Bariatric Surgery in Patients With Morbid Obesity and Type 2 Diabetes

GUNTRAM SCHERNTHANER, MD[1]
JOHN M. MORTON, MD[2]

There is an epidemic of obesity throughout the developed and much of the developing world (1–3). Obesity, typically measured as BMI ≥30 kg/m^2, has three subclasses: obesity 1 (30–34.9 kg/m^2); obesity 2 (35–39.9 kg/m^2); and extreme obesity (>40 kg/m^2). Extreme or morbid obesity is rapidly increasing in the U.S. and may have the potential of decreasing life expectancy. From 1986 to 2000, the prevalence of BMI >30 kg/m^2 doubled, whereas that of BMI ≥40 kg/m^2 quadrupled, and even extreme obesity of BMI ≥50 kg/m^2 increased fivefold (2). Of particular concern is the alarming increasing prevalence of obesity among children (1), suggesting that the epidemic will worsen before it improves. Epidemiologic studies have demonstrated that increasing BMI is a causative factor in many life-threatening comorbidities, including type 2 diabetes, cardiovascular disease, and cancer. BMI has been established as an independent risk factor for premature mortality (4). Obesity is a major independent risk factor for the development of type 2 diabetes and is associated with the rapid increase in the prevalence of type 2 diabetes (3). In the U.S., the majority diagnosed with type 2 diabetes are overweight, with 50% obese (i.e., BMI >30 kg/m^2) and 9% morbidly obese (BMI >40 kg/m^2) (5). This twin epidemic of obesity and diabetes carries severe consequence for premature mortality (6).

Lifestyle intervention programs with diet therapy, behavior modification, exercise programs, and pharmacotherapy are widely used in various combinations. Unfortunately, with extremely rare exceptions (7), clinically significant weight loss is generally very modest and transient, particularly in patients with severe obesity. In a recently published study (8), 80 adults with mild to moderate obesity (BMI 30–35 kg/m^2) were randomized to nonsurgical intervention (very-low-calorie diet, orlistat, and lifestyle change) or to surgical intervention (gastric banding); surgical treatment was significantly more effective than nonsurgical therapy in reducing weight, resolving the metabolic syndrome, and improving quality of life during a 24-month treatment program (8). At 2 years, the surgical group had greater weight loss, with a mean of 21.6% of initial weight loss and 87.2% of excess weight loss, whereas the nonsurgical group had a loss of 5.5% of initial weight and 21.8% of excess weight (P = 0.001). When morbidly obese patients with a BMI >40 kg/m^2 were willing to complete an intensive behavioral program, a remarkable weight loss of ~35% of the initial body weight was observed after 40 weeks,. For completers, average weight loss for women was 30.8 kg (23.9%) and for men was 42.6 kg (26.7%) over 39 weeks. However, long-term maintenance of weight loss is difficult for most individuals, as also noted in this particular study (7).

Bariatric surgery includes several surgical procedures that can be performed in obese patients. Per the 1991 National Institutes of Health Consensus Conference Guidelines, patients are considered as surgical candidates only if their BMI is ≥40 kg/m^2 or if their BMI is ≥35 kg/m^2 and they suffer from other life-threatening comorbidities, such as type 2 diabetes, hypertension, and cardiovascular disease. Presently, the three most common surgical procedures for obesity are the Roux-en-Y gastric bypass, the vertical banded gastroplasty, and the adjustable gastric band with sleeve gastrectomy and duodenal switch, which is less commonly performed. In the Swedish Obesity Study (SOS), the mean changes in weight and risk factors were more favorable among the subjects treated by gastric bypass than among those treated by banding or vertical banded gastroplasty (9). The maintained weight change over 10 years was 25% in the gastric bypass subgroup. In the year 2002–2003, worldwide, 146,301 bariatric surgery operations were performed by 2,839 bariatric surgeons, and 103,000 of these operations were performed in U.S./Canada by 850 surgeons (10).

The outcomes after surgically induced weight loss published in the last years are impressive (9,11,12). In a meta-analysis of 22,094 patients (mean age 47 years, mean BMI 46.9, 72.6% women), the mean percentage of excess weight loss was 61.2% for all patients (12). Excessive weight loss was higher for patients who underwent gastric bypass (61.6%) or gastroplasty (68.2%) compared with those who received gastric banding (47.5%). Remarkably, diabetes was completely resolved in 76.8% of patients and resolved or improved in 86.0%. Hyperlipidemia improved in ≥70% of patients, and hypertension was resolved in 61.7% and resolved and improved in 78.5%. Obstructive sleep apnea was resolved in 85.7% of patients and was resolved or improved in 83.6% of patients.

