

# Impact of Obesity and Bariatric Surgery on Cardiovascular Disease

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The prevalence of obesity is increasing rapidly and has become a major public health problem worldwide. More than half of the adult population in the United States is overweight or obese, and an estimated 5 to 10 million individuals are considered morbidly obese. With this increase in the prevalence of obesity has come an increase in the prevalence of heart disease. Studies indicate that body weight is an important independent predictor of the development of any heart disease and that its impact is felt disproportionately among women [1]. Obesity is associated particularly with an increased risk of heart failure: for each increment of 1 kg/m<sup>2</sup> in body mass index (BMI), there is a 5% increase in the risk of heart failure for men, and 7% for women [2].

Obesity leads to significant morbidity and mortality, and it is speculated that its increasing prevalence may begin to shorten overall life expectancy in the near future [3]. The morbidity and mortality rates rise proportionally to the degree of obesity, with a linear correlation demonstrated between BMI and mortality [4]. The risk of premature death in morbid obesity is doubled compared with nonobese individuals, and the risk of death from cardiovascular disease is increased fivefold [5].

Nonsurgical weight loss programs based on some combination of diet, exercise, and behavior modification commonly are ineffective in the long term [6]. Bariatric surgery offers an additional effective treatment option for long-term weight management for morbidly obese patients. In this article, we propose to review the current literature regarding the impact of obesity and bariatric surgery on cardiovascular disease.

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## **Impact of obesity on cardiovascular risk factors and disease**

It has become increasingly apparent that morbid obesity carries a heavy cardiovascular risk burden. Most cardiovascular risk factors and cardiovascular diseases occur with greater frequency and severity in patients who are morbidly obese. Given that cardiovascular disease represents by far the most common cause of serious morbidity and mortality in industrialized nations, the dramatic increase in obesity and morbid obesity seen over the last decade is clearly a profound public health concern [7].

### *The scope of cardiovascular risk factors and diseases impacted by obesity*

Morbid obesity increases the frequency and severity of the metabolic syndrome, defined by the National Cholesterol Education Project Adult Treatment Panel III as the coexistence of any three of the following five features: central obesity, high serum triglyceride levels, low serum high-density lipoprotein (HDL)-cholesterol levels, hypertension, and elevated fasting blood glucose level. The metabolic syndrome is a potent risk factor for cardiovascular disease [8]. Related metabolic abnormalities commonly observed in obese patients include insulin resistance, hyperinsulinemia, and type 2 diabetes mellitus. Other risk factors for cardiovascular disease that are more prevalent in obese patients are obstructive sleep apnea and proinflammatory and prothrombotic states. Through these risk factors and independent of them, obesity increases the risk of the following cardiovascular diseases: systemic hypertension, coronary artery disease, heart failure, and cardiac dysrhythmias [9]. Each of these diseases is more difficult to treat when it occurs in the presence of morbid obesity, and the functional limitation imposed by each is more pronounced in morbidly obese patients.

### *Metabolic syndrome and its components*

With the recent increase in rates of obesity and morbid obesity, a parallel increase in rates of metabolic syndrome has developed. The Third National Health and Nutrition Examination Survey (NHANES III) reported a nearly 24% prevalence of metabolic syndrome in US adults [10]. Disturbingly, there also appear to be rapid increases in its prevalence among children [11] and in countries in which it was until recently relatively uncommon [12]. Obesity, beyond being a cardinal feature of the metabolic syndrome, is also a critical trigger for it: a recent study suggested a prevalence of metabolic syndrome in obese patients that was nearly 10-fold higher than that in nonobese patients [13]. Obesity is so tightly linked with insulin resistance, hyperinsulinemia, and type 2 diabetes mellitus as to lead one group to discuss the global epidemic of “diabesity” [14]. In addition to the typical lipid abnormalities of elevated serum triglycerides and depressed serum HDL levels, obesity is also associated with elevated levels of oxidized low-density

lipoprotein (LDL), an especially atherogenic lipoprotein [15]. Proinflammatory and prothrombotic states are common in patients with the metabolic syndrome (although uncommonly included in its definition) and also appear common in obese patients [16,17]. Recent evidence strongly suggests that the inflammatory aspects of obesity may be pivotal in the metabolic derangements that frequently ensue [18]. Inflammation and thrombosis now have well-established pathogenic links to many cardiovascular diseases.

