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Gastrointestinal Surgery: Cardiovascular Risk Reduction and Improved Long-Term Survival in Patients with Obesity and Diabetes

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Abstract Whereas the initial focus of bariatric surgery primarily focused on weight loss and was considered by many clinicians and the public as a cosmetic-driven procedure, this surgical therapy is now recognized as a successful approach to reducing cardiovascular disease risk and the only substantial and sustainable weight loss treatment for most severely obese patients. In addition, as a result of the multiple metabolic-related benefits associated with bariatric surgery, efforts to understand physiologic and biochemical mechanisms have led to a dramatic increase in scientific discovery. This review focuses on bariatric research conducted during the past two decades in relation to cardiovascular disease risk and the effects of this surgical therapy on diabetes. Cardiovascular and diabetes mortality and morbidity associated with bariatric surgery are reviewed. The opportunity for bariatric (and/or metabolic) surgery to provide a preventive strategy for cardiovascular disease and diabetes as well as treatment therapy is presented for clinical consideration.

Keywords Bariatric surgery · Gastric bypass · Gastric banding · Diabetes · Mortality · Morbidity · Survival

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Introduction

The historical journey of bariatric surgery is somewhat unique to the field of medicine. From its early beginnings, the desired outcome was isolated to weight loss, and clinical and social skepticism was substantial. However, bariatric surgery is now widely accepted as a therapy that favorably impacts a myriad of medical comorbidities and is viewed as the only medical intervention offering both substantial and long-term weight loss for most patients classified as severely obese [1–3]. Bariatric surgery's unexpected association with remission of type 2 diabetes, reduced cancer incidence, and improved all-cause mortality following bariatric surgery, coupled with the prevalence of extreme obesity increasing in the United States at a rate greater than moderate obesity [4, 5], have poised this surgical therapy in the mainstream of clinical application and scientific discovery. One particular arena of rapidly emerging research has converged on the role bariatric surgery plays in the reduction of cardiovascular risk, with particular emphasis on diabetes. This article provides a review of mortality and morbidity outcomes related to diabetes and cardiovascular risk following bariatric surgical therapy.

Review

In preparation for this review, a search strategy designed to identify all studies linking to bariatric surgery and cardiovascular disease in the available medical literature was conducted by the McMaster Evidence-based Practice Center (MU-EPC), McMaster University, Hamilton, Ontario. Accessing Medline-OVID, Embase-OVID, Cochrane Controlled Trials Registry-OVID, Medline-In-Process and other non-indexed citations, search terms included 'bariatric surgery' and bariatric surgical procedure names such as 'gastric bypass', 'Roux-en-Y', 'vertical sleeve gastrectomy', 'vertical banded gastroplasty', 'adjustable gastric band', 'lap-band', and 'biliopancreatic diversion'. These search terms were combined with text words: 'cardiovascular disease', 'cardiovascular risk', 'coronary artery disease', 'diabetes', 'diabetes mellitus', 'hypertension', 'blood pressure', 'stroke', 'lipid blood level'. 'cholesterol', 'hdl', 'ldl', 'triglycerides', 'sleep apnea syndromes', 'diet', 'diet therapy', 'diet restriction', 'exercise therapy' , 'exercise', 'kinesiotherapy', and 'nonalcoholic fatty liver'. The search was limited to the English language, with search years conducted primarily between 1980 and 2012. In addition to the MU-EPC search, a hand search of key review articles related to bariatric surgery and cardiovascular-related mortality and morbidity as well as specific cardiac function-related manuscripts (i.e., bariatric surgery and echocardiography) was performed. Finally, a secondary review process included elimination of manuscripts whose research or review content was limited to perioperative findings, cost analysis, surgical technique, pharmaceutical impact, and small case study design.

The results of the search process are summarized in Fig. 1. Of the total 1113 identified manuscripts relating bariatric surgery to cardiovascular and metabolic risk, disease, and mortality, approximately 56 % were eliminated because they did not meet secondary review criteria. The remaining 493 identified manuscripts (44 %) were divided into four cardiovascular-related research categories, based upon the primary study objectives and outcomes: mortality and morbidity, mortality or morbidity alone, and research primarily focusing on bariatric surgery and physical activity, diet, and related behavioral findings. For each sub-category, studies were further separated into randomized control trials (RCT), review articles, and "other" reports such as prospective, case–control, and series-based studies (see Fig. 1). Studies reporting long-term mortality outcomes related to cardiovascular disease and diabetes were few (N=18; 3.7 %), compared with the number of studies related to a morbidity outcome (N=432; 87.6 %). Considering the length of time bariatric surgeries have been performed, the literal explosion of scientific reports within the past decade focused on effects of surgery on cardiovascular and metabolic outcomes is further evidence of the swift rise in scientific interest and discovery for bariatric surgery.

