in patients with less central obesity as measured by waist circumference.[39–41] Conversely, patients whose diabetes did not resolve were usually older or had a more prolonged preoperative disease course.[37,42,43]

### *Diabetes: possible mechanism(s) of control after surgery*

Rubino[30] outlined 3 possible mechanisms of the effect of bariatric surgery on glucose homeostasis: the effect of weight loss, intestinal malabsorption and hormonal changes.

Weight loss, as a mechanism, may play a role in the resolution of diabetes in obese patients who undergo gastric banding.[30] Indeed, Ponce and colleagues[44] demonstrated that after gastric banding the rate of diabetes resolution was greater 2 years postoperatively than after the first year, and improvement correlated with the degree of weight loss. However, several studies have demonstrated a return to euglycemia and normal insulin levels within days of RYGB or BPD, changes that occur well before any significant loss in weight.[37,45,46] Interestingly, restrictive techniques result in lower rates of diabetes remission than mixed procedures, suggesting that gastrointestinal tract changes after malabsorptive procedures are involved in diabetes control (48% for gastric banding v. 84% for RYGB and 98% for BPD).[19] Therefore, diabetes resolution is not a result of weight loss alone.

The rationale for intestinal malabsorption as a mechanism for diabetes control is derived from the fact that both hyperglycemia and free fatty acids induce insulin resistance and β-cell dysfunction by stimulating mitochondrial production of reactive oxygen species (ROS).[30,47] Therefore, in theory, by limiting the area over which nutrients are absorbed, there is less absorption of both glucose

and fat, leading to a reduction in the production of ROS and improved β-cell function and insulin sensitivity. While malabsorption is clinically evident after BPD,[48] it does not occur after standard RYGB,[49,50] suggesting that additional factors may play a role in glucose regulation.

It has been hypothesized that rerouting food through the gastrointestinal tract leads to changes in gut hormone secretion which, in turn, may mediate the antidiabetic effect of bariatric surgery.[30] Several studies have demonstrated changes in gut hormone levels after RYGB, including increased anorectic hormones that induce satiety (e.g., GLP-1, PPY) and decreased levels of orexigens like ghrelin, an appetite-stimulating hormone. Of note is the fact that GLP-1 increases the insulin response to nutrients and, in animal models, induces β-cell proliferation.[51,52] Therefore, perhaps it is the postsurgical endocrine effects that mediate the antidiabetic effect of RYGB.[53]

Alternatively, surgical resolution of T2DM may be related to the anatomic changes associated with RYGB. To this end, Rubino[30] proposed the hindgut and foregut hypotheses. The hindgut theory postulates that diabetes control is due to accelerated delivery of nutrients to the distal intestine, which boosts a "physiologic" signal (e.g., GLP-1) that improves glucose metabolism.[54–57] The foregut hypothesis states that excluding nutrients from the duodenum and proximal jejunum may inhibit the secretion of a signal that normally would induce insulin resistance and T2DM.[58,59] Using Goto-Kakizaki rats (a nonobese Wistar substrain in which T2DM develops early in life) Rubino and colleagues[60] demonstrated that a gastrojejunostomy-duodenal exclusion (GDE), a model for RYGB, improved diabetes. However, performing a simple gastrojejunostomy without the duodenal exclusion did not improve diabetes in the same animal model. In addition, glucose intolerance returned in GDE-treated animals when nutrient flow was surgically re-established through the proximal intestine despite preserving the gastrojejunostomy. Similarly, diabetes control improved in animals that originally underwent a simple gastrojejunostomy when the proximal intestine was excluded from nutrient flow, while leaving the gastrojejunostomy intact. From these studies and clinical observations, Rubino and colleagues concluded that, in individuals with diabetes, duodenal–jejunal exclusion improves glucose tolerance, characterizing T2DM as a possible duodenal–jejunal illness.