The long-term outcome data of a controlled surgical intervention study of obesity (Swedish Obesity Study) were recently reported by Lars Sjöström at the International Federation of Surgery for Obesity congress in Sydney as well as at the European Association for the Study of Diabetes (EASD) congress in Copenhagen (13). In the Swedish Obesity Study, a surgical group of 2,010 patients (matched by age, sex, BMI, and comorbidities) was compared with a nonsurgical control group consisting of 2,037 patients, and

From the [1]Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria; and the [2]Department of Surgery, Stanford University, Stanford, California.

Address correspondence and reprint requests to Professor Dr. Guntram Schernthaner, Department of Medicine I, Rudolfstiftung Hospital Vienna, Juchgasse 25, A-1030 Vienna Austria. E-mail: guntram.schernthaner@wienkav.at.

The authors of this article have no relevant duality of interest to declare.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: GLP, glucagon-like peptide.

DOI: 10.2337/dc08-s270

both groups were followed for 15 years. Surgically induced weight loss frequently resolved or markedly improved diabetes, reduced myocardial infarction by 43%, and provided a 31% reduction in overall mortality. In this single trial, weight loss induced by bariatric surgery had no effect on incidence of stroke. Interestingly, the benefit in the reduction of myocardial infarction and overall mortality was almost exclusively seen in diabetic patients. The less impressive effects observed in the nondiabetic patients of the Swedish Obesity Study (13) might be explained by the fact that the cardiovascular risk factor profile is frequently quite favorable in morbidly obese subjects despite the accumulation of >40 kg excess fat (14). The postoperative mortality was low and was kept at ~0.25%.

The significant reduction of total mortality in the well-performed randomized Swedish Obesity Study is in line with earlier observational studies reporting a reduced mortality in patients who underwent bariatric surgery (15,16). A retrospective analysis of 232 type 2 diabetic patients with morbid obesity (mean BMI 50 kg/m^2), who underwent either gastric bypass operation (n = 154) or did not undergo surgery (n = 78), demonstrated a mortality rate of only 9% in the surgical group during the 9-year follow-up compared with 28% in the nonsurgical control group (15). Patients in the control group had 4.5 times the incidence of death of patients in the surgical group. Notably, the improvement in the mortality rate in the surgical group was primarily due to a decrease in the number of cardiovascular deaths. An observational two-cohort study compared the outcome of 1,035 severely obese patients who underwent bariatric surgery with a control group of 5,746 age- and sex-matched severely obese patients who had not undergone weight reduction surgery (16). The mortality rate in the bariatric surgery cohort was 0.68% compared with 6.17% in control subjects, which translated to an impressive 89% reduction in the relative risk of death. Given that this was a retrospective analysis, the impact of the composition of the control group or practice patterns, particularly the use of cardiovascular preventive drugs, might have contributed to the huge difference between the two cohort studies.

It is now generally accepted that weight loss induced by bariatric surgery is the most effective therapy available for people who are extremely obese. It reverses, ameliorates, or eliminates major cardiovascular risk factors, including diabetes, hypertension, and lipid abnormalities. However, large epidemiological follow-up studies have shown that obesity per se increases cardiovascular risk, independent of other associated traditional cardiovascular risk factors (17,18). Adipose tissue is the predominant site of fat stores. Increasing obesity results in an overload of lipids within the body's natural storage sink (i.e., the adipocyte) followed by the necessary deposition of fat within ectopic sites such as muscle, liver, and pancreas. The resulting metabolic derangements are associated with insulin resistance, central obesity, and chronic inflammation as adipose tissue acts as an endocrine organ, producing and secreting a host of biologic mediators. There is now increasing evidence that these less well-characterized atherogenic biomarkers or mediators have an important role in obesity-related cardiovascular risk, such as chronic inflammation, endothelial dysfunction, and hypercoagulation (11,19–25). Recent studies have shown that weight loss induced by surgery results in an impressive reduction of insulin resistance (11,21), reduces relevant markers (C-reactive protein, interleukin-6, interleukin-18, and sCD40L) of chronic vascular inflammation (11,21–23), and decreases well-established cardiac risk factors that have been shown to be important predictors of cardiovascular morbidity and mortality (26–30). In addition, surgery improves endothelial dysfunction (24) and reduces key factors responsible for the increased atherothrombotic risk of the morbidly obese patients, such as tissue factor, factor VII, and plasminogen activator inhibitor (PAI)-1 (19,20).