### *Obstructive sleep apnea*

Obese patients have a high prevalence of obstructive sleep apnea (OSA). Although it is estimated that 7% of all adults have significant OSA [19], the risk triples for each standard deviation increase in BMI [20]. The prevalence of OSA in patients undergoing evaluation for bariatric surgery may approach 80% [21]. Obstructive sleep apnea has numerous adverse sequelae, including associations with several cardiovascular diseases, including systemic and pulmonary hypertension, coronary artery disease, heart failure, stroke, and atrial fibrillation [22].

### *Hypertension*

Systemic hypertension, like obesity and metabolic syndrome, has reached epidemic proportions in the United States. There is a clear link between obesity and hypertension, with data from NHANES III indicating an approximately threefold increase in the prevalence of hypertension in obese versus lean patients [23]. Although OSA appears to confer much of this increased risk [22], other mechanisms, including direct hemodynamic alterations, inflammation, and neurohormonal activation likely also play a role.

### *Coronary artery disease*

Given the tight associations between obesity, the metabolic syndrome, and hypertension, and the potent risk conferred by the metabolic syndrome and hypertension for the development of atherosclerosis, it is unsurprising that obesity is associated with an increased prevalence of coronary artery disease. Pathological studies have shown an association between obesity early in life and the formation of atherosclerotic lesions [24]. A number of studies have documented a clear association between obesity and clinically manifest coronary artery disease [16]. Furthermore, the diagnostic evaluation of these patients and their subsequent revascularization by either percutaneous or surgical means can be a challenge. Most recent data have suggested, however, that current diagnostic tools and revascularization techniques are safe and effective in this population [25–28].

### *Heart failure*

In the general population, longstanding obesity is a risk factor for heart failure even in the absence of traditional risk factors for coronary artery

disease [29]. Over time, morbid obesity results in structural myocardial changes, including increased left ventricular (LV) dimensions and mass, and impaired LV relaxation and systolic function [30]. The mechanisms underlying these changes are not well understood but likely include altered loading conditions related to associated comorbidities such as hypertension and OSA, insulin resistance, and abnormal neurohormonal and cytokine profiles. Surprisingly, despite being a risk factor for the development of heart failure, data suggest that obesity is protective in patients with established heart failure [31], a phenomenon termed *the obesity paradox*. This observation has not thus far been extended to morbidly obese patients. Both morbid obesity and heart failure markedly reduce functional capacity [32], and patients with the combination of the two conditions have severe functional limitation and poor survival. In addition, the presence of advanced heart failure makes weight loss by conventional means nearly impossible for these patients. Finally, the presence of morbid obesity generally disqualifies patients from consideration for cardiac transplantation.

### *Cardiac dysrhythmias*

Obesity increases the risk of cardiac dysrhythmias, including atrial fibrillation [33–35], ventricular ectopy, and sudden cardiac death [36,37]. There are numerous potential explanations for this association. Obesity is, again, associated with hypertension, OSA, coronary artery disease and its risk factors, and changes in cardiac structure and function, all of which are independent risk factors for cardiac dysrhythmias. More mechanistically, obesity has been shown to be associated with abnormalities in cardiac repolarization, as evidenced by prolongation of the QT interval and by an increase in late potentials [38,39]. In addition, pathological abnormalities of the cardiac conduction system have been observed in obese patients after sudden cardiac death [40].

### *Stroke*

Obesity has been shown recently to increase the risk of both ischemic and hemorrhagic stroke, independent of associated conditions known to increase stroke risk (metabolic syndrome, hypertension, OSA) [41]. In this study, obese male patients faced twice the risk of stroke as did their lean counterparts, and each one-unit increase in BMI over 25 kg/m<sup>2</sup> increased the risk of stroke by approximately 5%. The mechanisms for this independent association are not completely known but likely involve inflammatory and thrombotic pathways.