Bariatric Surgery and Long-Term Survival Multiple studies have reported a link between obesity and increased death rate, with greater risk of death when body mass index (BMI) is ≥35 as compared to a BMI of 30 to 34 [6–8]. However, whether or not voluntary weight loss through non-surgical therapy improves mortality is less clear, with observational studies suggesting no change [9], reduced [10], or improved [11] mortality subsequent to intentional weight loss. Possible explanations for these inconsistent findings are that it is difficult to determine in large studies whether or not weight loss has been intentional, and equally difficult to find enough patients with sustained (long-term) weight loss [12, 13]. In contrast, the reported increase in long-term survival for bariatric surgery populations when compared to severely obese control groups remains consistent among studies. Of the bariatric surgery long-term mortality studies [14–26], approximately half specifically report on long-term survival rates associated with cardiovascular disease and diabetes [15•, 16•, 17, 20, 22, 24–26].

As highlighted in Fig. 1, 11 studies that have combined mortality and morbidity results are noted. The five studies identified as randomized control trials (RCT) are actually five papers from the same study, the Program on the Surgical Control of Hyperlipidemias (POSCH) trial by Buchwald et al [27]. Of the three studies listed in the "other" category for combined mortality and morbidity, two report extended survival among bariatric surgery patients when compared to severely obese, non-operated controls [17, 19] while the study by Plecka et al. did not report improved mortality for bariatric surgery patients when compared to the general population rather than severely obese controls [26]. For the category of mortality only (Fig. 1), three of the four "other" studies reported a significant improvement in mortality for bariatric surgical patients when compared to severely obese controls [15•, 16•, 25], while the study by Omalu did not show improved survival for bariatric surgery patients when compared to the general population of Pennsylvania rather than severely obese controls [22]. Finally, the only RCT published study identified in Fig. 1 for mortality only was a report of the POSCH trial [24].

The Swedish Obese Subjects (SOS) study, which focused primarily on long-term mortality following bariatric surgery, involved 4047 obese participants, 2010 who had bariatric surgery (vertical banded gastroplasty, gastric banding, and gastric bypass) and 2037 matched controls who received conventional weight loss therapy [16•]. Over a period of up to 16 years, there were 129 deaths in the control group (6.3 %) compared to 101 in the bariatric surgery group (5.0 %), representing an unadjusted hazard ratio of 0.76 (95 % CI, 0.59 to 0.99; P=0.04). Although the SOS study

