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RESULTS OF BARIATRIC SURGERY

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■ **Abstract** Overweight and obesity are rapidly growing to epidemic proportions in the United States and globally. Since sustainable weight loss is only achieved by bariatric surgery, medicine has seen an explosion in the diversity and number of bariatric procedures performed over the past few years. Systematic studies of postoperative outcomes and investigations into the physiology and biology of weight loss provide a more comprehensive understanding of the sequelae of bariatric surgery. 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. Whereas there are conflicting data on the cardiovascular effects of peripheral, subcutaneous liposuction, malabsorptive bariatric procedures result almost universally in significant amelioration of insulin resistance, hypertension, dyslipidemia, and hepatic steatosis. Concomitant changes in adipocyte-derived hormones may provide mechanistic explanations to the observed improvements.

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INTRODUCTION

Overweight and obesity are rapidly growing to epidemic proportions in the United States and globally. In the year 2000, 65% of U.S. adults were overweight (body mass index, or BMI, >25 kg/m^2), accounting for approximately 180 million Americans (51, 70). Globally in 2003, the overweight population was estimated at one billion people, with 300 million of those being obese (BMI ≥ 30) (2). Not surprisingly, much interest and energy are now focused on treating not only obesity itself but also the deleterious metabolic and pathophysiological sequelae accompanying this disease. These metabolic sequelae are far-reaching, often leading to insulin resistance, diabetes, hypertension, and dyslipidemia—the constellation of which has been termed the "metabolic syndrome." The International Diabetes Federation (IDF) has recently released its definition of the metabolic syndrome, which is predicated upon racial- and gender-specific criteria for "central" obesity (Table 1)

TABLE 1 International Diabetes Federation criteria for the metabolic syndrome

Criteria
Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups)
plus any two of the following four factors:
raised TG level: 3 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
raised fasting plasma glucose: (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes
If above 5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

(3). The importance of such designations is the association with morbidity and mortality. In a large Scandinavian family study of 4483 subjects with varying degrees of altered insulin and/or glucose metabolism ranging from normal glucose tolerance to type 2 diabetes mellitus (T2DM), a three-fold increase in cardiovascular disease and a nearly six-fold increase in cardiovascular mortality were seen in patients with the metabolic syndrome (78).

The success rate of diet as the primary weight loss intervention (maintenance of all weight loss or maintenance of at least 9–11 kg of initial weight lost) was only 15% in a review involving more than 3000 study subjects with initial degree of overweight being 3%–89% in 12 studies and a BMI of 34.3–39.4 kg/m^2 in three studies; the subjects were followed for a median of five years (12). In a meta-analysis from the Cochrane database, Padwal et al. (113) investigated the efficacy of orlistat and sibutramine as oral antiobesity agents. The mean body mass indices of the subjects were 35.7 and 33.4 kg/m^2, respectively. Weight loss after at least one year was 2.7 kg and 4.3 kg more than placebo, and attrition rates were 33% and 43% for orlistat- and sibutramine-treated patients, respectively. This evidence suggests that diet with or without medication has proven ineffective as a sustainable mechanism for weight loss and weight control. Indeed, the National Institutes of Health (NIH) issued a consensus statement identifying bariatric surgery as the only means for sustainable weight loss (19).

In this setting, medicine has seen an explosion in the diversity and number of bariatric procedures performed over the past few years. From 1992 to 2003, the number of bariatric procedures performed in the United States increased greater than sixfold (140). They run the gamut from simple restrictive procedures done laparoscopically in an outpatient setting to complex gastrointestinal operations that involve some form of restrictive and malabsorptive components. Accordingly, the degree of accompanying weight loss and resolution of comorbidities is also wide-ranging. Systematic studies of postoperative outcomes and investigations into the physiology and biology of weight loss provide a more comprehensive understanding of the sequelae of bariatric surgery.

FAT AS AN ENDOCRINE ORGAN

Adipose tissue is the predominant site of fat stores; however, limited stores are also present in non-adipose organs such as the liver, pancreas, and muscle. Non-differentiated preadipocytes within adipose tissue develop into mature adipocytes via a process initiated by peroxisome proliferator-activated receptor-γ (PPARγ) and CCAAT/enhancer binding proteins (C/EBPs) (50). These cells then gain their lipogenic capacity, insulin sensitivity, cytoplasmic lipid accumulation, and the ability to manufacture and secrete multiple hormones and cytokines such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), resistin, leptin, adiponectin, visfatin (57, 89).

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 and have been labeled the metabolic syndrome (125). This accumulation of fat in muscle and liver is correlated with insulin resistance (162). Evidence of a correlation between BMI, insulin resistance, and waist circumference (24) has led to a focus on the distinction between android (central) and gynoid (peripheral) obesity, with "central" fat conferring a greater risk of metabolic and cardiovascular complications.

In visceral adipose tissue, catecholamines elicit a greater lipolytic response, and the antilipolytic effect of insulin is blunted with increasing doses of insulin (104) relative to peripheral adipose tissue. Visceral fat predominates the production of certain adipokines (e.g., resistin, adiponectin) and inflammatory cytokines (e.g., IL-6 and PAI-1) (89). Conversely, subcutaneous fat has a higher basal rate of lipolysis, hormone-sensitive lipase activity, antilipolytic action of insulin, insulin receptor substrate 1 (IRS-1) expression, lipoprotein lipase activity, fatty acid uptake by preadipocytes, and leptin production (reviewed in 89).