REVERSIBILITY OF DIABETES AFTER BARIATRIC SURGERY

— Of considerable interest for morbidly obese patients with diabetes is the observation that euglycemia and normal insulin levels occur within days after surgery, long before there is any significant weight loss (31). Morbid obesity per se is associated with profound insulin resistance and marked insulin hypersecretion, but the dynamics of β-cell function (i.e., β-cell glucose sensitivity, rate sensitivity, and potentiation) are preserved (11,32). On the other hand, overt diabetes and impaired glucose tolerance are characterized by a progressive loss of β-cell glucose sensitivity, independent of insulin resistance (33). It is well known that bariatric surgery leads to a large improvement in insulin sensitivity (two- to threefold increase), which can be seen early after surgery before any substantial weight loss has occurred (11,34,35). Interestingly, absolute insulin secretion decreases significantly after bariatric surgery, although detailed information in patients with overt and more advanced diabetes is still very limited.

The mechanisms underlying the dramatic effects of malabsorptive surgery on insulin sensitivity and β-cell function are poorly understood. Several mechanisms have been proposed for the early improvement of glucose tolerance after bariatric surgery (36). Among them, caloric restriction and changes in gut hormone release have received the most attention. Glucagon-like peptide (GLP)-1 has emerged as a potential key mediator, since patients after Roux-en-Y gastric bypass had increased postprandial plasma levels of peptide YY and GLP-1 favoring enhanced satiety (37). However, more recent studies have questioned that GLP-1 is responsible for reversal of diabetes after surgery (38,39). Morinigo et al. (38) have demonstrated that GLP-1 response to a meal is not a critical factor for the early amelioration in glucose homeostasis after gastric bypass. Six weeks after surgery, the GLP-1 increase was only significant in patients with normal glucose or impaired glucose tolerance, but not in the diabetic patients. In a longitudinal study (39), fasting GLP-1 concentrations decreased and peptide YY levels increased independently of each other in morbidly obese patients 2 years after dramatic weight loss, indicating that the relationship between these gut hormones seems to be more complicated than assumed before. A very recent three-year follow-up study (40) in diabetic patients has shown that reversibility of diabetes is dependent on the improvement of skeletal muscle insulin sensitivity, mediated by changes in the expression of genes regulating glucose and fatty acid metabolism in response to nutrient availability.

PERIOPERATIVE RISK AND CARE OF BARIATRIC SURGERY

— There is clear and convincing evidence that bariatric surgery is a powerful therapy in treating morbid obesity and its health consequences. The ideal target population for bariatric surgery are morbidly obese patients with diabetes and metabolic syndrome because of the enormous benefit derived by surgi-

cal treatment and the large risk of premature mortality engendered by diabetes and the metabolic syndrome (41). Given the paucity of alternative treatments for weight loss in this challenging population, early and prompt surgical referral of the morbidly obese patient with diabetes and metabolic syndrome is needed. Despite the high prevalence of comorbidity in this population, bariatric surgery can provide tertiary prevention of the complications of obesity.

Patient education and selection are important components in long-term success of bariatric surgery. While surgery provides important physiological reinforcement of a healthier lifestyle, patients must still make critical changes in their dietary, exercise, and sleep habits. Preoperative education ensures that patients are prepared to make these substantial changes in lifestyle (42). Surgery remains a tool, not a cure, for morbidly obese patients in their change in lifestyle. These habits are critical given that morbid obesity is a chronic disease and requires lifelong maintenance. Identification of preoperative characteristics of success after surgery remains elusive, and the best determinant of postoperative success is both patient and programmatic commitment (43).

The risk of complications may temper some enthusiasm for bariatric surgery. There are demonstrated differences between surgical techniques and outcomes (44). Randomized trial evidence reveals that the laparoscopic approach shortens time to return to work and decreases wound and pulmonary complications (45). Among the different surgical procedures, the rate of complications is inversely proportional to the amount of weight loss produced by each surgery (44). Beyond the type of procedure, there are identified risk factors for complications after bariatric surgery, including age, sex, BMI, comorbidities, and insurance status (46–50). It should be noted that the best demonstrated and most protective effect against complications is an experienced surgeon and hospital (46,49). In addition, complications may not affect long-term weight loss, which is the outcome that best predicts long-term mortality risk (51).