### *Obstructive sleep apnea: the effect of bariatric surgery*

Obstructive sleep apnea (OSA) is the most prevalent subtype of sleep-disordered breathing. It consists of repetitive obstruction of the upper airway during sleep in which ineffective respiratory efforts occur.[61] According to the American Academy of Sleep Medicine, OSA is present when individuals average at least 5 apneic or hypopneic events per hour. Obstructive sleep apnea is considered mild if the apnea–hypopnea index (AHI) is 5–14 events per hour, moderate if the AHI is 15–29 events per hour and severe if the AHI is 30 or more events per hour.[62,63] The medical sequelae of OSA include daytime hypertension, cardiac arrhythmias, increased risk of stroke, coronary artery disease and congestive heart failure.[59–62] In addition, 2 population-based cohort studies confirm that untreated OSA is an independent risk factor for death.[64–68]

An important risk factor for OSA is obesity.[69–72] The prevalence of OSA among obese individuals is high and correlates with increasing BMI.[70,73,74] In fact, in severely obese individuals, the prevalence ranges from 55% to 100%.[75,76] In addition, obese individuals often have more severe disease, as manifested by a higher AHI and lower nadir on nocturnal pulse oximetry.[70,77,78] Several studies have demonstrated that weight loss, even a modest amount, can effectively manage OSA.[79,80] As such, the positive effect of bariatric surgery on OSA has been repeatedly reported. Indeed, the meta-analysis by Buchwald and colleagues[19] demonstrated a significant improvement in the total patient population, with resolution of OSA in 85.7% of patients.

In 2009, Greenburg and colleagues[69] conducted a meta-analysis investigating the effect of bariatric surgery on OSA. The study demonstrated that bariatric surgery resulted in a mean decrease in BMI of 17.54 (from 55.28 to 37.74). This decrease was associated with a substantial improvement in the AHI. The overall effect size of the pooled, weighted data showed a reduction of 38.2 events per hour in the combined study results (from 54.7 to 15.8 events per hour), which represented a combined reduction of 71% in AHI. However, considering that the mean residual AHI was 15.78 events per hour and that an AHI of 15 or more events per hour represents moderate disease, most patients (62%) had residual disease. In fact, only 25% of patients in the 6 studies that reported individual patient data (representing 23% of all patients in the meta-analysis) were able to reach an AHI consistent with OSA resolution (< 5 events per hour). Interestingly, in logistic regression models, both younger age (odds ratio [OR] 1.08, 95% CI 1.01–1.16) and follow-up weight less than 100 kg (OR 0.18, 95% CI 0.46–0.72) independently predicted resolution of OSA.

These findings demonstrate that, while weight loss associated with bariatric surgery improved OSA, residual disease remains in most patients who, on average, are older and heavier. Symptoms of OSA may not correlate with severity (measured using polysomnographic criteria), and lack of "daytime sleepiness" does not indicate resolution of OSA.[69,81,82] This is important in light of the observation that patients experiencing the benefits of surgery-induced weight loss (e.g., improved mobility, agility and physical endurance) may feel well and believe that their OSA is "cured."[81] As such, they may be reluctant to remain compliant with therapy. The clinical significance is that even moderate

OSA (AHI 15–29 events per hour) can lead to cardiovascular complications of hypertension, cardiac arrhythmias, increased risk of stroke, coronary artery disease and congestive heart failure. Therefore, diagnostic sleep testing with repeat polysomnography should be pursued when a goal weight or stable weight is attained, as only follow-up polysomnography can identify patients who have achieved an AHI consistent with resolution of OSA.

### *Dyslipidemia: the effect of bariatric surgery*

Atherogenic dyslipidemia is strongly associated with visceral obesity. It is defined as elevated triglycerides, apolipoprotein B, small low-density lipoprotein (LDL) particles, and low high-density lipoprotein (HDL) cholesterol. Dyslipidemia in association with hypertension, insulin resistance, proinflammatory/thrombotic states and visceral obesity is collectively referred to as the metabolic syndrome (MetS).[75]

The MetS is a cluster of risk factors for cardiovascular disease and T2DM that occur together more often than by chance alone. It is diagnosed based on the presence of any 3 of the following 5 risk factors:

- visceral obesity/increased waist circumference, the values for which are population- and country-specific (e.g., in Canada and the United States, threshold values are ≥ 102 cm in men and ≥ 88 cm in women);
- elevated triglycerides (> 1.7 mmol/L [> 150 mg/dL]);
- reduced HDL cholesterol (< 1.04 mmol/L in men [< 40 mg/dL] and < 1.3 mmol/L [< 50 mg/dL] in women);
- elevated blood pressure (systolic > 130 and/or diastolic > 85 mm Hg); and
- elevated fasting glucose (> 5.55 mmol/L [100 mg/dL]).