Furthermore, visceral and subcutaneous fats differ in respect to their morphology and adipogenic capacity. Two preadipocyte populations exist in mesenteric, subcutaneous, and omental fat of humans. Relative to mesenteric or subcutaneous fat, the slowly replicating subtype comprises a statistically greater proportion of preadipocytes in omental tissue, has a lower lipid accumulating capacity, is more susceptible to TNF-α-induced apoptosis, and expresses less C/EBPα (adipogenic transcription factor) than does the rapidly replicating subtype. In fact, both preadipocyte subtypes accumulate less fat in omental tissue than in subcutaneous tissue (144), a finding that suggests a relative deficiency in visceral fat's ability to accommodate increasing fat stores, thereby leading to cellular injury.

Although the dichotomy of central and peripheral fat is revealing, visceral fat is not universally associated with the derangements of the metabolic syndrome (13, 84). Transgenic expression of human growth hormone (hGH) in the hypothalamus of the rat (13) induced late-onset obesity in males that is mostly visceral in nature and is due to adipocyte hyperplasia and not to hypertrophy—a finding that suggests that the visceral fat in these animals has a greater storage potential due to a greater number of adipocytes. The animals have normal fasting blood glucose, enhanced insulin sensitivity, and a lack of intrahepatocellular or intramyocellular fatty deposits. This evidence indicates that abdominal obesity cannot be the sole, fundamental cause of the metabolic syndrome. The lipodystrophies, despite their heterogeneity, further confound the dichotomy of peripheral and central obesity and lend credence to fat overload as a primary phenomenon leading to insulin resistance and the metabolic syndrome.

MALABSORPTIVE BARIATRIC PROCEDURES

Bariatric surgery includes several surgical procedures that can be performed in obese patients. Patients are considered as surgical candidates only if their BMI is $\geq$40 or if their BMI is $\geq$35 and they suffer from other life-threatening

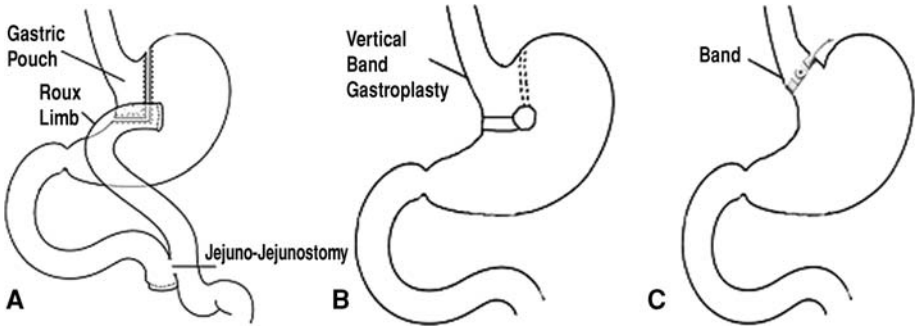

Figure 1 (*A*) Roux-en-Y gastric bypass; (*B*) vertical banded gastroplasty; (*C*) adjustable gastric banding.

comorbidities, such as T2DM, hypertension, and cardiovascular disease. Surgical procedures were first introduced in the 1950s with jejuno-ileal bypass (JIB) and biliopancreatic diversion (BPD), which cause weight loss by malabsorption. BPD is still employed in select regions of the world; however, the long-term nutritional consequences, including liver and renal failure, are such that JIB is no longer in widespread use. Restrictive procedures and nutritionally acceptable malabsorptive procedures have subsequently been developed that produce effective weight loss with fewer long-term consequences.

The three most common surgical procedures for obesity are shown in Figure 1 and are described below.

Roux-en-Y Gastric Bypass

The Roux-en-Y gastric bypass (RYGB) procedure combines restriction and malabsorption by creating a small gastric pouch (usually by complete transection of the upper stomach) and anastomosis of a Roux-en-Y loop of jejunum to the pouch, thus bypassing the stomach, duodenum, and proximal jejunum.

Vertical Banded Gastroplasty

In vertical banded gastroplasty, a vertical partition of the upper stomach with staples creates a small (20 mL) segment of stomach that fills rapidly with food and then empties slowly. The exit of the pouch is reinforced with a band of Marlex to prevent dilation.

Adjustable Gastric Band

The adjustable gastric band (AGB) procedure involves placement of a constricting band around the most proximal portion of the stomach to restrict food intake, thereby creating a narrow passage into the remainder of the stomach. An inflatable balloon incorporated into the band allows adjustment of the degree of outlet restriction.

Crookes (30) has recently reviewed in detail the specific bariatric surgical procedures, their perioperative complications, and controversial aspects of patient selection. Thus, the present review focuses on the metabolic sequelae of liposuction and malabsorptive and restrictive bariatric procedures.

