Obesity, Diabetes, and Cardiovascular Diseases Compendium

Treatment of Obesity
Weight Loss and Bariatric Surgery

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Abstract: **This review focuses on the mechanisms underlying, and indications for, bariatric surgery in the reduction of cardiovascular disease (CVD), as well as other expected benefits of this intervention. The fundamental basis for bariatric surgery for the purpose of accomplishing weight loss is the determination that severe obesity is a disease associated with multiple adverse effects on health, which can be reversed or improved by successful weight loss in patients who have been unable to sustain weight loss by nonsurgical means. An explanation of possible indications for weight loss surgery as well as specific bariatric surgical procedures is presented, along with review of the safety literature of such procedures. Procedures that are less invasive or those that involve less gastrointestinal rearrangement accomplish considerably less weight loss but have substantially lower perioperative and longer-term risk. The ultimate benefit of weight reduction relates to the reduction of the comorbidities, quality of life, and all-cause mortality. With weight loss being the underlying justification for bariatric surgery in ameliorating CVD risk, current evidence-based research is discussed concerning body fat distribution, dyslipidemia, hypertension, diabetes mellitus, inflammation, obstructive sleep apnea, and others. The rationale for bariatric surgery reducing CVD events is discussed and juxtaposed with impacts on all-cause mortalities. Given the improvement of established obesity-related CVD risk factors after weight loss, it is reasonable to expect a reduction of CVD events and related mortality after weight loss in populations with obesity. The quality of the current evidence is reviewed, and future research opportunities and summaries are stated. (*Circ Res*. 2016;118:1844-1855. DOI: 10.1161/CIRCRESAHA.116.307591.)**

Key Words: cardiac metabolism ■ hypertension ■ inflammation ■ obesity ■ sleep apnea

Indications for Bariatric Surgery

The fundamental basis for bariatric surgery for the purpose of accomplishing weight loss is the determination that severe obesity is a disease associated with multiple adverse effects on health, which can be reversed or improved by successful weight loss in patients who have been unable to sustain weight loss by nonsurgical means. The criteria for surgical intervention were established by a National Institutes of Health consensus panel

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Nonstandard Abbreviations and Acronyms	
BMI	body mass index
CVD	cardiovascular disease
HDLC	high-density lipoprotein cholesterol
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
LABS	longitudinal assessment of bariatric surgery
LAGB	laparoscopic adjustable gastric banding
LDL	low-density lipoprotein
LDLC	low-density lipoprotein cholesterol
NAFLD	nonalcoholic fatty liver disease
OSA	obstructive sleep apnea
RYGB	Roux-en-Y gastric bypass
TBW	total body weight

in 1991.[1] Failure of medical treatment to accomplish sustained weight loss is common among people with severe obesity. The biological factors involved in the limitations associated with maintaining weight loss are powerful.[2,3] Intense lifestyle intervention can produce averages of ≈10% at 1 year and maintain weight loss at 5.3% over 8 years. The weight loss accomplished is highly variable but is sufficient to accomplish improvement in medical and comorbidity control.[4] Pharmacotherapy may enhance short-term as well as longer-term weight loss.[5] Specific criteria established by the National Institutes of Health consensus panel indicated that bariatric surgery is appropriate for all patients with body mass index (BMI; kg/m^2) >40 and for patients with BMI 35 to 40 with associated comorbid conditions. These criteria have held up over the ensuing 24 years to the present, although specific indications for bariatric/metabolic surgical intervention have been identified for people with less severe obesity, such as people with BMI 30 to 35 with type 2 diabetes mellitus. The indications for bariatric surgery are evolving rapidly to consider the presence or absence of comorbid conditions as well as the severity of the obesity, as reflected by BMI.[6]

Obesity-related comorbidity is defined as conditions either directly caused by overweight/obesity or known to contribute to the presence or severity of the condition. These comorbid conditions are expected to improve or go into remission in the presence of effective and sustained weight loss. Obesity-related comorbid conditions are listed in the Table.

The requirements for patient selection include the BMI criteria described earlier and failure of medical therapy. Specific criteria regarding designation of the failure of medical therapy have not been formalized but generally include treatment in a variety of medically supervised settings. An understanding or insight into the pathogenesis of obesity and the requirement to reduce energy intake substantially if major weight loss is to be achieved is a requisite.[7] Candidates for bariatric surgery must be assessed for appropriate surgical risk, including the presence of cardiovascular, pulmonary other system disease and control of these comorbid conditions. These principles apply to surgical procedures in general. It is entirely possible, for example, that patients with an exceedingly high risk profile for cardiovascular disease (CVD) will have experienced end events that indicate that perioperative risk is excessive, and the likelihood of reversing CVD by improving the risk profile is unlikely to be successful. However, examples of the most severely obese patients whose perioperative risk may be improved by weight loss include patients with congestive heart failure, related anasarca, respiratory failure, and inability to ambulate.