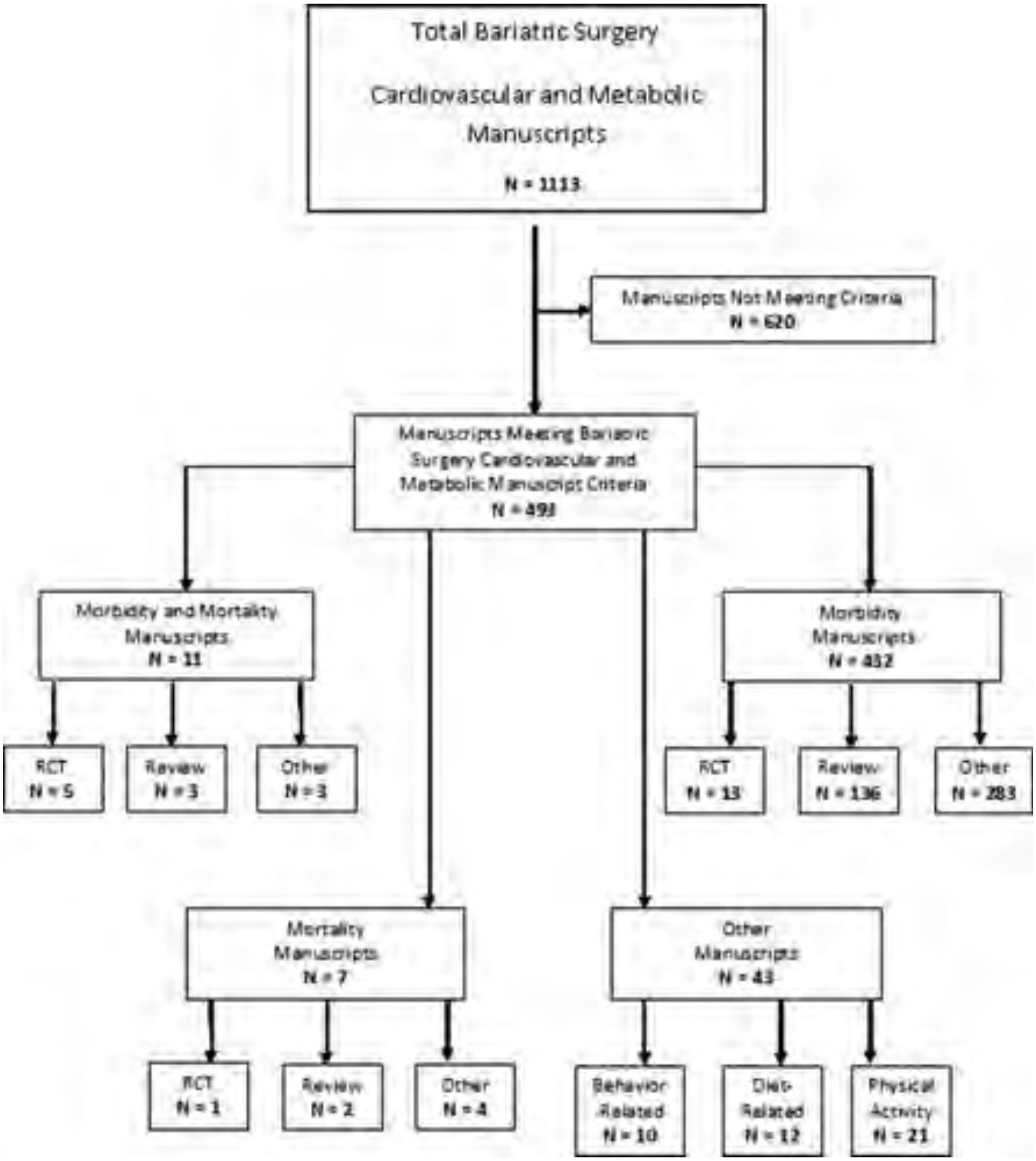

Fig. 1 Schematic detailing the literature search: bariatric surgery and cardiovascular risk and diabetes

was not sufficiently powered to determine specific-cause mortality, the most common causes of death were cardiovascular-related (53 in the control group; 43 in the surgery group), and among cardiovascular deaths, myocardial infarction, sudden death, and cerebrovascular damage were the most common [16•]. An important strength of the SOS mortality study was the prospective follow-up of weight and risk factors.

Zhang et al., accessing the International Bariatric Surgery Registry, submitted data from 18,972 patients to the National Death Index bureau for the primary purpose of associating risk factors with long-term survival following bariatric surgery [28]. Over a mean follow-up period of 8.3 years, there were 654 deaths (3.45 %). Significant baseline predictors of improved long-term survival were younger age, female gender, lower BMI, and no history of smoking, diabetes or hypertension. From this study, it would appear that despite the beneficial effects associated with bariatric surgery, presurgical risk factors such as diabetes and hypertension continue to influence long-term mortality.

Our group (Adams et al.) [15•] conducted a retrospective cohort study to compare long-term mortality among 7925 post-gastric bypass patients category matched (age, sex and BMI) to 7925 severely obese persons who had applied for drivers licenses and had not had weight loss surgery. During a mean follow-up of 7.1 years (18 years maximum), there were 213 reported deaths in the gastric bypass group compared to 321 deaths in the control group. After covariate adjustment, the all-cause death rate was 40 % lower in the surgery group when compared with controls (HR, 0.60; 95 % CI 0.45 to 0.67, $P<0.001$). Further analysis of cause-specific death rates between groups showed a 49 % reduction (HR, 0.51; 95% CI 0.36 to 0.73; $P<0.001$) for combined cardiovascular diseases (CVD) (coronary artery disease [CAD], heart failure, stroke, and other CVD) for the surgery group. Of these diseases, CAD was 59 % lower (HR, 0.41; 95 % CI 0.21 to 0.78; $P=0.006$) in the surgical group compared with controls, while heart failure and stroke were not significantly different between groups. Strikingly, the death rate for diabetes was 92 % lower among the gastric bypass group compared to controls (HR, 0.08; 9 5 % CI 0.01 to 0.47; $P=0.005$). An important limitation to this retrospective study was that history of weight subsequent to gastric bypass surgery or application for a driver's license were not available. However, long-term prospective bariatric surgery studies have demonstrated significant and sustained weight loss among bariatric surgical patients with minimal weight change among severely obese, non-operated control participants [1, 29].