METABOLIC CONSEQUENCES OF MALABSORPTIVE AND RESTRICTIVE BARIATRIC PROCEDURES

Effects on Blood Pressure

Improvement in blood pressure seems to be a universal result of bariatric surgery, irrespective of the specific operation performed. In 73 hypertensive patients followed for 10 years after BPD, 56% and 80% resolved their hypertension in 2 and 10 years, respectively (5). Sugerman et al.'s report (143) of 521 hypertensive RYGB patients found resolution in 69% at one year and 66% at five to seven years after operation. Those patients with resolution lost significantly more excess weight (66%) than did those who did not resolve (57%) their hypertension (143). Another series of 134 hypertensive RYGB patients with a median follow-up of four years showed similar results with resolution in 62% and improvement (i.e., use of fewer antihypertensive medications) in 25% (154). Laparoscopic adjustable gastric banding (LAGB) resulted in resolution of hypertension in 52%–74% of patients followed between 12 and 44 months after operation (42, 55, 118). As with RYGB, excess weight loss (EWL) was greater in the subset of patients who resolved their hypertension relative to those whose hypertension merely improved (118).

The apparent relationship between weight loss and resolution of hypertension is reasonable considering the strong epidemiologic evidence of a positive correlation between BMI and hypertension (20), and waist circumference and hypertension (80). Such a correlation begs the question as to the mechanism driving the relationship. As one might expect, the sympathetic nervous system (SNS) seems to be the common pathway through which multiple factors affect blood pressure.

Since the 1970s, a link between diet and the SNS has been shown. Young & Landsberg (159, 161) showed that rats fed either sucrose or a "cafeteria" diet displayed increased SNS activity that affected thermogenesis. This was followed by investigations in spontaneously hypertensive rats in which fasting was found to result in a 20% reduction in blood pressure (160). In a study of six human subjects, norepinephrine turnover and blood pressure were shown to increase with increasing energy intake (111). Furthermore, in a cross-sectional study of 572 men, 24-hour urinary norepinephrine levels positively correlated with BMI and increased caloric intake, and those subjects that were hyperglycemic and/or hyperinsulinemic had higher 24-hour norepinephrine levels relative to "normal" subjects (147).

A retrospective review of 100 patients undergoing vertical-banded gastroplasty with RYGB found abnormally high plasma renin, aldosterone, and angiotensin-converting-enzyme levels in morbidly obese patients with central obesity (132). In both central and peripheral obese patients, all hormone levels fell with weight loss. The fall in renin, however, was only significant in the peripherally obese

subjects. When plotted against % EWL in these subjects, angiotensin-converting-enzyme levels fell most rapidly and to the greatest degree, showing a predicted 30% reduction with ~50% EWL by at least eight months postoperatively (Figure 2). This change may occur sooner, but further studies earlier in the postoperative period are needed to refine any predictions.

Other hormonal mechanisms may contribute to obesity-related hypertension as well. Insulin, for example, enhances sympathetic outflow in rats (92) and humans (131). Additionally, chronic hyperleptinemia, whether due to exogenous administration, genetic manipulation (7), or diet induction (120), results in blood pressure elevation that is thought to be mediated via the SNS.

Hormonal Effects

Adipokines

ADIPONECTIN Despite the fact that adiponectin is produced solely by adipose tissue, obese individuals manifest lower adiponectin plasma levels than those seen in nonobese healthy controls. Adiponectin is the 244 amino acid, 30 kDa protein product of the apM1 gene transcript and is similar to collagen VIII and X (10, 97). Its production is specific to adipose tissue and its plasma concentration correlates negatively with insulin resistance and fat mass (153). When injected intraperitoneally into mice it increases hepatic insulin sensitivity (14). In the setting of decreased adiponectin gene expression, insulin resistance develops in mice. Conversely, exogenous administration of adiponectin to lipoatrophic mice reverses insulin resistance, and this is thought to be mediated by increased fatty acid uptake and metabolism, resulting in lowered hepatic and intramyocellular triglyceride accumulation (157). Adiponectin expression is selectively upregulated in the omental adipose tissue of morbidly obese patients with T2DM compared with morbidly obese subjects with normal oral glucose tolerance test (A. Torquati, unpublished findings). Studies to determine expression of the adiponectin receptors in these samples are still ongoing.

Hotta and colleagues (74) have shown that fasting plasma adiponectin levels are lower in T2DM than in nondiabetic subjects. Among the diabetic subjects, those with coronary artery disease had lower plasma adiponectin levels. Interestingly, plasma adiponectin levels rise after RYGB (150) and reach levels of lean controls (49), a finding that potentially supports the notion of an inverse relationship between fat mass and plasma adiponectin levels.

RESISTIN In 2001, Steppan and colleagues (141) identified an adipocyte-derived protein, named it resistin (resistance to insulin), and showed that it contributes to impaired glucose metabolism. Intraperitoneal administration of recombinant resistin to obese mice (diet-induced) resulted in insulin resistance, while simultaneous administration of antibodies to the protein improved glucose utilization. The same group of investigators recently demonstrated that resistin induces the gene expression of suppressor of cytokine signaling-3 (SOCS-3)—the product of which

is known to abrogate insulin signaling—thereby providing a potential mechanistic understanding of resistin's action (142). This apparent link between diabetes, obesity, and resistin has not manifested itself fully in the bariatric population. There are disparate reports regarding the relationship of resistin to BMI; some have noted its elevation in the setting of obesity (38, 150) whereas others have found no correlation with BMI (67, 93). Furthermore, in a study of 34 morbidly obese patients whose BMI fell from 49.6 to 34.9 (kg/m^2) six months after gastric bypass, resistin levels did not change (3.5 and 3.4 ng/mL pre- and postoperatively, respectively). Although resistin may contribute to the insulin resistance associated with obesity, there is no clear evidence that bariatric surgery acts on resistin to alter glucose metabolism postoperatively.