Age has been repeatedly demonstrated to be a factor influencing outcome after bariatric surgery. In a study examining bariatric surgery outcomes for Medicare patients, the rate of complications for those <65 and >65 years equalized when patients were treated by experienced surgeons (46). Male sex has also been identified as a risk factor for complications after bariatric surgery. Male sex may lead to more complications due to increased technical difficulty caused by a higher BMI, more visceral fat, and potentially more advanced comorbidities (47–49). In the U.S. (52), in various European countries (53,54), as well as in New Zealand (55), ~80% of bariatric surgery patients are women. The proportion of men undergoing bariatric surgery does not reflect the sex distribution of morbid obesity. Clearly, male morbidly obese patients seek surgical care less often, which may be due to general decreased access to care by men as well as a greater social acceptance of the morbidly obese male. Increased BMI is also recognized as a risk factor for complications due primarily to technical ability to complete the operation and the potential for worsened comorbidity in these patients (49). Finally, certain comorbidities have been demonstrated to increase complication rates including diabetes, chronic obstructive pulmonary disease, sleep apnea, and hypertension (47,49). Studies have substantiated the risk of Medicare insurance status upon bariatric surgery outcomes (46,48). Most likely, Medicare insurance status is a proxy for age, socioeconomic status, and disability. Although patients with the most risk factors carry the greatest risk for surgery, those high-risk patients may also derive the most benefit from bariatric surgery given the disease burden they carry (56).

All of these risk factors are nonmodifiable before surgery. As mentioned previously, the single consistent protective factor for complications is both surgeon and hospital volume. The volume-outcome effect is well established in surgery and, unlike the other risk factors for complications, modifiable. For bariatric surgery, it has been demonstrated that a high-volume surgeon and high-volume hospital leads to decreased morbidity and mortality (46,50). In the U.S., this volume outcome effect has been recognized by the Centers for Medicare and Medicaid Services who now require that Medicare patients only undergo surgery at Bariatric Surgery Centers of Excellence (57). Numerous criteria compose a Bariatric Surgery Center of Excellence, but the primary criteria are surgeon volume >50 cases and hospital volume >125 cases annually. While a referral to a Bariatric Surgery Center of Excellence may lead to decreased morbidity and mortality, this referral pattern must be balanced with appropriate and sufficient access to care for a vulnerable population without other therapeutic options.

Surgical volume is a surrogate measure for a wide expanse of practice patterns that determine best outcomes. More research is required to determine which practice patterns most effect outcomes including preoperative weight loss, advanced surgical training, and surgical assistant status (58,59). Given this need for further research, clinically derived prospectively maintained databases regarding bariatric surgery are required (56,60).

LONG-TERM RESULTS OF BARIATRIC SURGERY: COMPLICATIONS, FAILURES, AND WEIGHT GAIN

— The long-term complications and outcomes was recently analyzed in a 12-year follow-up study (53) of 1,791 consecutive patients receiving laparoscopic adjustable gastric banding (LABG) in Italy. Overall, 106 (5.9%) patients required reoperation (band removal in 3.7% and band repositioning in 2.7%). Port-related complications occurred in 200 patients (11.2%), and 41 patients (2.3%) underwent further surgery due to unsatisfactory results. A case-control study involving 821 surgically treated patients versus 821 treated by medical therapy showed a statistically significant difference in survival in favor of the surgically treated group (53). Based on their findings, the authors concluded that LAGB can achieve effective, safe, and stable long-term weight loss with a low complication rate in experienced hands. In contrast, a 10-year long-term follow-up study of 317 patients receiving LAGB in Switzerland (54) showed high long-term complication and failure rates. Overall, 105 (33.1%) of the patients developed late complications, including band erosion in 9.5%, pouch dilatation/slippage in 6.3%, and catheter- or port-related problems in 7.6%. Major reoperation was required in 21.7% of the patients. The mean excess weight loss at 5 years was 58.5% in patients with the band still in place. The failure rate increased from 13.2% after 18 months to 36.9% at 7 years. According to the experience of the Swiss authors with a 5-year failure rate of 37% and 7-year success rate (excess weight loss >50%) in only 43%, LAGB should no longer be con-