## **Impact of obesity on cardiac structure and function**

Chronic obesity is associated with changes in cardiac structure and function, which appear to be dependent on both the severity and the

duration of obesity [30]. Left ventricular hypertrophy and increased cardiac mass generally are observed in obese patients, and measures of diastolic left ventricular function often are abnormal, even in the absence of overt heart failure [42]. Left [30] and right [43] ventricular dilatation and impaired systolic function may also occur in obese patients. Fatty infiltration of the heart (*adipositas cordis*) has been reported in obese patients and may contribute to the abnormalities of cardiac structure and function observed [5]. Hemodynamic alterations are known to exist in obese patients, primarily increased cardiac output and filling pressures. The mechanisms of altered cardiac structure and function in obesity may include altered hemodynamic load, metabolic abnormalities, inflammation, coronary artery disease, and, perhaps, direct myocardial effects of adipocyte-related hormones.

### **Effects of bariatric surgery on cardiovascular risk factors**

Numerous studies have documented the beneficial impact of weight loss on most cardiovascular risk factors. Given the high rate of successful weight reduction with bariatric surgery, it is unsurprising that the literature is replete with studies documenting its favorable impact on these risk factors

#### *Metabolic syndrome and its components*

Bariatric surgery results in complete resolution or significant improvement in type 2 diabetes in the overwhelming majority of patients; this reached 86% in one study of patients followed up for 7 years after gastric bypass [44]. In a meta-analysis of 136 studies, nearly 77% of patients had resolution of type 2 diabetes after bariatric surgery [45]. The rate of resolution seemed to vary depending on the type of surgery, with combined restrictive or malabsorptive procedures having a higher rate of resolution compared with purely restrictive procedures. This effect appears to be durable, with one study finding an 83% resolution rate at 14 years after gastric bypass [46]. This durability, however, is dependant on maintenance of weight loss for the long term. In the Swedish obesity study, the resolution rate of type 2 diabetes decreased from 72% at 2 years to 36% at 10 years, with the recurrence being accompanied by a significant increase in body weight [47].

Significant improvements in lipid profiles after bariatric surgery have been shown in several studies, including reductions in total cholesterol, LDL cholesterol, and triglycerides and increases in HDL cholesterol. Improvements occur in more than 70% of patients, with the maximum improvement occurring after malabsorptive surgical procedures [45]. In a more integrated analysis, Lee and colleagues [48] reported a nearly 96%

resolution of metabolic syndrome associated with significant weight loss 1 year after bariatric surgery.

### *Obstructive sleep apnea*

Surgical weight loss results in resolution of OSA and obesity hypoventilation syndrome in approximately 85% of patients [45]. Significant improvement in cardiac dysrhythmias associated with OSA has also been shown after gastric bypass surgery [49].

### *Hypertension*

Intentional weight loss, both dietary and surgical, results in reductions in blood pressure, with a 1% decrease in body weight being associated with an approximate 1 mm Hg decrease in systolic blood pressure and an approximate 2 mm Hg decrease in diastolic blood pressure [50]. In a series of 1025 patients undergoing gastric bypass surgery, a 69% resolution of hypertension at 1 year and 66% resolution at 7 years were found [44]. The rate of complete resolution or significant improvement of hypertension was 79% in a meta-analysis of 136 studies relating to obesity surgery [45]. Interestingly, in the Swedish obesity study the 2- and 10-year resolution rates for hypertension after obesity surgery (34% and 19%, respectively) were much lower, although still better than the resolution rates in control subjects (21% and 11%, respectively) [47]. This may be a reflection of the poor weight loss results achieved in this study in which the majority of the patients underwent a restrictive surgical procedure (vertical banded gastroplasty), which is known to have a significant failure rate and weight recidivism.