LEPTIN Leptin is the product of the OB gene (165), and its production and secretion are significantly higher in subcutaneous adipocytes relative to visceral adipocytes (77, 107, 148). Plasma leptin and adipocyte mRNA levels are higher in obese subjects, and the levels positively correlate with percent body fat (25). Leptin is released by adipocytes in response to nutrient supply and acts in the brain to downregulate food intake and in the periphery to increase energy consumption, especially by muscle tissue. Obese humans manifest peripheral resistance to leptin associated with blunted relative diurnal excursion and dampened pulsatility (134), and this has been thought to contribute to increasing fat storage in muscle and liver, conditions that positively correlate with insulin resistance (163). After bariatric procedures—be they solely restrictive or also malabsorptive—leptin invariably falls and its fall is correlated with weight loss (28, 37, 85, 91). Serum leptin binding protein increased significantly one year after LAGB, correlating negatively with falling BMI and resulting in an increase in bound leptin from 7% to 33%.

Other Hormones

GHRELIN Ghrelin is a 28 amino acid peptide (83) secreted mainly by endocrine cells within the oxyntic mucosa of the gastric fundus. The electron microscopic morphology of these endocrine cells suggests that ghrelin cells are those identified as X cells in the dog, A cells in the rat, and P/D1 cells in the human (34, 44, 128). The exact physiology of ghrelin remains largely a mystery. Ghrelin levels vary diurnally, exhibiting preprandial and 1 AM peaks and postprandial troughs (31). The vagus nerve appears to play a role in the governance of ghrelin secretion and the subsequent physiologic effects. In rats, vagotomy suppressed the rise in ghrelin normally seen with nutrient deprivation but did not affect the baseline ghrelin levels or the expected postprandial fall in ghrelin (155). Additionally, blockade of gastric afferent vagal signals abolished ghrelin-induced feeding in rats (35). Furthermore, there is a preponderance of evidence that the gastric fundus plays a central anatomic role and also a functional role in ghrelin secretion and regulation. Gnanapavan (61) showed the gastric fundus to have the highest level of ghrelin

mRNA expression compared with 33 other human tissues. In a small study of obese patients undergoing laparoscopic BPD (n = 3), LAGB (n = 7), and laparoscopic RYGB, (n = 6), Fruhbeck et al. (56) showed a 30% increase in ghrelin levels after BPD and gastric banding, but a 70% decrease in ghrelin levels after RYGB at four to six months postoperatively. Since only RYGB results in isolation and defunctionalization of the gastric fundus, the implication is that fundic continuity is important in the regulation of plasma ghrelin (56).

Not surprisingly, ghrelin levels are seen to be linked to nutritional status. Anorexic patients show ghrelin concentrations that are approximately twice the normal fasting levels (11). Conversely, Cummings et al. (31) showed that obese patients have approximately 25% lower ghrelin levels than do normal weight patients while maintaining diurnal variability. Diet-induced weight loss resulted in a move toward normalization of ghrelin levels, whereas RYGB led to suppression of ghrelin levels to approximately 25% of preoperative levels and (31). The decline in ghrelin levels shown by Cummings in RYGB patients at ≥9 months postoperatively was also shown by Lin at the time of gastric transection during RYGB. Lin measured intraoperative ghrelin levels at various time points during the RYGB procedure and showed an immediate 25%–30% fall from preoperative ghrelin levels at the time of gastric division (95). Interestingly, however, Korner et al. (85) found that patients studied at least one year after RYGB had active ghrelin levels similar to age- and BMI-matched controls (matched at reduced weight) and both of these groups had ghrelin levels lower than lean controls.

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) GLP-1 is an insulinotropic hormone (incretin) that is secreted in response to hyperglycemia. GLP-1 induces satiety in humans when infused intravenously and results in reduced spontaneous food intake (52). Additionally, GLP-1 delays gastric emptying (110) and diet-induced weight loss results in reduced postprandial levels of GLP-1 (4). There is some discrepancy as to the effects of bariatric surgery on GLP-1 secretion. Naslund and colleagues (109) reported reduced GLP-1 levels in obese subjects and a rise toward values similar to lean controls after JIB procedures. Interestingly, six subjects studied 20 years after BPD showed four- to fivefold higher plasma GLP-1 levels relative to lean controls (109). Alternately, Rubino and coworkers (133) looked at 10 laparoscopic RYGB patients and found no significant differences in GLP-1 levels at three weeks postoperatively. This latter study, however, may have been underpowered given the timing of the investigation, or the differences in bariatric operative procedure may account for the disparate results.