sidered as the procedure of choice for obesity (54). On the other hand, a long-term follow-up study of 342 severely obese patients who underwent gastric bypass in New Zealand (55) showed excellent long-term outcomes. BMI and percent excess weight loss after 1, 5, and 10 years were 28.7 and 89%, 31.2 and 70%, and 31 and 75%, respectively. In addition, 62% of individuals with hypertension before surgery were cured and 25% had improved and 85% of those with type 2 diabetes were cured and 10% had improved. Thus, the excellent outcomes, in terms of weight loss and improvement in comorbidities, seen in both the short and medium term after gastric bypass, were well maintained into the longer term. Recently, Christou et al. (61) reported long-term results of 228 gastric bypass patients who were followed up for a mean of 11.4 years (range 4.7–14.9); 63.2% of them were morbidly obese (BMI <50 kg/m^2) and 36.8% were extremely obese (BMI ≥ 50 kg/m^2). The extremely obese patients lost more rapidly from the preoperative BMI to the lowest BMI and gained more rapidly than the morbid obese patients thereafter ($P < 0.0001$). In the morbidly obese patients, the mean BMI before surgery was 44.3 kg/m^2; the nadir BMI was 26.4 kg/m^2 and occurred 1.9 years after surgery but increased again to 31.0 after 11.4 years after surgery. In the extreme obese patients, the initial mean BMI of 56.2 kg/m^2 decreased to 31.4 kg/m^2 at 2.2 years after surgery, but increased significantly to 38.3 kg/m^2 after 11.6 years after surgery. Satiety is a prominent feature of weight loss after gastric bypass and persists in those patients with an excellent result. Patients who regain large amounts of weight say they are eating almost as much as before the operation. One patient died of pulmonary embolus on the second postoperative day, resulting in a 0.36% 30-day operative mortality. Seven patients died after surgery at 4.8 years of suicide, 5.7 years of suicide, 6.6 years of liver failure, 8 years of unknown cause, 8.8 years of pulmonary embolus, 8.8 years of cardiac failure, and 13 years of cerebrovascular accident, for a 3.2% long-term post-operative mortality. In conclusion, significant weight gain occurred continuously in patients after reaching the nadir weight after gastric bypass. Remarkably, despite this weight gain, the long-term mortality remained low at 3.1%. Other long-term studies (>10-year follow-up) reported much lower late failure rates (31,62,63). Hess et al. (62) were able to follow 167 of 182 patients (92%) >10 years after biliopancreatic diversion with duodenal switch. They found that 87 (52%) had lost at least 80% of excess weight and that only 6% lost >50% of excess weight. Scopinaro et al. (63) reported excess weight loss of 74% at 10 years, 75% at 12 years, and 77% at 18 years, with no difference between morbid obese and extreme obese patients. Pories et al. (31) showed a remarkable stability of postoperative weight after gastric bypass for up to 14 years. Their study of 608 patients with a 97% follow-up showed a 58% loss of excess weight after 5 years and a BMI of 33.7 kg/m^2. After 10 years, the excess weight loss was 55% and the BMI was 34.7 kg/m^2.

CONCLUSIONS — Even though there are varying degrees of evidence for different surgeries, there is a clear preponderance of evidence for all weight loss surgeries to be vastly superior to traditional weight loss therapies in promoting weight reduction. Obesity is an independent risk factor for cardiovascular disease and contributes strongly to additional risk factors such as hypertension, diabetes, hyperlipidemia, and biochemical inflammatory markers. Cardiac risk among surgically treated morbidly obese patients is greatly diminished by weight loss, comorbidity resolution, and advantageous alteration of biochemical cardiovascular risk factors.

Obesity is a worldwide epidemic with serious medical and economic consequences. The only effective and enduring therapy for morbid obesity is weight loss surgery. Weight loss surgery has the unique ability to solve many different health concerns through a single intervention. Certain risks exist for weight loss surgery that can be mitigated by surgical experience and patient selection, education, and lifelong surveillance. Strong evidence supports the well-known benefits of weight loss surgery including weight loss, comorbidity resolution, quality of life improvement, and increased lifespan. Weight loss surgery is a lifesaving intervention in the right patients and in the right hands.