## **Bariatric surgery in patients with cardiovascular disease**

Bariatric surgery can be performed safely in patients with preexisting cardiovascular disease. In a study comparing outcomes of bariatric surgery in 52 patients with coronary artery disease (CAD) and 507 patients without CAD, a modest increase in the incidence of nonfatal cardiovascular events was observed in CAD patients (5.8% versus 1.4%) with no increase in mortality rate [51]. After a mean follow-up of 2.5 years, 63% of patients achieved more than 50% excess weight loss, with an accompanying major improvement in several risk factors linked to cardiovascular disease. In a retrospective analysis of 77 morbidly obese patients with preexisting cardiac disease (45 with coronary artery disease, 32 with heart failure), Roux-en-Y gastric bypass was performed with acceptable morbidity and excellent results [52]. We recently reported our outcomes from bariatric surgery in 14 morbidly obese patients with severe heart failure and left ventricular ejection fraction of  $\leq 35\%$  [53]. There was no mortality and acceptable morbidity with a median hospital length of stay of 3 days.

Although bariatric surgery can be performed safely in patients with pre-existing cardiovascular disease, many of these patients are at significant risk for peri- and post-operative complications. They should be managed by a multidisciplinary team, with a thorough preoperative evaluation, optimization of cardiovascular status, and careful perioperative monitoring.

### **Effect of bariatric surgery on cardiovascular disease**

Several randomized, controlled trials have found that multiple risk factor reduction programs coupled with weight reduction result in slower progression or regression of anatomic CAD and decreased anginal symptoms [54,55]. In the Framingham cohort, a 10% reduction in body weight resulted in a 20% decrease in the risk of cardiovascular disease [56]. Furthermore, it is well established that improvements in risk factor profiles in patients with established CAD result in decreased rates of progression of atherosclerosis and reduced cardiac hospitalizations [57]. It should follow that bariatric surgery, which results in significant improvements in cardiovascular risk factor profiles, should have a beneficial effect on cardiovascular morbidity and mortality. Support for this idea is lent by the Program On the Surgical Control of the Hyperlipidemias (POSCH) trial, in which patients who had a partial ileal bypass showed a 23% decrease in total cholesterol levels and a 38% decrease in LDL cholesterol levels, resulting in a 60% decrease in the need for coronary intervention and a 20% reduction in the risk of mortality at a mean follow-up of 18 years [58].

#### *Coronary artery disease*

Bariatric surgery appears to slow the progression of atherosclerotic disease. In a study of carotid artery atherosclerosis in 20 patients treated with gastroplasty and 19 obese patients treated with dietary recommendations, the rate of progression was three-fold higher in controls compared with patients in the surgical group [59]. In a large observational cohort study, the incidence of coronary events (angina, myocardial infarction, and pulmonary edema) over a 5-year follow-up period was significantly reduced in patients undergoing bariatric surgery compared with controls. In addition, the number of percutaneous and surgical revascularization procedures was significantly lower in the surgical group [60].

#### *Heart failure*

Although a number of studies have examined the impact of bariatric surgery on the abnormalities of cardiac structure and function that accompany morbid obesity, few have documented its impact on the clinical syndrome of heart failure. We have recently reported beneficial effects of bariatric surgery in a cohort of morbidly obese patients with severe systolic LV failure.

Improvements in NYHA functional class and LV ejection fraction were noted at 6 and 12 months of follow-up compared with age, sex, ejection fraction and BMI matched controls [61].

### *Cardiac dysrhythmias and stroke*

No reports exist as to the impact of bariatric surgery on the risk of cardiac dysrhythmia or stroke. A small, uncontrolled study of patients undergoing vertical banded gastroplasty noted a significant reduction in the corrected QT interval on follow-up 8 to 10 months after surgery, leading the investigators to speculate that this might decrease the risk of ventricular dysrhythmias [62].

### *Overall mortality*

Several recent studies have indicated a survival advantage for patients undergoing bariatric surgery compared with control groups. In the Swedish obesity study, the adjusted overall mortality rate was reduced by 32% in the surgical group. The decrease in mortality was comprised of reductions in both cardiovascular and cancer deaths [63]. A more recent analysis compared a surgical cohort of 1468 patients undergoing laparoscopic adjustable gastric banding to a cohort of more than 2000 obese controls and found a 73% reduction in the mortality rate in the surgical group [64]. In the largest comparative study to date, 8172 patients who had undergone gastric bypass surgery were followed up for up to 18 years and found to have a 40% reduction in mortality rate compared with controls matched for age, sex, and BMI. This survival advantage was again associated with reductions in cardiovascular and cancer deaths [65].