Inflammatory Changes

There is a growing consensus that obesity is an inflammatory condition (33) and that chronic inflammation acts as a trigger for insulin resistance (66). Many of the metabolic and hemodynamic abnormalities associated with obesity and T2DM may be related to altered production of proinflammatory factors and adipokines

by adipose tissue, particularly in the intra-abdominal (visceral) location. Genes involved in inflammatory pathways are upregulated in adipose tissue in obesity (138). Subcutaneous adipose tissue from obese humans and animals expresses increased amounts of TNF-α (71, 73, 115) and IL-6, leading to increased hepatic production of C-reactive protein (CRP). In turn, this leads to increased production of adhesion molecules from endothelial cells, such as soluble intercellular adhesion molecule-1, vascular adhesion molecule-1, and monocyte chemotactic protein-1 (reviewed in 121). A recently published study of a prospective, nested case-control study involving 32,826 women of the Nurses' Health Study cohort strongly supports the role of inflammation in the pathogenesis of T2DM. Elevated levels of CRP were good predictors of T2DM and could mediate the association of TNF-αR2 (TNF-α receptor 2 as a measure of plasma TNF-α) and IL-6 with type 2 diabetes (76).

The inflammatory response associated with obesity appears to be "triggered and to reside predominantly" in adipose tissue and primarily in its visceral location (68). About one-third of circulating IL-6 may originate from adipose tissue (105), with omental fat producing threefold more IL-6 in comparison to subcutaneous fat (53). Similarly, stromal vascular cells present in adipose tissue also express receptors for several of the cytokines, such as TNF-α, IL-6, and IL-1β. Recent observations by Weisberg et al. (152) and by Xu et al. (156) indicate that a significant proportion of the visceral fat in obese humans and mice consists of macrophages with an estimated content equivalent to nearly 50% of the total omental mass in morbidly obese subjects. Interestingly, macrophages were found to account for expression of almost all of the adipose tissue TNF-α and of significant amounts of iNOS and IL-6 (152). It is perhaps revealing that upregulation of the macrophage-specific inflammatory genes occurs progressively in diet-induced obesity and precedes the increase in plasma insulin levels (156). Furthermore, the adipocyte fatty acid–binding protein, aP2, which is expressed by both macrophages and adipocytes, promotes insulin resistance in both genetic and diet-induced obesity (72) and has been shown to promote atherosclerosis (96), thus linking these features of the metabolic syndrome. Interestingly, the expression of inflammatory cytokines such as TNF-α is dramatically reduced in adipocytes and macrophages null for aP2 expression (98).

Although weight loss with diet and exercise has been shown to improve IL-6 and TNF-α levels significantly (81), the effect of bariatric surgery on inflammation has not been consistent in the literature. PAI-1 fell significantly after VBG, BPD, or VBG + JIB as early as four months postoperatively and reached control levels (119, 149). CRP also fell four months after bariatric surgery but remained significantly elevated relative to controls (149). In eight VBG patients with preoperative TNF-α levels >10 pg/ml, there was a significant fall in TNF levels at 14 days and at 6 months. No difference was seen in six patients with levels <10 pg/ml (88). In other studies of patients undergoing VBG, BPD, and AGB, neither TNF-α nor IL-6 fell significantly when measured between four and twelve months postoperatively (90, 149). Likewise, Molina (106) found no change six months after gastric bypass in

soluble TNF receptors 1 and 2—adipocyte receptors known to be upregulated in obesity.

Lipid Changes

Obesity is commonly associated with dyslipidemia. Residori et al. (127) published a retrospective review of 300 patients undergoing bariatric surgery; 71% of the patients were confirmed to have hyperlipidemia. The deleterious effects of dyslipidemia are evidenced by the improvement in cardiovascular events and mortality seen with statin therapy for longer-term primary and secondary prevention (1, 45, 135, 136). Bariatric procedures may act then indirectly to improve cardiac morbidity and mortality in the extent to which they effect advantageous changes in the lipid profile in the long term (Figure 3).

Obesity-related chronic inflammation provides an alternative mechanism to explain the dyslipidemia associated with obesity and overweight. IL-6 and TNF-α increase very-low-density lipoproteins and triglycerides (TGs) by inhibiting lipoprotein lipase, increase nonesterified fatty acids (NEFAs) by heightening lipolysis, and increase hepatic secretion of TG. Furthermore, TNF-α leads to elevated hormone-sensitive lipase activity and lowered fatty acid–binding protein (27).

In procedures involving a malabsorptive component [i.e., BPD (58), biliointestinal bypass (26), RYGB (21, 29), and silastic ring gastric bypass (39)], total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) fell universally and significantly anywhere from 1–72 months postoperatively. A more dramatic fall in LDL, however, resulted in improved total cholesterol-HDL ratios (TC/HDL), implying more buoyant and less atherogenic lipid molecules. Interestingly, purely restrictive procedures have not been shown consistently to result in improvements in TC or LDL, and HDL is only moderately and inconsistently increased postoperatively. Nevertheless, the lipid changes after restrictive procedures resulted in significant improvement in TC/HDL like that seen after malabsorptive procedures (26, 43, 139). Triglycerides exhibit a modest, but significant, decline irrespective of the bariatric procedure chosen.

Energy Expenditure Changes

Although genetic and environmental variables are involved in obesity development, the simple and often small imbalance between energy intake and expenditure is the direct link to weight regulation. An average adult in the United States gains about one pound each year between 35 and 65 years of age, and this is believed to be a result of a 50–100 kcal/day difference between intake and expenditure. The components of energy expenditure are resting energy expenditure (REE), the thermic effect of food, and energy expenditure during physical activity (EE_{ACT}). REE varies significantly among individuals and correlates with fat-free mass but less so than with fat mass (123, 124). By extrapolation, the development and maintenance of overweight and obesity can be viewed as an extreme energy imbalance in which

intake is exceedingly great, REE is exceedingly low, or there is a combination of both.