Omalu et al. [30] reported on mortality data of all bariatric surgical procedures performed on Pennsylvania residents over a 9 year period (January 1995 to December 2004). Surgical patients were matched for age and sex, but not BMI, to the general Pennsylvania population. There were 440 deaths associated with 16,683 bariatric operations (2.6 %). After exclusion of deaths in the first 30 days following surgery, the age- and sex- specific death rates for the bariatric surgical group were "substantially higher" when compared with the Pennsylvania general population. Coronary heart disease accounted for greatest number of deaths among the surgical group (76 deaths; 19.2 %). In addition to CAD, there were 18 "other" CVD deaths (4.6 %), 12 stroke deaths (3.0 %), and four congestive heart failure deaths (1.0 %). There were six reported deaths resulting from diabetes (1.5 %). This study is unique to other reported bariatric surgery reports because the primary aim was to determine possible variation in death rates between severely obese patients who undergo bariatric surgery and the general population. These findings would suggest that even if improved mortality (i.e., cardiovascular- and diabetes-related) had occurred in patients who had bariatric surgery, mortality was still greater than that of the general population. The authors did conclude, however, that their study could not "determine whether surgery reduced mortality compared with patients with class III obesity (i.e., ≥35) who did not undergo surgery [22].

Somewhat similar to the study by Omalu et al. [30], who compared all post-bariatric patients in Pennsylvania with the state's general population, Plecka et al. [26] compared each patient who participated in bariatric surgery in Sweden between 1980 and 2006 (N=13,273) to ten age- and sex-matched controls who were randomly selected from Sweden's Patient Register for the purpose of analyzing hospital obesity-related comorbidities and "overall mortality." After bariatric surgery, the adjusted hazard ratios (HRs) for the post-bariatric surgery group when compared to the Swedish general population were 1.56 (95 % CI 1.35 to 1.81) for myocardial infarction, 2.05 (95 % CI 1.84 to 2.31) for angina pectoris, 2.13 (95 % CI 1.88 to 2.42) for stroke, 2.80 (95 % CI 2.61 to 3.01) for hypertension, 2.44 (95 % CI 2.23 to 2.67) for diabetes, and 1.24 (95 % CI 1.15 to 1.34) for overall mortality [26]. Like the findings reported by Omalu et al., the results of the study by Plecka et al. further demonstrate that reduction in cardiovascular risk and improved survival following bariatric surgery does not reach levels comparable with the general population. However, a unique twist in the data presented by Plecka, et al. was the separate reporting of the 4,161 bariatric patients who underwent gastric bypass surgery. The gastric bypass only group "no longer had a higher risk of diabetes," HR of 1.23 (95 % CI 0.88 to 1.72) or myocardial infarction, HR of 0.78 (95 % CI 0.42 to 1.45). These findings were not found for the restrictive only surgical patients. The authors concluded that: "Gastric bypass, but not restrictive surgery, in patients with morbid obesity seems to reduce the risk of diabetes and myocardial infarction to population levels, but the risk of death remains increased [26]."

Johnson et al. recently reported the findings of a retrospective mortality cohort study of severely obese patients with a common history of cardiovascular events (myocardial infarction, angina or stroke) who underwent bariatric surgery (N=309) or orthopedic or gastrointestinal surgery (N=903) [25]. After 5 years follow-up, the unadjusted all-cause mortality was 2 % in the bariatric surgery group compared to 19 % (P<0.001) in the control group, representing a 40 % reduction in death rate (HR, 0.60; 95 % CI 0.36 to 0.99). The distinct finding of this study is that in patients with cardiovascular disease history, those who undergo bariatric surgery have reduced all-cause death rates when compared to CVD patients whose surgery was orthopedic- or gastrointestinal-related [25]. Finally, Buchwald et al. conducted a multiclinic, randomized, prospective secondary intervention trial, the POSCH trial, for the purpose of determining whether or not a partial ileal bypass surgery to lower total cholesterol and LDL-cholesterol and raise HDL-cholesterol "had a favorable impact on overall mortality and on mortality and morbidity attributable to coronary heart disease [24, 31–33]." Over an 8 year period, 838 post-myocardial infarction patients (men and women) with elevated total cholesterol and LDL-cholesterol were randomly assigned to either dietary intervention or dietary intervention plus partial ileal bypass surgery. The mean follow-up period was 9.7 years. Results demonstrated an improved lipid profile among the surgical group as well as a 35 % decrease in CHD-mortality rate. The surgical group also had significant reduction ($P<0.001$) in nonfatal myocardial infarction and CAD bypass graft and percutaneous transluminal coronary angioplasty [24].