Table. Obesity Comorbid Conditions

Premature Mortality
Cardiovascular
Hypertension
Atherosclerotic CVD, myocardial infarction, stroke
Congestive heart failure
Cardiac arrhythmias
Metabolic
Type 2 diabetes mellitus, prediabetes
Dyslipidemia
Nonalcoholic fatty liver disease (NAFLD)/steatohepatitis
Inflammation
Pulmonary
Obstructive sleep apnea
Asthma
Musculoskeletal
Degenerative arthritis
Immobility
Pain
Reproductive
Polycystic ovarian syndrome (female)
Infertility
Sexual dysfunction
Genitourinary
Impaired renal function
Nephrolithiasis
Stress urinary incontinence
Central nervous system
Impaired cognition
Headache
Pseudotumor cerebri
Psychosocial
Impaired quality of life
Depression
Other psychopathology
Cancer

CVD indicates cardiovascular disease.

Preoperative psychological assessment is commonly done to identify patients who require preoperative intervention or disqualification altogether. Active substance abuse is a standard contraindication to surgery. Although a requirement for mandatory preoperative weight loss among all patients is not justified

by published literature, individual patients deemed to be at exceedingly high risk because of the severity of obesity, and its comorbid conditions are appropriate in selected cases. The literature surrounding psychological evaluation and its likelihood to predict success is evolving.[8] Psychological assessment before bariatric surgery may identify patients with psychopathology, such as major depression, binge eating disorder, substance abuse, among others, that may impact the decision to proceed with surgery or indicate referral for further preoperative assessment and intervention.[9] In addition, psychological assessment may contribute to predicting postoperative weight loss.[9–11]

Specific Bariatric Surgical Procedures

Surgical procedures in the past have been considered to function as restrictive in which the size of the gastric pouch is greatly reduced, malabsorptive in which malabsorption of nutrients contributes to weight loss, and a combination of restrictive and malabsorptive components. It is now clear that this construct is an oversimplification and, to some extent, inaccurate. There is ample evidence that neural and endocrine signaling pathways affecting eating behaviors, reduction of appetite, satiety, energy intake, and possibly physical activity are all operative to a variable extent (Figure).

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) was developed by Mason in the 1970s in response to unacceptable complication rates that followed ileojejunal intestinal bypass, a procedure which resulted in malabsorption, diminished food intake, and substantial weight loss with its associated benefits but unacceptable complication rates.[12] In this procedure, the stomach is transected, creating a gastric pouch of ≈1 ounce capacity. A Roux-en-Y gastrojejunostomy is done, thus diverting ingested nutrients from the body of the stomach, duodenum, and proximal jejunum. The vagal trunks are not disturbed but a variable number of branches to the body of the stomach are divided in the process of dividing the stomach. Associated endocrine changes are described below. Although malabsorption of energy-containing nutrients is minimal, if any, malabsorption of calcium, iron, and vitamin B12 and possibly other micronutrients occurs.

Sleeve Gastrectomy

In this procedure, ≈80% of the body of the stomach is resected, creating a tubular stomach based on the lesser curvature of the stomach. No gastrointestinal to small intestine anastomosis is required. Although some restriction on food intake may occur, gastric emptying is accelerated.

Biliopancreatic Diversion With Duodenal Switch

This is a more complex procedure in which a sleeve gastrectomy is done. An anastomosis between the proximal duodenum and bypassed intestine is accomplished, thereby creating a degree of malabsorption of nutrients. This procedure is infrequently performed because of higher incidence of short- and long-term complications.

Implantation of Devices

Adjustable Gastric Banding

An adjustable gastric band is placed about the proximal stomach to constrict the size of the gastric pouch and outlet. The rate of gastric emptying can be adjusted by a balloon connected to a subcutaneous port.

Intermittent Vagal Blockade

In this procedure, leads are placed about the vagal trunks at the diaphragm to produce intermittent vagal blockade. Weight loss occurs by reduction of appetite and establishment of early satiety. The intermittent blockade is hypothesized to avoid neural adaptation as occurred in the past with truncal vagatomy. A device for this purpose has been approved by the Food and Drug Administration.[13]

Gastrointestinal Endoscopic Devices

Although several endoscopically placed devices or suturing procedures are under development, placement of gastric balloon(s) has recently been approved by the Food and Drug Administration.[14]

Bariatric Surgery Safety

Although the benefits of weight loss among individuals with severe obesity, particularly those with comorbid conditions, are unquestioned, these benefits must be considered in the context of surgical complications. In the past, complications including perioperative mortality were as much as 10-fold more frequent than that occur at the present time. For example, a population-based study by Flum and Dellinger reported 2% mortality after gastric bypass, considerably higher than 0.5% commonly reported by those surgeons who chose to report their outcomes.[15] In response, the bariatric surgical community enacted several changes to result in this improved safety record. Included was the identification of the importance of surgeon and center experience, the establishment of pathways, care protocols, and quality initiatives, and incorporation of all of these aspects of care into an accreditation of centers program, presently administered by the American Society for Metabolic and Bariatric Surgery and the American College of Surgeons.[16] The transition to laparoscopic methodology occurred during the same time period and also contributed to the improved safety.