Albeit debatable, of the required 3 factors, one has to include increased waist circumference.[83]

Alarmingly, the prevalence of MetS has been reported to be 24% in the adult population in the United States,[84] the significance of which lies in the fact that it is associated with increased risk of death from coronary heart disease, cardiovascular disease or all-cause mortality. Specifically, a prospective cohort study was conducted by Malik and colleagues[85] to examine the impact of MetS on coronary heart disease, cardiovascular disease and all-cause mortality. Results demonstrated that in the coronary heart disease population, those with MetS die twice as frequently (hazard ratio [HR] 2.02) and that in patients with pre-existing cardiovascular disease, those with MetS die 4 times more frequently (HR 4.19) than those without. Overall mortality was increased in patients with MetS (HR = 1.40), and in those who also had pre-existing cardiovascular disease this rate was even higher (HR 1.87). Finally, patients with even 1 or 2 MetS-related risk factors were at increased risk of death from coronary heart disease and cardiovascular disease (HR 2.10 and 1.73, respectively), although MetS predicted coronary heart disease, cardiovascular disease and total mortality more strongly than its individual components.

Several series examining the effect of bariatric surgery on dyslipidemia have reported significant improvement in lipid profiles after bariatric surgery. There are marked reductions in LDL, increased HDL and decreased triglycerides.[76] In the Swedish Obesity Study,[34] significant improvements were observed in triglyceride and HDL levels at 2 and 10 years in the surgical versus the control group (increased HDL: % difference 18.7%, 95% CI 20.1%–17.3% at 2 years and 13.6%, 95% CI 16.5%–10.6% at 10 years; decreased TG: % difference 29.9%, 95% CI 27.4%–32.5% at 2 years and 14.8%, 95% CI; 10.4%– 19.1% at 10 years). In the entire cohort, while total cholesterol was significantly different at 2 years (1%, 95% CI 0.1%–1.9%), there was no significant difference at 10 years. However, subgroup analysis demonstrated that in the RYGB subgroup ($n$ = 34) total cholesterol, triglycerides and HDL were all significantly improved at 10 years (% difference 12.6%, 28% and 47.5%, respectively).

While the effect of RYGB on dyslipidemia is impressive, the Swedish Obesity Study included only 34 patients. However, its findings are supported by a retrospective study by Zlabek and colleagues,[86] who examined the lipid profiles of 168 patients preoperatively and 1 and 2 years after laparoscopic RYGB. After 1 year, total cholesterol decreased by 12.5%, LDL decreased by 19.4%, HDL increased by 23.2%, triglycerides decreased by 41.2% and the percentage of dyslipidemic patients decreased from 82.3% to 28.1% ($p < 0.001$). In addition, 14.6% of patients were taking lipid-modifying medications postoperatively compared with 26% preoperatively ($p = 0.049$). After 2 years, total cholesterol decreased by 7.2%, LDL decreased by 21.7%, HDL increased by 40.3%, triglycerides decreased by 27.3% and the percentage of dyslipidemic patients decreased from 94.4% to 27.8% ($p < 0.001$).

In the meta-analysis by Buchwald and colleagues,[19] hyperlipidemia, hypercholesterolemia and hypertriglyceridemia were significantly improved across all surgical procedures at 2 year follow-up. The percentage of patients whose conditions improved was typically 70% or higher, with maximum improvements in hyperlipidemia in the BPD-DS (99.1%, 95% CI 97.6%–100%) and RYGB groups (96.9%, 95% CI 93.6%–100%). In the total population, there was a significant decrease in total cholesterol (mean change 0.86 mmol/L [33.20 mg/dL], 95% CI 0.6–1.13 mmol/L [23.17–43.63 mg/dL], $n$ = 2573), LDL (mean change 0.76 mmol/L [29.34 mg/dL], 95% CI 0.46–1.06 mmol/L [17.76–40.93 mg/dL], $n$ = 879) and triglycerides (mean change 0.9 mmol/L [79.65 mg/dL], 95% CI 0.73–1.08 mmol/L [64.60–95.58 mg/dL], $n$ = 2149). Although the total population did not demonstrate a significant increase in HDL, significant improvements were seen in the RYGB (mean change 0.12 mmol/L [4.63 mg/dL], 95% CI 0.04–0.2 mmol/L [1.54–7.72 mg/dL],

$n$ = 623) and VBG groups (mean change 0.13 mmol/L [5.02 mg/dL], 95% CI 0.02–0.24 mmol/L [0.77–9.27 mg/dL], $n$ = 253). Taken together, these studies suggest that bariatric surgery not only allows for sustained weight loss, but is a viable treatment option for correcting dyslipidemia in morbidly obese individuals.