Interestingly, in a study of 33 obese (BMI ~31) females subjected to a strict dietary regimen of 420–800 kcal/d, 18 women lost sufficient weight to reach their ideal body weight. When these 18 subjects were compared to 14 normal weight females (BMI ~21) and to the 15 obese subjects who did not reach their ideal body weight, no difference in energy expenditure was detected (8). Such findings led to the hypothesis that bariatric procedures might effect weight loss and weight maintenance by altering REE.

However, Bobbioni-Harsch et al. (17) found that weight loss in 50 gastric bypass patients is a function of alterations in energy intake. This is supported by work done in 30 GBP patients studied an average of 14 months after operation. Fat mass, percent body fat, and BMI fell significantly in the face of concomitant decrements in TEE, REE, and EE_{ACT} (32). Additionally, 36 women studied before and after LAGB demonstrated a significant decrease in lean body mass, fat mass, and resting metabolic rate (a surrogate measure of REE) (28). These reports point to a greater role of energy intake restriction, over and against an increase in REE, in the energetic changes associated with bariatric surgery.

Glucose Metabolism and Insulin Resistance

Bariatric procedures, including RYGB (143, 154), AGB (55, 101, 118), and BPD-RYGB (117), have been shown to improve and even resolve abnormalities associated with type 2 diabetes. Studies from the Pories laboratory (75) showed that RYGB leads to sustained improvements of plasma glucose, insulin, and glycosylated hemoglobin levels in about 80% of patients with diabetes and in about 90% of patients without diabetes who were noted to be glucose intolerant. The mechanism and the timing behind these improvements remain unknown. Most of the work thus far attributes the improvements in glucose homeostasis to significant loss of body fat. However, there is recent evidence to argue against this being the only mechanism. Klein et al. (82) showed that after removal of peripheral fat in humans by liposuction in amounts equivalent to 9% of total body mass or 18% of total fat mass, there is no improvement in insulin resistance, glucose, blood pressure, or other cardiovascular risk factors. On the other hand, studies in obese adults have shown that a weight loss of 5%–10% of total body weight, achieved by caloric restriction, is sufficient to cause improvements in plasma insulin and glucose and to reverse abnormal glucose tolerance. Additionally, with bariatric surgery, the postsurgical reversal of glucose tolerance begins long before any significant weight loss has occurred. Rubino and colleagues (133) studied 10 patients both before and three weeks after RYGB. Despite a nonsignificant fall in mean BMI from 46.2 kg/m^2 to 43.2 kg/m^2, mean preoperative and postoperative plasma insulin levels were 24.6 and 12.6 μU/mL, respectively ($p = 0.01$), and mean serum glucose fell from a baseline of 114 mg/dL to 85 mg/dL ($p = 0.005$) at three weeks after RYGB. Glucose and insulin levels fall as early as three to

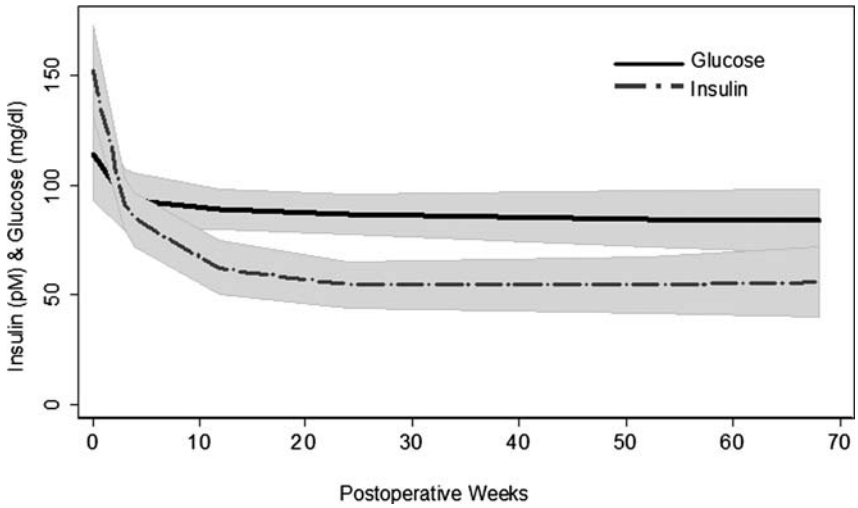

Figure 4 Fractional polynomial curves of glucose and insulin after malabsorptive bariatric surgery.

four weeks after the operation (Figure 4). Glucose levels stabilize and the fall in insulin appears to drive the improvement in the homeostasis model assessment of insulin resistance (HOMA-IR), implying a marked improvement in the efficiency of insulin-dependent glucose utilization. HOMA provides a simple and accurate method for determining β-cell function and insulin resistance based on plasma insulin and glucose levels (103). Based on fractional polynomial predicted curves of the percent excess weight loss and HOMA-IR, the greatest improvement in HOMA-IR occurs within four to six weeks of the bariatric procedure and correlates with approximately 10%–15% excess weight loss (Figure 5). HOMA-IR is essentially normalized at 12 weeks, corresponding to ∼30% excess weight loss. In general, the mechanisms underlying the metabolic improvements following bariatric surgery remain almost completely unexplored. Preliminary data show that the improvement in insulin sensitivity ($n = 45$) occurs as early as 10 days postoperatively—when the loss in body weight is less than 2%.