Incomplete retention or follow-up in reported clinical series has been a limitation to interpretation of registry-based reports on bariatric surgical safety.[17] The multicenter bariatric surgery research consortium funded by National Institutes of Health, known as longitudinal assessment of bariatric surgery (LABS), however, achieved 100% 30-day follow-up among 2458 participants.[18] The LABS Consortium–reported 30-day mortality was 0.3% in all patients, 0.2% for RYGB, and 2.1% for open gastric bypass. There was no mortality among laparoscopic adjustable gastric banding (LAGB) patients. A serious complication occurred in 4.1% of all patients, 4.8% laparoscopic gastric bypass, 7.8% open gastric bypass, and 1.0% LAGB. Patient factors in this study that predicted major complication include extremes of BMI, obstructive sleep apnea, inability to walk 200 feet, and a history of deep vein thrombosis. Factors in other studies include age, sex (male), other comorbidities, and smoking.[19] Provider factors predicting complications include surgeon and center experience.[20] Registries report slightly lower perioperative mortality as well as data regarding less severe complications, such as wound infection or dehydration, although among patients with 80%

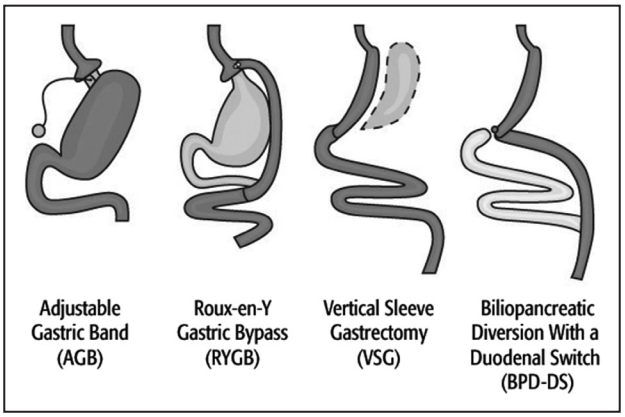

Figure. Diagram of surgical options. Image credit: Walter Pories, MD, FACS.

to 85% 30-day follow-up.[17,20] These mortality and complication rates compare very favorably to multiple commonly performed surgical procedures, such as coronary bypass graft, arthroplasty, cholecystectomy, and hysterectomy.[21,22]

Mid- and longer-term complications have been well described, although determination of their incidence is limited by progressively greater numbers of patients lost to follow-up.[23] These include intestinal obstruction, marginal ulcer, ventral hernia, and gallstones. Metabolic complications reported include nephrolithiasis and hypoglycemia. Mineral and vitamin deficiencies as well as weight regain are reported in variable numbers of patients. Reports of micronutrient deficiencies vary substantially as follows: iron, 33% to 55%; calcium/vitamin D, 24% to 60%; vitamin B12, 24% to 70%; copper, 10% to 15%; and thiamine, <5%.[24] Established guidelines recommend routine nutrient supplementation to include multivitamins, iron, minerals, calcium, and vitamin D.[25]

Complications specific to LAGB placement continue to occur in the longer-term at ≈2% per year. These long-term complications include erosion of the gastric wall by the band, slippage or herniation of the body of the stomach, thereby creating obstruction within the band, and complications of the port, including infection. Combined with disappointing long-term weight loss (see below), application of LAGB in the United States and Europe has diminished dramatically recently.[26]

Regarding gastrointestinal endoscopic devices, the literature looks promising but does not have long-term data.[13] Weight loss is modest while the device safety is good. The safety record of the Food and Drug Administration–approved device is excellent but the sustainability of the long-term weight loss after the approved 6-month intervention remains to be determined.[27]

In summary, both perioperative and long-term complications occur after all bariatric surgical procedures. Multiple steps have been taken in the recent years to reduce perioperative mortality to the presently reported, minimum comparable to other commonly performed surgical procedures. Longer-term complications requiring reoperation or micronutrient deficiencies require careful surveillance and prompt intervention. These complications are generally judged to occur with sufficiently low frequency and severity so as to not constitute a contraindication to the performance of bariatric surgery in general.