ADDENDUM — After submission of this review, two important long-term outcome studies (64,65) performed in patients after gastric bypass surgery were published. Sjöström et al. (64) conducted a prospective, controlled study of bariatric surgery called the Swedish Obese Subjects (SOS) study, in which 2,010 overweight patients wishing surgery were matched with 2,037 obese patients not desiring surgery. At 10 years, weight losses ranged from 14 to 25% among subjects who had undergone bariatric surgery as compared with only 2% among control subjects. In the surgery group, there was a significant reduction in the adjusted hazard ratio for death (29%) after an average follow-up of 10.9 years. Adams et al. (65) conducted a retrospective cohort study with 7,925 severely obese control subjects obtained from driver's license records that were matched to 7,925 patients who had undergone gastric bypass surgery. During a mean follow-up of 7.1 years, adjusted long-term mortality from any cause in the surgery group decreased by 40%. Cause-specific mortality in the surgery group decreased from diabetes by 92%, from coronary artery disease by 56%, and from cancer by 60%. The reduction of mortality from diabetes and cancer are particularly noteworthy. However, rates of death not caused by disease, such as accidents and suicide, were 58% higher in the surgery group than in the control group.

References

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM: Prevalence of overweight and obesity in the United States 1999–2004. *JAMA* 295: 1549–1555, 2006
2. McTigue K, Larson JC, Valoski A, Burke G, Kotchen J, Lewis CE, Stefanick ML, Van Horn L, Kuller L: Mortality and cardiac and vascular outcomes in extremely obese women. *JAMA* 296:79–86, 2006
3. Yoon K, Lee J-H, Kim J-W, Cho JH, Choi Y-H, Ko S-H, Zimmet P, Son HY: Epidemic obesity and type 2 diabetes in Asia. *Lancet* 368:1681–1686, 2006
4. Calle EE, Thun MJ, Petrelli JM: Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 341: 1097–1105, 1999
5. Leibson CL, Williamson DF, Melton LJ 3rd, Palumbo PJ, Smith SA, Ransom JE, Schilling PL, Narayan KM: Temporal trends in BMI among adults with diabetes. *Diabetes Care* 24:1584–1589, 2001
6. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody, Hayflick L, Butler RN, Allison DB, Ludwig DS: A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 352:1138–1145, 2005
7. Anderson JW, Grant L, Gotthelf L, Stifler LT: Weight loss and long-term follow-up of severely obese individuals treated with