## **Effects of bariatric surgery on cardiac structure and function**

A number of studies have examined the effect of weight loss on cardiac structure and function, only a few of which have evaluated the effects of diet-induced weight loss. A randomized, controlled trial of weight reduction through diet and exercise in obese patients resulted in significant reductions in left ventricular hypertrophy and mass [66]. In an uncontrolled study of diet and exercise-induced weight loss in obese women, BMI, blood pressure, and cardiac output all decreased significantly, whereas markers of compliance improved [67]. Short and longer-term diet and exercise weight loss programs also have been shown to decrease heart rate and enhance parasympathetic cardiac tone [68,69].

Several studies have assessed the effects of surgically induced weight loss on cardiac structure and function, a number of which have been previously reviewed [5]. The results from five of these studies are summarized in Table 1 [70–75]. As can be seen, substantial weight loss through surgical intervention

Table 1  
Effects of surgically induced weight loss on cardiac structure and function

Study	N	Preop weight (kg)	Preop BMI	Surgical procedure	Follow-up (mo)	Postop weight (kg)	Postop BMI (kg/m <sup>2</sup> )	Cardiac assessment: observations
Alpert, 1985 [70]	34	135 ± 8	—	Gastric restriction	4.3 ± 0.3	79 ± 6	—	Echo: LVFS% increase, LVIDD decrease (in subset (n = 13) with preop LV dysfunction)
Sugerman, 1988 [71]	18	[% IBW 225 ± 46]	—	Various	3–9	[% IBW 167 ± 57]	—	RHC: PAP decrease, PAOP decrease
Karason, 1997 & 1998 [72,73]	41	117 ± 15	39 ± 4	“Weight-reducing gastric surgery”	12	84 ± 14	29 ± 3	Echo: CO decrease, E/A increase, LVEF increase, LVM decrease, relative WT decrease
Kanoupakis, 2001 [74]	16	139 ± 24	49 ± 8	Vertical banded gastroplasty	6	94 ± 24	34 ± 7	ETT: peak VO <sub>2</sub> increase Echo: LV wall thickness decrease, IVRT decrease, E/A increase
Willens, 2005 [75]	17	160 ± 43	54 ± 11	Roux-en-Y gastric bypass	7.6 ± 3.6	121 ± 43	40 ± 11	Echo: LVM decrease, mitral and tricuspid annular early diastolic velocity increase

*Abbreviations:* CO, cardiac output; E/A, ratio of transmitral early to atrial peak flow velocity; Echo, echocardiogram; IBW, ideal body weight; IVRT, isovolumic relaxation time; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVIDD, left ventricular internal dimension in diastole; LVM, left ventricular mass; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; Relative WT, ratio of mean left ventricular wall thickness to left ventricular chamber radius; RHC, right heart catheterization; VO<sub>2</sub>, oxygen consumption.

consistently results in improved left ventricular hypertrophy and frequently in improved measures of systolic and diastolic performance. One weakness of most studies published to date is the absence of an appropriate control group. Of note, however, Karason and colleagues [72,73] included as control groups in their study patients who were obese and received only dietary counseling and patients who were lean. In neither control group did body weight or cardiac parameters change during the study period. A more integrated view of the effects of bariatric surgery may come from measures of exercise performance. In a study of 31 morbidly obese patients undergoing bariatric surgery, substantial weight reduction resulted in a decrease in oxygen use per unit of work and an increase in total exercise time [76]. No changes in cardiac function were observed after surgery, however, emphasizing the importance of noncardiac factors in determining exercise performance, especially after the dramatic physiologic changes induced by profound weight loss.

### **Putative mechanisms for the cardiovascular effects of bariatric surgery**

A number of putative mechanisms have been put forward to explain the beneficial effects of weight loss on cardiac structure and function. These include improvements in loading conditions, neurohormonal and metabolic profiles, and circulating levels of proinflammatory cytokines and markers of the systemic inflammatory state. Similar mechanistic explanations have been advanced to explain the benefits of the procedure on cardiovascular risk factors and manifest cardiovascular disease. One potential added mechanism is alterations in the expression of adipokines such as leptin and adiponectin, which have recently been shown to have direct effect on cardiac and vascular structure and function.