Weight Loss After Bariatric Surgery

Weight loss after bariatric surgery has been studied in both short- and long-term settings. With weight loss being the primary objective of bariatric surgery, mean weight loss is uniformly reported. It is important to recognize, however, the high variability of weight loss after apparently standardized operative procedures, such as RYGB or LAGB.[28] After RYGB, the LABS consortium reported similar and rapid weight loss 6 months after surgery by stratifying of weight loss into 5 separate trajectories ranging from 12% total body weight (TBW) loss to 45% TBW 3 years after surgery. Similarly, for LAGB, trajectories are identified for most but not all patients 1 year after surgery. Factors involved in the high degree of variation of weight loss have been examined and reported but do not fully explain the extent of the variability. Predictors of weight loss vary among several reports and include both patient and provider factors. These factors include but are not limited to the presence of specific comorbid conditions, such as diabetes mellitus, sex, age, and behavioral variables, including physical activity and eating behaviors.[10] Weight loss after RYGB in the first 3 years reported 30% to 35% TBW.[29] Initial reports of weight loss after LAGB in Australia suggested that weight loss was similar to that seen after RYGB. Data from the United States as well as Europe, however, have not confirmed comparable weight loss after LAGB, closer to 15.9% TBW at 3 years.[21] As noted earlier, this lesser weight loss, compared with RYGB, has led to a substantial reduction in the application of LAGB as treatment for severe obesity. The weight loss after biliopancreatic diversion/duodenal switch tends to be slightly greater than that after RYGB, whereas weight loss after sleeve gastrectomy is comparable or is slightly less than RYGB in several reports.[30–33] Those studies with nonsurgical comparator groups, primarily the Swedish Obese Subjects trial and a prospective clinical trial with a population base comparator from Utah, indicate that the nonsurgical patients do not experience long-term weight loss. This is not unexpected, given the requirement that patients selected for surgery undergo and fail medical treatment before selection for surgical intervention. Longer-term follow-up has been reported by Pories as well as the Swedish and Utah studies. All show rapid weight loss during the first 12 months after RYGB followed by modest regain of weight until approximately year 3 to 5. After year 3 to 5, weight loss tends to be maintained in the 30% TBW range.[34–36] Thus, it is well established that maintenance of weight loss after RYGB at 10 to 20 years is maintained.

In general, procedures less invasive or those that involve less gastrointestinal rearrangement such as LAGB, vagal blocking, and endoscopic procedures such as balloon placement accomplish considerably less weight loss but have substantially lower perioperative and longer-term risk. A research need is a more effective determination of the likely weight loss that will be achieved after any of these interventions, including lifestyle intervention and medication,

and the amount of weight loss needed to achieve a specific response such as improved control or remission of a specific comorbid condition. At such time, as a more accurate identification of the weight loss required to achieve a specific clinical outcome and the relative risk involved is determined, it will be possible to more accurately identify appropriate candidates for specific procedures, taking into account the expected weight loss and risk profiles.

Expected Benefit on CVD Risk Factors

The ultimate benefit of weight reduction, whether medical or surgical, relates to the reduction of the comorbidities, quality of life, and all-cause mortality. Despite the importance of assessing these risks and taking steps to implement effective medical management with variable success,[37] surgery has proven to be more effective.[35,36] To be covered in this section are the following: body fat distribution, dyslipidemia defined as hypertriglyceridemia and low high-density lipoprotein cholesterol (HDLC) and variable increases in low-density lipoprotein (LDL) cholesterol (LDLC), hypertension and prehypertension, insulin resistance, diabetes mellitus and prediabetes mellitus, nonalcoholic fatty liver disease (NAFLD), inflammation (high-sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], white blood cell count, oxidized LDL, intracellular adhesion molecule-1, and adiponectin), vascular reactivity, and obstructive sleep apnea.

Body Fat Distribution

The relationship of obesity to CVD events relate in part to alterations in body fat distribution, that is, increased central/visceral versus subcutaneous/peripheral, the so-called metabolic syndrome phenotype.[38–40] This distribution of excess body fat relates to an excess delivery of free fatty acids to the liver wherein defects in insulin action result with subsequent impact on other components of the metabolic syndrome, that is, dyslipidemia, glucose intolerance, NAFLD, and inflammation among others.[41] With medical weight loss, percentage reductions in visceral adipose tissue are similar to or exceed other adipose tissue depots but this relative benefit is somewhat reduced with more weight loss.[42]

In general, in patients without diabetes mellitus, the relative amounts of loss of visceral adipose tissue from 3 to 12 months postbariatric surgery are similar or greater than the percentage loss of total or subcutaneous adipose tissue,[43–45] but at 24 months were variably greater in the visceral depot.[46,47] After LABG, a preferential mobilization of visceral fat was observed at 2 and 6 months, as compared with total and subcutaneous AT; but this outcome was reserved only for patients with excessive amounts of visceral adipose tissue before surgery, and this preferential visceral fat reduction occurs only in those.[47] When changes in body composition were compared after malabsorptive biliointestinal bypass and restrictive LAGB during a 4-year follow-up, the effects of biliointestinal bypass were greater on total fat loss and trunk fat.[48] When omentectomy accompanies a laparoscopic RYGB procedure, changes in glucose homeostasis, lipid levels, and adipokine profile at 90 days postoperatively have been variably reported.[49,50]

Dyslipidemia

The dyslipidemia of obesity reflects mostly the insulin-resistant metabolic environment that accompanies excess body fat. This includes hypertriglyceridemia, lower levels of HDLC, variable increases in apolipoprotein B and very low density lipoprotein cholesterol, and small dense LDL and high-density lipoprotein.[51] Although LDLC can be increased in moderately to severely obese patients, this is not nearly as prevalent as the aforementioned lipid and lipoprotein abnormalities. In a meta-analysis of 75 papers in which follow-up lipids were measured ≤4 years post RYGB, baseline and follow-up levels of LDLC were reported in 48 studies, and baseline LDLC was123±7 mg/dL.[52] Although heterogeneity among studies for LDLC and all other lipids was high, subgroup analyses revealed reductions in LDLC by intervals of 1 month up until 4 years (standard mean difference −1.31 to −0.52, 95th% confidence intervals (CI); $P<0.00001$). HDLC levels were assessed in 47 studies. Herein, a time-dependent trend was noted. At an interval ≤6 months, no significant change in HDLC was seen; however, by 12 months, an increase was seen (standard mean difference +1.10, +0.57 to +1.63, 95% CI; $P<0.0001$), an effect maintained through all subsequent time points assessed, including at 4 years. Plasma triglycerides were examined in 55 studies with no change at 1 month but highly significant effects of RYGB on triglycerides were seen ≤4 years (standard mean difference −0.57, 95% CI, −0.76 to −0.37; $P<0.00001$).