### *Hypertension: the effect of bariatric surgery on systolic, diastolic and pulse pressure*

Obesity is a major risk factor for hypertension, and there is ample epidemiological evidence supporting the association between increased weight and increased blood pressure.[87–90] In addition, many studies have demonstrated that weight loss lowers blood pressure.[91,92] In general, a decrease of 1% in body weight leads to a 1 mm Hg decrease in systolic blood pressure and a 2 mm Hg decrease in diastolic blood pressure.[93–95]

As previously detailed, bariatric surgery has a dramatic effect on sustained weight loss. Therefore, by extension, bariatric surgery should decrease blood pressure. Indeed, Buchwald and colleagues[19] showed a significant reduction in hypertension in the total patient population and across all surgical procedures. In particular, the percentages of patients in the total population whose hypertension resolved or improved were 61.7% and 78.5%, respectively. Interestingly, these results were obtained up to 2 years postoperatively, but were not sustained at longer time points.

The Swedish Obese Study[38] examined the effect of obesity on hypertension by analyzing the 8-year incidence of hypertension in obese patients treated with bariatric surgery (VGB, GB and RYGB, $n$ = 346), versus matched severely obese controls ($n$ = 346). The results demonstrated that over 8 years, while there was a significant decrease in body weight in the surgical compared with the control group (120.4 [standard deviation (SD) 16.0] kg to 100.3 [SD 17.8] kg v. 114.7 [SD 17.8] kg to 115.4 [SD 19.2] kg), there was no difference in systolic blood pressure. Specifically, over the first 6 months, a period of rapid weight loss in the surgical group, systolic blood pressure decreased by 11.4 (SD 19.0) mm Hg and diastolic blood pressure decreased by 7.0 (SD 11.0) mm Hg. Over the following 6 months, when weight loss occurred at a slower rate, systolic blood pressure increased, and the reduction in diastolic blood pressure stopped. Therefore, from the first year to the eighth year, there was a gradual increase in both systolic and diastolic blood pressure. In the control group, there was a gradual increase in systolic blood pressure (5.5 [SD 19.0] mm Hg, $p$ = 0.001) over 8 years, but a reduction in diastolic blood pressure (2.2 [SD 10.5] mm Hg, $p$ = 0.002). Consequently there was no difference in systolic blood pressure between the surgical and control groups after 8 years. Therefore, although the 2-year incidence of hypertension was lower in the surgical arm (3.2% v. 9.9%, $p$ = 0.032), there was no difference after 8 years (26.4% v. 25.8%, $p$ = 0.91), suggesting that not even a maintained 16% weight loss was sufficient to achieve a reduction of the 8-year incidence of hypertension in severely obese patients. Of interest, subgroup analysis demonstrated that in patients treated with RYGB, there was a decrease in systolic and diastolic blood pressure at 10 years (4.7% and 10.4%, respectively, both $p < 0.10$).[34]

To further understand these results, the authors analyzed the change in weight to find a relationship between weight and blood pressure. Over 7 years, the surgical group regained 11.1 (SD 13.1) kg, and patients were subdivided into above median or below median groups. Subsequently, when the effect of weight regain was analyzed, the study showed that a larger relapse in body weight was associated with a larger regain in blood pressure (systolic blood pressure increased by 14.7 [SD 21] mm Hg in the above median group and 8.4 [SD 21] mm Hg in the below median group, $p$ = 0.018; diastolic blood pressure increased by 7.3 [SD 12] and 2.9 [SD 11] mm Hg in the above median and below median groups, respectively, $p$ = 0.004).[38]

These results suggest that the direction of ongoing weight change is more closely related to blood pressure than the initial body weight. However, change in weight aside, Sjöström and colleagues[96] postulated that time/aging may also play a role. As such, they performed a post hoc analysis to separate the effect of aging from the effect of weight change per unit of time. Both the surgical and control groups were divided into 5 time groups based on follow-up (i.e., 3, 4, 6, 8 or 10 years of follow-up). In addition, for both groups, 5 independent variables were analyzed in relation to final blood pressure to separate the effects of weight change per year from the effect of time:

- inclusion weight,
- weight change (usually weight loss) during the first year (period I),
- weight change per year between the end of the first year and the second to last observation (period II),
- weight change per year between the second to last observation and the last observation (period III), and
- time between the intervention and the last observation.