Bariatric Surgery and Cardiovascular and Diabetes Risk Reduction As identified in Fig. 1, at least 13 RCT morbidity-related bariatric surgery studies have been published [34–40, 41•, 42, 43, 44•, 45, 46], three of which were from the same POSCH trial. The great majority of bariatric surgery publications are studies related to CVD and diabetes morbidity outcomes. At least 283 publications are identified in Fig. 1 with a representative few indicated with this sentence [1, 17, 19, 29, 45, 47–51, 52•, 53]. In addition, multiple reviews relating bariatric surgery and CVD and diabetes have been published, just to mention a few [54, 55••, 56–61]. A recently published American Heart Association (AHA) Statement carefully detailed the association between bariatric surgery and cardiovascular risk factors, including a thorough review of effects of weight loss surgery on weight, diabetes mellitus, lipid profile and inflammation, nonalcoholic fatty liver disease (NAFLD), systemic hypertension, sleep apnea, cardiac function, and survival benefit [62••]. The AHA Statement also reviewed lifestyle-related aspects of bariatric surgery in relation to CVD such as diet, physical activity and lifestyle changes.

A randomized, parallel-group trial, by Sovik et al. explored the effects of gastric bypass and duodenal switch upon cardiovascular risk factors of patients whose pre-surgical BMI was between 50 and 60 kg/m^2 [45]. Patients were randomized to one of the two bariatric surgical procedures (gastric bypass, N=31; duodenal switch, N=29) and followed for two years. With a follow-up rate of 97 %, patients undergoing duodenal switch had greater weight loss, total- and LDL-cholesterol reduction and adverse events compared to the gastric bypass patients. However, improvements in all other CVD risk factors (i.e., reductions in blood pressure, glucose, insulin and C-reactive protein) were similar between patient groups [45]. Three bariatric surgery, diabetes-related randomized control trials have been published, one in 2008 by Dixon et al. [35] and two in 2012 by Schauer et al. [44•] and Mingrone et al. [41•]. Each study compared the effect of bariatric surgical procedures versus non-surgical intensive medical therapy on patients diagnosed with diabetes. Two years after an intervention (gastric banding verses intense medical therapy), Dixon et al. reported type 2 diabetes remission with banding to be 73 % compared with 13 % in those who had conventional-therapy [35]. Using criteria for defining diabetes remission proposed by Buse et al. [63], Mingrone et al. reported a 75 % diabetes remission after two years follow-up for patients undergoing gastric bypass, 95 % for biliopancreatic diversion, and no remission for patients participating in the conventional medical therapy group [41•]. Finally, Schauer et al. randomly assigned patients to undergo gastric bypass, sleeve-gastrectomy, or medical-therapy [44•]. After one-year follow-up, they reported that 42 % with gastric bypass, 37 % with sleeve-gastrectomy and 12 % with intense medical therapy achieved the study's primary endpoint of a glycated hemoglobin level of ≥6 %.

Sjöström, et al., reported the effects of bariatric surgery on lifestyle, CVD risk factors and diabetes after ten years follow-up in the SOS study [29]. At 10 years, the surgical group had greater remission of diabetes, hypertriglyceridemia, low levels of HDL-cholesterol, and hypertension when compared to the control group. There were no statistical differences between groups with regards to remission of hypercholesterolemia. Incidence rates of diabetes and hypertriglyceridemia were lower in the surgical group compared with controls but there were no reported between-group differences at 10-years for hypercholesterolemia and hypertension incidence [29]. Figure 2 represents the remission ("recovery") of diabetes, lipids, hypertension and hyperuricemia for SOS study participants at both 2 and 10 years follow-up [29, 51]. These data provide a sense of change in remission rates over time for patients undergoing bariatric surgery. Sjöström, et al., also published the rates of myocardial infarction and stroke among SOS bariatric surgery patients versus controls subsequent to baseline participation [52•]. They reported a lower rate of first time MI or stroke occurring in the bariatric surgery group (199 events; total N=2010 patients) compared to the severely obese control group (234 events; total N=2037 controls). The adjusted hazard ratio was reported to be 0.67 (95 % CI 0.54 to 0.83; $P<0.001$). Finally, Carlsson et al. recently (2012) reported on the prevention of type 2 diabetes by comparing rates of incident diabetes among surgical patients in the SOS study compared with the obese control group [64]. With a follow-up of up to 15 years, there were 110 bariatric surgical patients who had developed diabetes compared to 392 control participants (HR, 0.17; 95 % CI 0.13 to 0.21).