an intense behavioral program. *Int J Obes* 31:488–493, 2006
8. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, Strauss B, Marks S, Schachter L, Chapman L, Anderson M: Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 144: 625–633, 2006
9. Sjöstrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H, Swedish Obese Subjects Study Scientific Group: Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 351:2683–2693, 2004
10. Buchwald H, Williams SE: Bariatric surgery worldwide 2003. *Obes Surg* 14: 1157–1164, 2004
11. Kopp HP, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, Roka R, Schernthaner G: Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol* 23:1042–1047, 2003
12. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K: Bariatric surgery: a systematic review and meta-analysis. *JAMA* 292: 1724–1737, 2004
13. Sjöström L: Bariatric surgery in diabetic patients: what is the evidence? 42nd EASD Meeting, Copenhagen, Denmark, 2006. *Diabetologia* (Suppl. 1) 2006
14. Barakat HA, Mooney N, O'Brien K, Long S, Khazani PG, Pories W, Caro JF: Coronary heart disease risk factors in morbidly obese women with normal glucose tolerance. *Diabetes Care* 16:144–149, 1993
15. MacDonald KG, Long SD, Swanson MS, Brown BM, Morris P, Dohm GL, Pories WJ: The gastric bypass operation reduces the progression and mortality of NIDDM. *J Gastrointest Surg* 1:213–220, 1997
16. Christou NV, Sampalis JS, Liberman M, Look D, Auger S, McLean AP, MacLean LD: Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg* 240:416–423, 2004
17. Kim KS, Owen WL, Williams D, Adams-Campbell LL: A comparison between BMI and Conicity index on predicting coronary heart disease: the Framingham Heart Study. *Ann Epidemiol* 10:424–431, 2000
18. Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G, Janzon L: Influence of obesity on cardiovascular risk: twenty three-year follow up of 22,025 men from an urban Swedish population. *Int J Obes* 26:1046–1053, 2002
19. Primrose JN, Davies JA, Prentice CR, Hughes R, Johnston D: Reduction in factor VII, fibrinogen and plasminogen activator inhibitor-1 activity after surgical treatment of morbid obesity. *Thromb Haemost* 68:396–399, 1992
20. Kopp CW, Kopp HP, Steiner S, Kriwanek S, Krzyzanowska K, Bartok A, Roka R, Minar E, Schernthaner G: Weight loss reduces tissue factor in morbidly obese patients. *Obes Res* 11:950–960, 2003
21. Hanusch-Enserer U, Cauza E, Spak M, Endler G, Dunky A, Tura A, Wagner O, Rosen HR, Pacini G, Prager R: Improvement of insulin resistance and early atherosclerosis in patients after gastric banding. *Obes Res* 12:284–291, 2004
22. Schernthaner GH, Kopp HP, Kriwanek S, Krzyzanowska K, Satler M, Koppensteiner R, Schernthaner G: Effect of massive weight loss induced by bariatric surgery on serum levels of interleukin-18 and monocyte-chemoattractant-protein-1 in morbid obesity. *Obes Surg* 16:709–715, 2006
23. Schernthaner GH, Kopp HP, Krzyzanowska K, Kriwanek S, Hoellerl F, Koppensteiner R, Schernthaner G: Soluble CD40L in patients with morbid obesity: significant reduction after bariatric surgery. *Eur J Clin Invest* 36:395–401, 2006
24. Krzyzanowska KA, Mittermayer F, Kopp HP, Wolzt M, Schernthaner G: Weight loss reduces circulating asymmetrical dimethylarginine concentrations in morbidly obese women. *J Clin EndocrMetab* 89:6277–6281, 2004
25. Kopp HP, Spranger J, Möhlig M, Krzyzanowska K, Pfeiffer AF, Schernthaner G: Effect of weight loss on plasma levels of adiponectin in association with markers of chronic subclinical inflammation and the insulin resistance syndrome in obese subjects. *Int J Obes (Lond)* 29:766–771, 2005
26. Blankenberg S, Tiret L, Bickel C Peetz D, Cambien F, Meyer J, Rupprecht HJ: Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. *Circulation* 106:24–30, 2002
27. de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, McCabe CH, Cannon CP, Braunwald E: Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. *Circulation* 107:690–695, 2003
28. Heeschen C, Dimmeler S, Hamm CW, van den Brand MJ, Boersma E, Zeiher AM, Simoons M: Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med* 348: 1104–1111, 2003
29. Williams B, Hagedorn J, Lawson E, Galanko J, Safadi B, Curet M, Morton JM: Gastric bypass reduces biochemical cardiac risk factors, SOARD. *Surg Obes Relat Dis* 3:8–13, 2007
30. Krzyzanowska K, Mittermayer F, Wolzt M, Schernthaner G: Asymmetric dimethylarginine predicts cardiovascular events in patients with type 2 diabetes. *Diabetes Care* 30:1834–1839, 2007
31. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, et al.: Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 222:339–350, 1995
32. Camastra S, Manco M, Mari A, Greco AV, Frascerra S, Mingrone G, Ferrannini E: Beta-cell function in severely obese type 2 diabetic patients: long-term effects of bariatric surgery. *Diabetes Care* 30:1002–1004, 2007
33. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA: β-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493–500, 2005
34. Wickremesekera K, Miller G, Naotunne TD, Knowles G, Stubbs RS: Loss of insulin resistance after Roux-en-Y gastric bypass surgery: a time course study. *Obes Surg* 15:474–481, 2005
35. Camastra S, Manco M, Mari A, Baldi S, Gastaldelli A, Greco AV, Mingrone G, Ferrannini E: Beta-cell function in morbidly obese subjects during free living: long-term effects of weight loss. *Diabetes* 54: 2382–2389, 2005
36. Cummings DE, Overduin J, Foster-Schubert KE, Carlson MJ: Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. *Surg Obes Relat Dis* 3:109–115, 2007
37. le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, Shurey S, Ghatei MA, Patel AG, Bloom SR: Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg* 243:108–114, 2006
38. Morinigo R, Lacy AM, Casamitjana R, Delgado S, Gomis R, Vidal J: GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects. *Obes Surg* 16:1594–1601, 2006
39. Reinehr T, Roth CL, Schernthaner GH, Kopp HP, Kriwanek S, Schernthaner G: Peptide YY and glucagon-like peptide-1 in morbidly obese patients before and after surgically induced weight loss. *Obes Surg* 17:1571–1577, 2007
40. Rosa G, Mingrone G, Manco M, Euthine V, Gniuli D, Calvani R, Calvani M, Favuzzi AM, Castagneto M, Vidal H: Molecular mechanisms of diabetes reversibility after bariatric surgery. *Int J Obes (Lond)* 31:1429–1436, 2007
41. Malik S, Wong N, Franklin S, Kamath TV, L'Italien Gj, Pio JR, Williams GR: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 110:1245–1250, 2004
42. Giusti V, DeLucia A, DiVetta, Calmes JM, Heraief E, Gaillard RC, Burckhardt P,