Alternatively, some of the improvements following bariatric surgery could be related to a redistribution of energy stores with acute reductions in muscle triglyceride content (mTG). Significant correlation exists between insulin resistance of obesity and type 2 diabetes and mTG content (100, 114), and specifically with intramyocellular (inside fiber) lipid (9, 65, 87, 99, 137, 151). Increased mTG is associated with decreased insulin-stimulated glycogen synthase activity (116) and lower glycogen stores (94). High mTG probably reflects excess muscle fatty acid uptake over oxidative capacity, which is usually associated with increased intracellular levels of long-chain fatty acyl-CoA (LCA-CoA) esters (48). There is a negative correlation between human skeletal muscle LCA-CoA content and whole body insulin action (47), most likely because of a reduction in the activity of

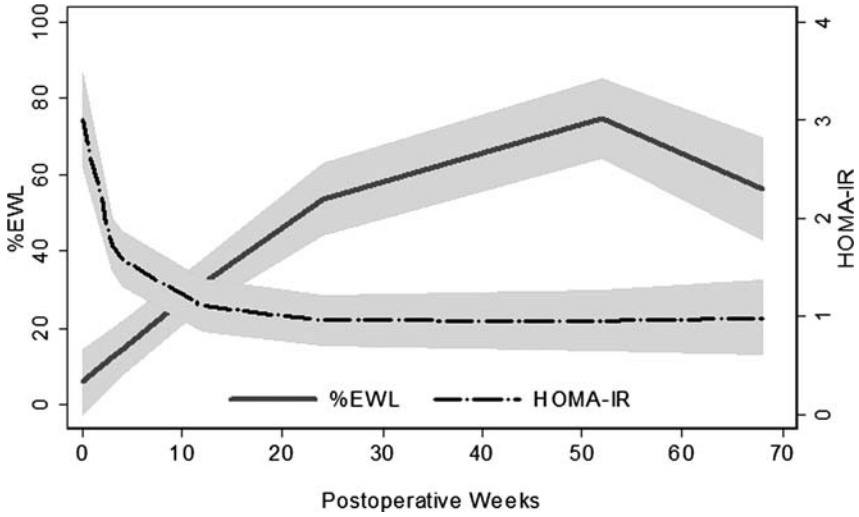

Figure 5 Homeostasis model assessment of insulin resistance (HOMA-IR) improvement after malabsorptive bariatric surgery. % EWL, percent excess weight loss.

human skeletal muscle hexokinase (145). Weight loss following bariatric surgery was associated with significant reductions in vastus lateralis LCA-CoA content at two time points, the first being six months following biliopancreatic surgery (65, 122) and the second at one year following the surgery (75). These findings, which suggest that muscle lipid metabolism has improved, could contribute to the enhanced insulin action.

Hepatic Changes

Nonalcoholic fatty liver disease (NAFLD) ranges from mild steatosis to frank cirrhosis. In multiple series of bariatric patients undergoing liver biopsy at the time of the bariatric procedure for morbid obesity, 63%–96% had changes consistent with NAFLD; 26%–41% of those met criteria (absence of significant alcohol use, macrovesicular fatty change with lobular or portal inflammation with or without Mallory bodies, fibrosis, or cirrhosis) for nonalcoholic steatohepatitis (NASH), while 1%–2% were cirrhotic (16, 18, 41, 86, 112). Furthermore, in a study of 103 medical patients, Adams and coworkers (6) showed that the fate of NAFLD over a four-year period is variable, with 37% progressing, 29% regressing, and 34% remaining stable. When baseline cirrhotic patients were excluded, the presence of type 2 diabetes mellitus and an increasing BMI were independent predictors of progression (6).

The mere presence of obesity, however, cannot fully account for the pathologic changes seen in NAFLD leading to NASH and overt cirrhosis. Day and James have proposed the requirement of "two hits" for liver injury to manifest itself

(36, 79). As noted above, steatosis is present in upwards of 96% of morbidly obese patients, acting as the first hepatic hit. The second hit can be in the form of oxidative stress resulting in lipid peroxidation, abnormal cytokine production, or altered fatty acid metabolism and insulin resistance (79). Insulin resistance leads to hyperinsulinemia, which can exacerbate mitochondrial dysfunction in that insulin blocks mitochondrial fatty acid oxidation. An overload of NEFA in the hepatocyte leads to peroxisomal β-oxidation and generation of reactive oxygen species. Additionally, cytochrome P450-2E1 (CYP2E1) is overexpressed in NASH and can produce free radicals from byproducts of NEFA metabolism (36). Reactive oxygen species activate the stellate cells in the hepatic interstitium, and they begin to lay down collagen that positively feeds back, further activating the stellate cell and adding insult to injury (54).