Our group (Adams, et al.) also recently reported the long-term results of bariatric surgery (gastric bypass) on cardiovascular risk factors and diabetes after 6 years [1]. This prospective Utah-based study has studied participants who sought and underwent gastric bypass surgery (N=418), patients who sought gastric bypass surgery but did not have surgery (control group 1; N=417) and a randomly selected group of severely obese participants who were not seeking weight loss surgery (control group 2; N=321). The design of this study [65] and the 2-year follow-up results [47] have

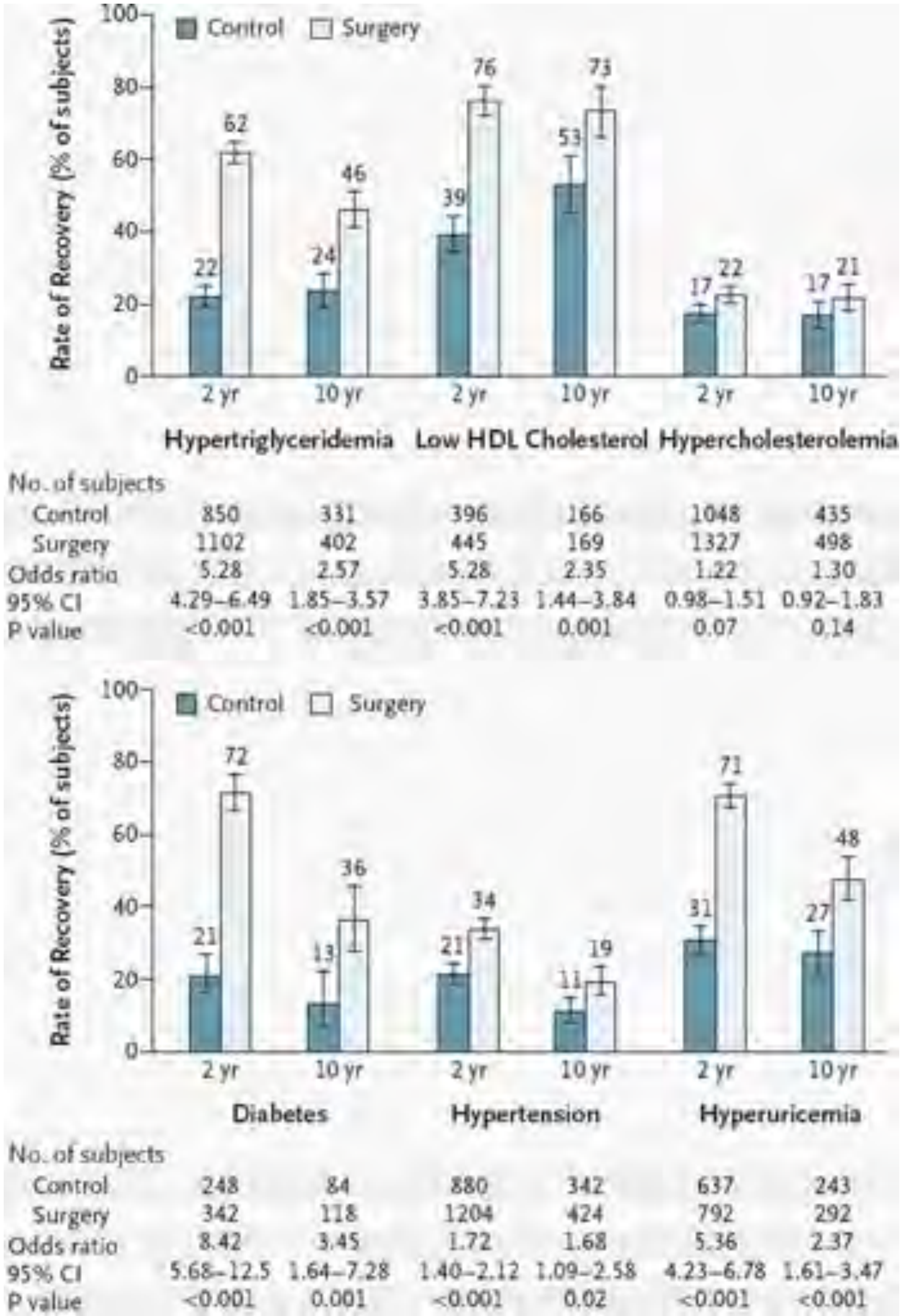

Fig. 2 Recovery from diabetes, lipid disorders, hypertension, and hyperuricemia over 2- and 10-year periods among the SOS study participants who completed 2 and 10 years of the study. Bars and percentage values above bars are unadjusted recovery rates. I bars represent the corresponding 95 % confidence intervals. Under each panel, the odds rations, 95 % CI for the odds ratios and the P-values have been adjusted for gender, age, and body mass index at the time of inclusion in the intervention study. (With permission from Sjostrom et al. [29]. Copyright © (2004) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

been previously published. Similar to the SOS study findings, at 6 years follow-up, all major CVD risk factors (lipids, blood pressure, glucose, insulin, HbA_{1c}) were significantly improved in the surgical group when compared to the two control groups [1]. In addition to a 6-year remission rate of 62 % in diabetes in the surgical group, the 6-year incidence of diabetes was reduced following gastric bypass surgery when compared to the control groups (2 % [95 % CI, 0 % to 4 %] vs 17 % [95 % CI, 10 % to 24 %] OR, 0.11 [95 % CI, 0.04 to 0.34] compared with control group 1 and 15 % [95 % CI, 9 % to 21 %] OR, 0.21 [95 % CI, O.06 to O.67] compared with control group 2; both $P<0.001$) [1]. In addition to diabetes-related improvements, the reported remission rates of hypertension (6 years) were also significantly improved in the surgical versus control group (42 %, [95 % CI, 32–52 %] versus 18 %, [95 % CI 9–27 %], OR,