From another large series that included 73 studies in which patients were examined for nearly 4 years, metabolic surgery produced a decrease in LDLC from 116 to 90 mg/dL and triglycerides from 188 to 127 mg/dL and an increase in HDLC from 46 to 55 mg/dL.[53] When data from the LABS-2 study were examined, the prevalence of dyslipidemia improved at 3 years post RYGB in 62% of patients[28] and fasting hypertriglyceridemia (>200 mg/dL) remitted in 86% patients, while low HDLC (<40 mg/dL) in 86%.[24] Important to consider is that all of these studies did not report data about the use of lipid-altering medications post surgery.[54]

The reduction in LDLC ≤2 years post metabolic surgery, however, only seems to occur for operations with more weight reduction, that is RYGB or biliopancreatic diversion versus sleeve gastrectomy or LAGB, although increases in HDLC and reductions in triglycerides can occur with all.[55–58] Plasma levels of the proatherogenic lipoprotein, lipoprotein (a), are not changed after metabolic surgery.[59,60]

Hypertension

Obesity is often associated with hypertension (blood pressure >140/90), and in the Edmonton Obesity Staging System, 98% of 5787 obese patients had at least one comorbidity, and hypertension was present in 76%.[61] Although difficult to assess from many publications that cite population statistics, the prevalence of hypertension in the severely obese population is ≈65%,[62] not that different from the prevalence in Edmonton. However, from the most recent data from National Health and Nutrition Examination Survey (2010), 52% of American subjects with a BMI ≥35 kg/m^2 had treated or untreated hypertension versus 43% with a BMI ≥30 but ≤35 kg/m^2.[63] Now, how effective is metabolic surgery in correcting this common comorbidity of excess body fat?

The effects of metabolic surgery on the prevalence of hypertension are variable, procedure-related, and time-dependent. During the active weight loss phase, blood pressure decreases and antihypertensive drugs are often discontinued.[64] However, after weight stabilization, the results are less clear, perhaps related to the duration of hypertension preoperatively. In a systematic review and meta-analysis of 21 studies, using a variety of surgical approaches reduced the relative risk of hypertension at intervals between 24 and 50 months by 46±8%, and hypertension risk reached a nadir when BMI was reduced by 10 kg/m^2.[65] Data from LABS-2 demonstrated that cohort persistent remediation from hypertension at 3 and 6 years was nearly 40%,[28] and the Utah-Obesity study demonstrated a 2- and 6-year relative risk of remission of hypertension of 8.2 and 2.90, respectively.[66] However, the Swedish Obesity Study revealed recidivism of hypertension at 6 to 8 years of follow-up with no significant difference from baseline.[67] Whether this relates to permanent changes in the arterial wall based on years of hypertension preoperatively remains unclear.

Diabetes Mellitus and Prediabetes Mellitus

The last decade has been one to not only document the benefit of metabolic surgery in patients with type 2 diabetes mellitus and glucose tolerance, but produce sufficient data from randomized controlled trials to render metabolic surgery as an option for the treatment of type 2 diabetes mellitus. The most recent update and convincing study is from the Rubino group that performed an open-label, randomized controlled trial to compare medical or surgery by RYGB or biliopancreatic diversion in 60 patients aged 30 to 60 years with a BMI of ≥35 kg/m^2 and a history of type 2 diabetes mellitus of at least 5 years, and 53 completed a 5-year follow-up.[68] Diabetes mellitus remission was defined at 2 years, as a hemoglobin A1c concentration of ≤6.5% and a fasting plasma glucose of ≤5.6 mmol/L without pharmacological treatment for 1 year. Overall, 50% of the 38 surgical patients sustained a diabetes mellitus remission at 5 years, compared with none of the 15 medically treated patients (P=0.0007). A similar medical versus surgical trial for the treatment of type 2 diabetes mellitus was performed in 150 patients with uncontrolled type 2 diabetes mellitus (hemoglobin A1c –9.3±1.5%) by Schauer et al with a 91% follow-up at 3 years.[69] The primary end point of a hemoglobin A1c of ≤6.0% was met by only 5% of the medical group versus 38% of RYGB patients and 24% with sleeve gastrectomy, all in the setting of much less use of glucose-lowering medications in the surgical groups than in the medical-therapy group. As expected, the amount of weight reduction was only ≈4.0% in the medical group versus 22% to 24% in the surgical groups. In 4 randomized trials wherein RYGB was further compared with sleeve gastrectomy, there was no significant difference between procedures with the reduction in hemoglobin A1c or fasting plasma glucose or the change in weight, BMI, or the number or type of drugs used to treat type 2 diabetes mellitus.[30,31] Overall, the amounts of weight loss have been a definite predictor of diabetes mellitus remission. When LABG versus RYGB was controlled for weight loss, RYGB was clearly superior to LABG in the induction of remission. It has, therefore, been demonstrated that both weight loss and RYGB contribute to the superior remission of diabetes mellitus after gastric bypass compared with LABG.[70] Recurrence of diabetes mellitus after induction of remission may occur in as many as 58% of patients 15 years after bariatric surgery, predominantly in those who had gastric banding.[36] Further research is needed to determine the long-term benefit of gastric bypass and sleeve gastrectomy in patients with type 2 diabetes mellitus.