Suter M: Impact of preoperative teaching on surgical option of patients qualifying for bariatric surgery. *Obes Surg* 14:1241–1246, 2004
43. Van Hout GC, Verschure SK, van Heck GL: Psychosocial predictors of success following bariatric surgery. *Obes Surg* 15: 552–560, 2005
44. Maggard M, Shugarman L, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG: Meta-analysis: surgical treatment for obesity. *Ann Intern Med* 142:547–559, 2005
45. Puzziferri N, Austrheim IT, Wolfe BM, Wilson SE, Hguyen NT: Three-year follow-up of a prospective randomized trial comparing laparoscopic versus open gastric bypass. *Ann Surg* 243:181–188, 2006
46. Flum DR, Salem L, Brockel Elrod J, Dellinger EP, Cheadle A, Chan L: Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. *JAMA* 294:1903–1908, 2005
47. Fernandez AZ, DeMaria EJ, Tichansky DS, Kellum JM, Wolfe LG, Meador J, Sugerman HJ: Multivariate analysis of risk factors for death following gastric bypass for treatment of morbid obesity. *Ann Surg* 239:698–703, 2004
48. Poulose Bk, Griffin MR, Zhu Y, Smalley W, Richards WO, Wright JK, Melvin W, Holzman MD: National analysis of adverse patient safety events in bariatric sugery. *Am Surg* 71:406–413, 2005
49. Livingston EH, Ko CY: Assessing the relative contribution of individual risk factors on surgical outcome for gastric bypass surgery: a baseline probability analysis. *J Surg Rsch* 105:48–52, 2002
50. Liu JH, Zingmond D, Etzioni DA, O'Connell JB, Maggard MA, Livingston EH, Liu CD, Ko CY: Characterizing the performance and outcomes of obesity surgery in California. *Am Surg* 69:823–828, 2003
51. Morton JM, Downey J, Hagedorn JC, Encarnacion BE, Ketchum E, Curet M, Hernandez-Boussard T: Post-operative complications do not affect weight loss. *JACS* 2008. In press
52. Santry HP, Gillen DL, Lauderdale DS: Trends in bariatric surgical procedures. *JAMA* 294:1909–1917, 2005
53. Favretti F, Segato G, Ashton D, Busetto L, De Luca M, Mazza M, Ceoloni A, Banzato O, Calo E, Enzi G: Laparoscopic adjustable gastric banding in 1,791 consecutive obese patients: 12-year results. *Obes Surg* 17:168–175, 2007
54. Suter M, Calmes JM, Paroz A, Giusti V: A 10-year experience with laparoscopic gastric banding for morbid obesity: high long-term complication and failure rates. *Obes Surg* 16:829–835, 2006
55. White S, Brooks E, Jurikova L, Stubbs RS: Long-term outcomes after gastric bypass. *Obes Surg* 15:155–163, 2005
56. Wolfe BM, Morton JM: Weighing in on bariatric surgery: procedure use, readmission rates, and mortality. *JAMA* 294: 1960–1963, 2005
57. http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=160. Accessed December 2006
58. Hsu GP, Morton JM, Jin L, Safadi BY, Satterwhite TS, Curet MJ: Laparoscopic Roux-en-Y gastric bypass: differences in outcome between attendings and assistants of different training backgrounds. *Obes Surg* 15:1104–1110, 2005
59. Schauer P, Ikramuddin S, Hamad G, Gourash W: The learning curve for laparoscopic Roux-en-Y gastric bypass is 100 cases. *Surg Endosc* 17(2):212–5. Epub 2002 Dec 4, 2003
60. Nguyen NT, Morton JM, Wolfe BM, Schirmer B, Ali M, Traverso LW: The SAGES bariatric surgery outcome initiative. *Surg Endosc* 19):1429–1438, 2005
61. Christou NV, Look D, Maclean LD: Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. *Ann Surg* 244:734–740, 2006
62. Hess DS, Hess DW, Oakley RS: The biliopancreatic diversion with the duodenal switch: results beyond 10 years. *Obes Surg* 14:408–416, 2005
63. Scopinaro N, Marinari G, Camerini G, Papadia F: 2004 ABS Consensus Conference: Biliopancreatic diversion for obesity: state of the art. *Surg Obes* 1:317–328, 2005
64. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM: Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.* 357:741–52, 2007
65. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC: Long-term mortality after gastric bypass surgery. *N Engl J Med.* 357:753–61, 2007