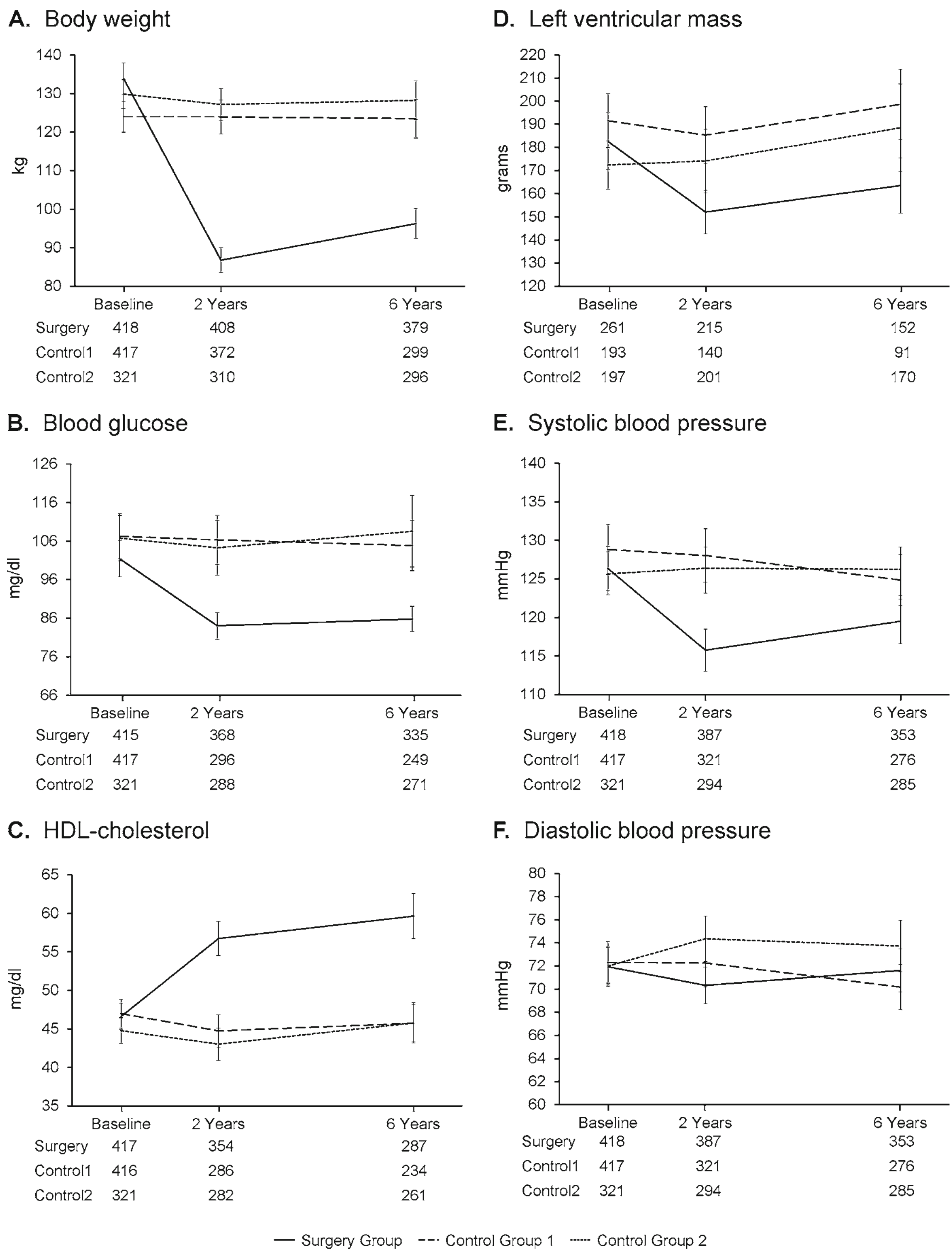

Fig. 3 Changes in key clinical variables over six years. Unadjusted mean values and multiple comparison-adjusted 95 % confidence intervals are presented for surgical and control groups 1 and 2 measured at baseline, examination one (two years) and examination three (six years) for body weight (**a**), blood glucose (**b**), HDL-C (**c**), left-ventricular mass (**d**), systolic blood pressure (**e**), and diastolic blood pressure (**f**)

2.9 [95 % CI, 1.4-6.0] and 4 2 % versus 9 %, [95 % CI 3–15 %], OR, 5.0 [95 % CI, 2.1-11.9]). Further, the remission of low HDL-C rates were improved in the gastric bypass compared with control groups (67 % [95 % CI, 57–77 %] versus 34 %, [95 % CI, 23–45 %], OR, 3.8 [95 % CI, 2.0-7.2] and 67 % versus 18 %, [95 % CI, 8–28 %], OR, 6.2

[95 % CI, 2.7-14.1]), and similar remission rates were reported for LDL-C and triglycerides [1].

The Utah-based study showed baseline unadjusted LV mass of 183 grams for the surgical patients decreased 36 grams (−20 % from baseline) at two years and 17 grams (−9 % from baseline) at six years. For the control groups, baseline LV mass of 174 grams and 193 grams increased 4 grams and 2 grams (+2 % and +1 % from baseline, respectively) at six years. These changes in LV mass from baseline to years two and six were significantly different in the surgery group compared with controls ($p<0.05$ for both exams and for both control groups). The significant six-year reduction in LV mass in the surgical group versus controls was not explained by change in systolic blood pressure. Increased LV mass is also a well-documented risk factor for both heart failure and cardiovascular mortality [66]. Karason et al. measured LV mass in a subset of the SOS study surgical (N=38) and control (N=25) participants at baseline and one year after surgical intervention and showed a reduction in the LV mass of the post-surgical group of 28 grams [67]. Several other investigators have