A related glucose-centric topic is the prevention of type 2 diabetes mellitus in severely obese patients by metabolic surgery. Using a systematic review and meta-analysis wherein medical versus surgical approaches were examined in patients with impaired fasting glucose or impaired glucose tolerance, nonsurgical approaches reduced new-onset type 2 diabetes mellitus by 14% to 56% using several different interventions, whereas bariatric surgery was 90% effective.[71] The factors that were associated with effectiveness were weight loss, young age, and fasting insulin levels. In a separate systematic review and meta-analysis that extended the outcome to an admixture of patients with normal glucose tolerance, impaired fasting glucose with or without impaired glucose tolerance at baseline, medical strategies reduced new onset type 2 diabetes mellitus from 15% to 63% based on the various types of intervention, whereas metabolic surgery was 84% successful.[72]

Nonalcoholic Fatty Liver Disease

NAFLD is diagnosed by either imaging or histology with no alternative explanation for fatty liver, including alcoholic liver disease. Of interest many times, liver transaminases are normal with biopsy-proven NAFLD.[73] The prevalence varies around the world but is typically more common in Western nations (20%–40%), and using proton magnetic resonance spectroscopy in 2287 subjects from a multiethnic, population-based sample (32% white, 48% black, and 18% Hispanic), the prevalence was highest in Hispanics (45%), with 33% in whites and 24% in blacks.[74] This high prevalence is similar to that of the metabolic syndrome and reflects the insulin resistance related to both. NAFLD is present in ≈90% of patients who qualify for metabolic surgery, and ≈33% of these have biopsy-proven nonalcoholic steatohepatitis,[75] a precursor of more serious liver disease, including cirrhosis, and need for transplantation. In fact, patients with nonalcoholic steatohepatitis by biopsy have an increased risk of death within a median follow-up of 10.2 years after bariatric surgery.[76] Although medical management including weight loss, pioglitazone, vitamin E, pentoxifylline, ursodeoxycholic acid and most recently liraglutide has had variable effect, bariatric surgery has proven more effective.[77]

Data from the Swedish Obesity Study, a nonrandomized study of 3570 obese subjects which compared several types of bariatric operations including RYGB and gastric banding to medical management for ≤10 years, revealed a reduction in alanine aminotransferase at 2 years that was maintained at 10 years versus the nonsurgical control group.[78] Retrospective or cohort studies in general have demonstrated that improvement of NAFLD is more likely after RYGB than after other interventions; however, data at present are insufficient to indicate reductions in liver-specific mortality, liver transplantation, or quality of life.[79] One study examined the impact of metabolic surgery on NAFLD in 381 patients at baseline with second and

third biopsies at 1 and 5 years, postoperatively.[80] At both 1 and 5 years, major reductions in steatosis and ballooning degeneration ensued with no change in inflammation. And in the 27% of patients diagnosed with nonalcoholic steatohepatitis, steatosis and ballooning also improved after 5 years, but fibrosis and inflammation did not. In some patients, fibrosis actually increased, an outcome that was associated with more severe obesity and insulin resistance. Perhaps the largest study to examine the benefit of bariatric surgery was performed in 1236 obese patients (BMI −48.4±7.6 kg/m^2) wherein RYGB (n=681) was compared with adjustable gastric banding (n=555).[81] At baseline, NAFLD was present in 86% and as severe in 22% patients. In general, RYGB patients had a higher BMI and more severe NAFLD. All NAFLD parameters improved after surgery (P<0.001) but improved more after RYGB than after gastric banding and the amount of weight loss related to this benefit. Overall, metabolic surgery seems to be the best treatment for NAFLD in patients who qualify for surgery.