#### *Altered loading conditions*

Loading conditions are improved in obese patients after weight loss in a number of ways: via decreased circulating blood volume, cardiac output, intracardiac filling pressures, and systemic and pulmonary arterial pressure. The improvement in OSA usually seen after weight loss likely contributes to several of these changes. Interestingly, decreases in LV mass after weight loss appear to be largely independent of decreases in systemic arterial pressure [77], raising the likelihood that other mechanisms are at play. Neurohormonal activation, most notably of the sympathetic nervous system, is improved after weight loss [78] and might be expected to contribute to improvements in LV structure and function. Inflammatory and prothrombotic markers are similarly improved [79]. There is now ample evidence that inflammation contributes to many types of cardiovascular pathophysiology [80]. Again, the improvement in OSA that follows weight reduction likely

contributes to these improvements in neurohormonal and inflammatory profiles [81].

### *Altered adipokine profile*

Weight loss in obese patients is associated with partial normalization in circulating levels of adipokines, including leptin and adiponectin [82]. Emerging data suggest that these changes may play a role in the improvements seen in cardiovascular risk factors, cardiac structure and function, and clinical cardiovascular disease. Precise mechanisms, however, remain uncertain.

Leptin is a cytokine produced primarily by adipocytes; it acts via hypothalamic pathways to suppress appetite and increase metabolic rate [83]. Serum leptin levels are increased in obesity, although experimental work, coupled with the observation that appetite and metabolic parameters do not normalize in many obese patients despite high circulating leptin levels, raises the speculation that human obesity is a leptin-resistant state [84].

Leptin has been found to have direct cardiac and vascular effects, and leptin receptors are found in both cardiac [85] and vascular [86] tissue. Interestingly, leptin levels are elevated in nonobese patients after myocardial infarction [87] and in the presence of heart failure [88]. Conflicting data exist as to the effect of leptin on cardiac hypertrophy, suggesting a complex relationship between leptin, its determinants, and cardiac mass [89,90]. Leptin levels have been found to decrease after bariatric surgery and to correlate with reductions in left ventricular hypertrophy [91]. High circulating leptin levels have been shown to be an independent risk factor for coronary artery disease [92] and for restenosis after coronary stenting [93]. Paradoxically, leptin signaling appears to be protective in experimental models of ischemia-reperfusion [94,95], suggesting differential effects of leptin according to experimental setting, site of action, or the specific disease state.

Adiponectin is also a cytokine produced by adipocytes but, in contrast to leptin, its plasma levels are significantly reduced in obesity. Adiponectin appears to exert insulin sensitizing and anti-inflammatory effects, and to have a protective effect against atherogenesis [96]. Clinical studies have found a relationship between low serum levels of adiponectin and increased risk of new-onset insulin resistance [97] and type 2 diabetes [98]. Although some studies have found an inverse relationship between serum adiponectin concentration and subsequent risk of myocardial infarction [99], others have found no relationship between the two [100]. The presence of adiponectin has been found to correlate positively with mortality in patients with chronic heart failure [101], perhaps reflecting the wasting condition known to be associated with poor prognosis in these patients. Interestingly, treatment of patients with type 2 diabetes with an angiotensin-converting enzyme inhibitor increased vascular adiponectin gene expression and improved endothelial function [102]. Bariatric surgery has also been shown to increase adiponectin levels [103], although the relationship between the increase

and the beneficial cardiovascular effects of weight loss induced by the surgery has not been definitively established.

## Summary

Morbid obesity is a growing public health concern with multiple associated cardiovascular comorbidities. Bariatric surgery has emerged as a safe and effective treatment for morbidly obese patients at risk for, or already suffering from, cardiovascular disease. Weight loss induced by the surgery has been shown to improve cardiovascular risk factors, cardiac structure and function, and the clinical course of established cardiovascular disease. The role of adipocyte-derived cytokines in mediating cardiovascular pathophysiology in obesity—and its modulation after weight loss—is under active investigation.

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