conducted studies that explore the effects of bariatric surgery on cardiac function, geometry and mass [49, 68–74]. Finally, the six-year maximal exercise treadmill time among the Utah-based study participants was significantly greater by 181 sec (95 % CI, 114–249) and 135 sec (95 % CI, 79–190) for the surgical group compared with each control group, respectively. Figure 3 illustrates 2 and 6 years change in CVD risk factors as measured in the Utah-based study [1].

The promising results from the randomized control trials and the prospective studies reported above provide encouragement for diabetes management as well as diabetes prevention (i.e., lower incidence when compared to severely obese controls). Although diabetes remission rates declined somewhat over time, it is possible that the years of improved glycemic control after bariatric surgery may have ultimately lessened microvascular disease [75]. Further, remission and potential reduction in incidence rates for CVD risk factors such as hypertension and hyperlipidemias as a result of bariatric surgery appear likely to result for severely obese patients who present with these disorders.

Conclusion Retrospective mortality studies and the SOS prospective mortality study have reported greater survival in patients who have undergone bariatric surgery when compared to matched severely obese, non-operated controls. Increased cardiovascular- and diabetes specific mortality has also been associated with post-bariatric surgery patients. In addition to lengthened survival following bariatric surgery, improvement in cardiovascular risk factors, remission of chronic disease (hypertension, hyperlipidemia, and diabetes) and reduced incidence of diabetes have been reported. Bariatric surgery provides not only a successful therapy for sufficient and sustainable weight loss but also an opportunity for treatment and prevention of cardiovascular disease, including diabetes.

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