Inflammation

Systemic inflammation is routinely assessed by nonspecific metrics such as the erythrocyte sedimentation rate or hsCRP, but other biomarkers can also be utilized, that is, IL-6, white blood cell count, oxidized LDL, intracellular adhesion molecule-1, and adiponectin. After medically managed weight reduction, in general, the fall in hsCRP relates to the amount of weight reduction.[82,83] Adiponectin is an adipokine that is not proinflammatory but anti-inflammatory and also is associated with insulin sensitivity. A systematic review that examined weight loss using low calorie diets and exercise reported an 18% to 48% increase in adiponectin.[84] Of note, the one study that reported an increase in adiponectin by 48% was a Mediterranean diet that resulted in a 15% weight reduction, suggesting this change is also related to the amount of weight loss.[85]

Subjects undergoing metabolic surgery that lost 33% of their original weight had a highly significant median hsCRP reduction from 0.83 to 0.18 mg/d ensued.[86] In another study wherein gastric stapling was compared with gastric banding and patients were defined at baseline as low versus high CVD risk based on a hsCRP of <1.0 mg/mL versus >3.0 mg/mL, the mean reduction in hsCRP for high CVD risk patients was greater for gastric stapling versus gastric banding, −1.10±0.94 mg/L versus −0.67±0.82 mg/L, respectively.[87] After sleeve gastrectomy levels of hsCRP and IL-6 decreased and adiponectin increased, however, these measurements were made at 1 year, a time at which nadir weight and weight stability may have not been assured.[88] In another 1-year analysis after metabolic surgery, there was a significant decrease in levels of IL-6 (P<0.001) and hsCRP (P<0.001) and increase in plasma levels of adiponectin (P<0.001), and levels of IL-6 and hsCRP correlated with BMI.[89] However, in another study, 1-year post-gastric banding, hsCRP levels decreased from 1.33±1.21 mg/dL to 0.40±0.61 mg/dL but IL-6 and tumor necrosis factor-α levels did not change.[90] Additional data also support the variability of metabolic surgery to decrease levels of IL-6.[90–92] In a retrospective study in which 62 subjects who underwent a RYGB and a median follow-up of 15 months, there was a greater reduction in hsCRP with more surgical weight loss.[93] This relationship between change in BMI/weight postoperatively and reduced inflammation also relates to adiponectin.[94] Of interest, when patients with or without remission of type 2 diabetes mellitus post RYGB were compared ≤24 months postoperatively, the nonremission group had a higher number of leukocytes (6867 versus 5424), hsCRP (0.27 versus 0.12 mg/dL), MCP-1 (monocyte chemoattractant protein-1; 118 versus 64 ng/mL), and lower adiponectin (9.4 versus 15.4 ng/mL) than the remission group.[95] Additional benefits of gastric bypass on inflammation and CVD risk may also relate to reduced levels of oxidized LDL and lipoprotein-associated phospholipase A2.[96]

Vascular Reactivity

Endothelial dysfunction, a nitric oxide–dependent component of reduced vascular reactivity, is defined as an imbalance between relaxing and contractile endothelial factors that is common in patients with severe obesity.[97,98] After weight loss, there is evidence that improvements in endothelial function can occur, but this outcome is inconsistently apparent, and convincing evidence for normalization is lacking.[99]

At a early interval after RYGB, weight loss led to significant improvements in brachial artery diameter and endothelial-independent vasodilation.[100] A similar reduction in flow-mediated dilatation was noted at 6 months S/P gastric banding.[101] When subjects lost an average of 33% of their original weight, flow-mediated dilation showed significant improvements after surgery from 7.4% to 18.9% (P<0.001).[86] A recent systematic review included 8 studies on flow-mediated dilation (9 data sets; 269 patients) and 4 on nitrate-mediated dilation (4 data sets; 149 patients). After 3 to 24 months following 4 different types of bariatric surgery (mostly RYGB), there was a significant improvement in flow-mediated dilation (mean difference: 5.65%; 95% CI: 2.87, 8.03; P<0.001), whereas nitrate-mediated dilation did not change (mean difference: 2.173%; 95% CI: −0.796, 5.142; P=0.151), and the percentage change in BMI was associated with changes in flow-mediated dilation (Z=−4.26, P<0.001) and nitrate-mediated dilation (Z=−3.81, P<0.001).[102] Most of these observations of vascular reactivity were performed at relatively brief intervals after surgery; thus, as for hypertension, the duration of reduced vascular reactivity associated with obesity may contribute to the response post metabolic surgery.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is common in patients with severe obesity, ≈35% to 45% of patients at the time of bariatric surgery.[103,104] With nonsurgical approaches to weight reduction and OSA, the benefit typically relates to the amount of weight reduction and the severity of the OSA, and in general, metabolic surgery is more successful than nonsurgical approaches.[104] A systematic review of the metabolic surgical literature examined 69 studies in which 13 900 patients were included and RYGB, sleeve gastrectomy, gastric banding and BPD were compared.[103] Although BPD was associated with the best results and gastric banding with the least beneficial outcome on OSA, all operations realized major reductions with >75% of patients experiencing resolution or at least some improvement.