The results demonstrated that blood pressure at the last examination was more closely related to time (aging) and ongoing weight change than to initial body weight and initial weight loss. In addition, in the surgical group, the effect on blood pressure of 1 elapsed year was 2.5–4 times greater than the effect of 1 kg regained.

Interestingly, as noted previously,[38,96] while systolic blood pressure increased in both groups, diastolic blood pressure decreased in the control group but increased in the surgical group. Therefore, given that elevated pulse pressure is associated with increased risk of coronary artery disease,[97–99] an analysis of bariatric surgery on pulse pressure was undertaken. In particular, given systolic blood pressure increases over a person's lifespan and diastolic blood pressure decreases at a rate of 1–2 mm Hg per decade after

60 years of age,[100,101] a rapid increase in pulse pressure is expected after the age of 60. As such, Sjöström and colleagues[96] examined whether the increase in pulse pressure could be detected earlier in obese individuals and whether it could be decreased by gastric surgery. Their results demonstrated that the decrease in diastolic blood pressure was observed 10 years earlier in weight-stable severely obese controls (i.e., 49 years old at inclusion) and decreased at a rate of 3.2 mm Hg after a mean follow-up of 5.5 years (compared with 1–2 mm Hg every 10 years after 60 years of age in nonobese patients). In addition, pulse pressure increased faster in the control than the surgical group. Specifically, examining the change in blood pressure from inclusion to last observation, there was no difference in systolic blood pressure between the 2 groups (surgery: 1.4 mm Hg, 95% CI 0.4–2.4; control: 1.6 mm Hg, 95% CI 0.6–2.7), but there was a significant difference in diastolic blood pressure (surgery: –1.5 mm Hg, 95% CI –2.1 to –0.9; control: –3.2 mm Hg, 95% CI –3.8 to –2.5; $p < 0.001$). This resulted in a significant difference in pulse pressure (surgery: 2.9, 95% CI 2.1–3.7; control = 4.7, 95% CI 3.9–5.6; $p < 0.001$), suggesting that a maintained large weight reduction reduces the rate of increase in pulse pressure seen in weight-stable severely obese patients.

These results indicate that the effect of obesity and surgically induced weight loss on blood pressure is not a simple relationship. Although obesity is associated with increased risk of hypertension, many obese individuals are not hypertensive.[102] Indeed, reviews of smaller surgical series have shown that normotensive or mildly hypertensive obese individuals do not achieve a significant reduction in blood pressure after gastric bypass compared with individuals with substantially elevated blood pressure.[92] Therefore, while surgically induced, sustained weight loss does not seem to have a beneficial effect on blood pressure, it does lower pulse pressure which, as mentioned, is an independent predictor of coronary artery disease and cardiovascular mortality.[97–99]

## Conclusion

Obesity has a profound effect on blood pressure; total, LDL and HDL cholesterol; and T2DM, which are all risk factors associated with coronary heart disease. Given that coronary heart disease is a leading cause of mortality in adults in the United States[103] and that bariatric surgery results in a substantial improvement in coronary heart disease risk factors, the effect of bariatric surgery on the projected risk for coronary heart disease has been evaluated by several authors.[104,105] Using the Framingham risk score to estimate the postoperative reduction in 10-year risk for coronary heart disease, Vogel and colleagues[104] demonstrated that the risk of coronary heart disease decreased by 39% in men and 25% in women, with an overall decrease in predicted 10-year risk for coronary heart disease from 6% (SD 5%) and 4% (SD 3%), respectively ($p < 0.001$). In addition, subgroup analysis demonstrated that for those without coronary heart disease, men compared favourably with the age-matched general population, with a final 10-year risk of 5% (SD 4%) versus an expected risk of 11% (SD 6%; $p < 0.001$). Likewise, women achieved a level below the age-adjusted expected 10-year risk in the general population, with a final risk of 3% (SD 3%) versus 6% (SD 4%; $p < 0.001$).

Taken together, when the individual effects of bariatric surgery on obesity-related comorbidities are integrated, it results in a profound decrease in risk for coronary heart disease and overall mortality. In addition, given the low risk of surgery itself,[35] bariatric surgery has become is a powerful treatment option to help control the obesity epidemic.

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