When a systematic review of the surgical versus nonsurgical approach to modifying obesity-related sleep disordered

breathing (not OSA) was inspected, 19 surgical (n=525) and 20 nonsurgical (n=825) studies reporting primary end points of change in BMI and apnea hypopnea index were examined.[105] Unfortunately, the surgical versus nonsurgical groups were not matched in terms of BMI or the amount of weight reduction, 51.3 versus 38.3 kg/m^2 and −11.9 versus −3.1 kg/m^2 BMI units, respectively. However, both groups experienced a benefit in apnea hypopnea index, 29/h versus 11/h, respectively. Despite apnea hypopnea index being substantially reduced, clinical OSA indicating continued continuous positive airway pressure use was common.[106]

Mechanisms for Cardiometabolic Benefit of Metabolic Surgery

Gut hormones, changes in bile acid metabolism, and the microbiome all relate to the benefits of metabolic surgery on cardiometabolic risk.[107] Changes in gut hormones relate to changes in energy balance and include increases in peptides that increase satiety, that is, glucagon-like peptide-1, gastric inhibitory polypeptide, peptide tyrosine tyrosine or pancreatic peptide $YY_{3–36}$, oxyntomodulin, and gastrin) and those that reduce hunger-promoting factors, that is, ghrelin.[108] Moreover, although studies done at intervals ≤12 months postmetabolic surgery have demonstrated reductions in energy expenditure when expressed per fat-free mass, modest increases were identified when data were expressed per body weight.[109] Thus, some contribution from both sides of the energy balance equation may be operational in maintaining reduced weight after surgery.

Bile acid metabolism clearly changes postmetabolic surgery and mechanisms to implicate these alterations to benefit include their beneficial effects on satiety, gut hormones, incretins, energy metabolism, and the gut microbiome, with the majority of these effects mediated via the bile acid receptors farnesoid X receptor and transmembrane bile acid receptor 5.[108] Elevation of bile acids is commonly seen postmetabolic surgery,[110] and in murine models of atherogenesis activation of farnesoid X receptor and transmembrane bile acid receptor 5 reduced the expression of proinflammatory cytokines and chemokines within the arterial wall and atherosclerotic plaque volume.[111] Finally, the gut microbiome is modified after metabolic surgery, and this change seems to play an important role in the metabolic benefits gained from bariatric surgery. Two types of surgeries, RYGB and VBG, result in similar changes in the microbiome, an effect that can be maintained for at least a decade. Moreover, when microbiota from bariatric surgery patients are transferred into germ-free mice, decreases in fat mass ensue.[112] All of these mechanisms may be closely related and reflect changes in glucose, lipid/lipoprotein metabolism, and inflammation that ultimately may be the mediators of reduced CVD risk. This is clearly an incredibly important area of research that may be applicable far beyond metabolic surgery and related weight reduction.

Current Evidence for Reduction in CVD Events Versus Impact on All-Cause Mortality

Effect of Bariatric Surgery on Long-Term Survival

It has not been possible to conduct a prospective randomized clinical trial of bariatric surgery versus continued nonsurgical treatment (usual care) of severe obesity adequately powered and of sufficient duration to assess the impact on CVD events and longevity. Given the improvement of established obesity-related CVD risk factors after weight loss, it is reasonable to expect a reduction of CVD events and related mortality after weight loss in populations with obesity. The Look Action for Health in Diabetes (Look AHEAD) trial randomized 5145 individuals with obesity and with type 2 diabetes mellitus to intensive lifestyle intervention or usual care.[113] After median follow-up of 9.6 years, weight loss was 6.0% in the intensive lifestyle intervention group versus 3.5% in the usual care participants. Despite improved CVD risk factor status for all metrics except LDLC, a reduction of CVD events or mortality was not demonstrated. In contrast, the Swedish Obese Subjects study reported weight loss after a variety of bariatric surgical procedures to be 17% 5 years after surgery, 16% in 15 years, and 18% in 20 years postsurgery.[114] Weight was essentially unchanged in the usual care group matched for multiple clinical parameters. This weight loss in the surgical group was associated with a reduction of CVD events: adjusted hazard ratio 0.67; 95% CI: 0.54 to 0.83; P<0.001. In addition, mortality was reduced: hazard ratio 0.71; P=0.001.[115] More recently, a systematic review and meta-analysis of 14 studies included 29 208 patients who underwent bariatric surgery, with a follow-up 2 to 14.7 years.[116] These studies took place in the United States, Canada, Italy, Australia, and Sweden. Although not analyzed or reported by Kwok et al, weight loss among the studies varied from 15% to 30% or more depending primarily on the specific bariatric surgical procedure performed. Overall mortality was reduced >50% (odds ratio 0.48). The incidence of myocardial infarction (odds ratio 0.46) and stroke (odds ratio 0.49) was also reduced.[117]

Quality of Evidence

The great majority of published literature regarding bariatric surgery consists of observational data.[29,35] A limited number of these observational trials with several-year follow-up have constructed comparator groups, matched from nonsurgical populations. Medical and ethical considerations have prevented conduct of an adequately powered randomized control trial to test the hypothesis that bariatric surgery is superior to usual care.[53,66] However, recently, several randomized control trials have successfully been conducted evaluating medical versus surgical intervention as primary treatment for type 2 diabetes mellitus.[68,114]

Summary and Conclusions

It is reasonable to hypothesize that the greater improved CVD and mortality after bariatric surgery compared with lifestyle intervention is a function of the substantially greater weight loss that follows surgery, although neuroendocrine factors after gastrointestinal modification may also contribute. The survival benefit occurs primarily as the result of reduced CVD death, although reduced death because of all types of cancers also contributes substantially to this survival benefit.[118–120]

Disclosures

None.

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