In the normal animal liver, TNF-α administered systemically in vivo or to hepatocytes in vitro stimulates hepatocyte growth whereas steatosis appears to act as a first hit, thereby sensitizing the cells to deleterious effects of TNF-α (146). Likewise, Yang et al. (158) demonstrated that genetically obese rodents (ob/ob mice and Zucker fa/fa fatty rats) injected with lipopolysaccharide are prone to TNF-α injury in that their hepatocytes exhibit injury to lower levels of TNF-α; interferon-gamma (hepatocyte sensitizer to TNF-α) is overproduced, and mRNA levels of interleukin 10 (TNF inhibitor) are reduced (158). They postulate a fundamental dysfunction of Kupffer cells leading to impaired clearance of lipopolysaccharide, and subsequently a state of low-grade, chronic endotoxemia and inflammation that may then lead to insulin resistance secondarily.

Hepatic adrenergic activity may also predispose and/or aggravate hepatic toxicity in the obese patient. As mentioned previously, obesity is associated with a heightened noradrenergic state. Dubuisson and colleagues (46) have shown that chemical denervation of hepatic noradrenergic fibers in rats demonstrating carbon tetrachloride (CCl_4)-induced hepatic fibrosis results in a 60% reduction of hepatic fibrosis. Noradrenergic, alpha-1 blockade with prazosin revealed a reduction in fibrosis of 83%.

The result of bariatric surgery on NAFLD is generally, but not universally, favorable. Of historical interest are the hepatic changes seen after JIB. In a review of 453 patients who underwent JIB for morbid obesity, 10% developed liver disease at 15 years, 5% developed acute liver failure, and 8% developed cirrhosis by 15 years (126). Hocking et al. (69) reported similar results in 100 JIB patients followed an average of 65 months with serial liver biopsies. Twenty-nine percent of patients had worsening hepatic changes and 7% developed cirrhosis (69). Due to these and other serious complications, JIB has been almost universally abandoned as a surgical treatment for morbid obesity.

Clark et al. (23) reported on 16 patients who were found to have hepatic steatosis at the time of RYGB and who were biopsied again at elective hernia repair. The average BMI fell from 51 to 33 over an average of 305 days between biopsies. Steatosis resolved in 13, improved in 2, and remained stable in one (23). Mottin's group (108) reported on 90 patients found to have steatosis (cirrhotics were

excluded) at the time of VBG with RYGB and who were subsequently biopsied percutaneously one year later. Steatosis was "cured" in 54%, improved in 28%, and remained stable in 18%, correlating with excess weight loss of 85.9%, 78%, and 72.5%, respectively ($p < 0.03$). In 36 patients with NAFLD who underwent LAGB with liver biopsy and subsequent repeat biopsy on average 26 months after the bariatric procedure (BMI fall: 47 → 34), a statistically significant improvement in steatosis, lobular inflammation, fibrosis, Mallory bodies, and ballooning degeneration was noted. There was no improvement, however, in portal inflammation or portal fibrosis (40). Furthermore, in a recent study of 70 laparoscopic bariatric patients (41 laparoscopic roux-en-Y gastric bypass, 23 sleeve gastrectomy, and 6 LAGB) who underwent intraoperative and postoperative liver biopsies an average of 15 months later, hepatic steatosis, inflammation, and fibrosis improved significantly in conjunction with a mean excess weight loss of 59% (102). The results after BPD, however, are not so favorable. In a series of 104 BPD patients who underwent reoperation with hepatic biopsy on average 41 months after BPD (86), steatosis decreased significantly and correlated with weight loss—mean BMI fell from 47 to 31 kg/m^2. Fibrosis increased in 42 patients, decreased in 28 patients, and remained stable in 34 patients, resulting in a net increase in fibrosis among these cases. Inflammation resolved in 11 of 18 initial patients with the finding; but mild inflammation developed in 10 others. Eleven of the initial fourteen patients found to have cirrhosis had a repeat biopsy. Nine of eleven had reversal of grade 4–5 fibrosis. Three patients developed cirrhosis, but only one did not have an obvious additional risk factor for cirrhosis (e.g., binge-drinking or biliary obstruction).

The improvements in hepatic disease generally seen after bariatric surgery are certainly multifactorial. They may well be due to amelioration of the chronic inflammatory state present in obesity, mitigation of noradrenergic levels in the liver, improvement in insulin resistance, and/or mitigation of NEFA delivery to, and deposition in, hepatocytes that contribute to steatosis and the development of reactive oxygen species.

METABOLIC CONSEQUENCES OF LIPOSUCTION IN BARIATRIC PROCEDURES

Although abdominal adiposity has received considerable attention in regard to insulin resistance, there is a substantial proportion of body fat in the lower extremities of obese individuals. Yet because this fat depot is generally not related to insulin resistance, little attention has typically been given to this type of adiposity. Recent studies utilizing computed tomography and magnetic resonance imaging have altered this perspective by demonstrating that adipose tissue located beneath the fascia lata as intermuscular adipose tissue is negatively correlated with insulin sensitivity in adults (63) and children (130). In contrast, having more thigh subcutaneous adipose tissue is generally not related with insulin sensitivity (63, 64).

Liposuction, a cosmetic operation widely used by plastic surgeons for body contouring, involves the removal of large amounts of subcutaneous adipose tissue. It is a simple and safe procedure that involves the subcutaneous infusion of a solution containing a local anesthetic followed by aspiration of subcutaneous fat through microcannulas. In recent years, several studies have examined the physiologic effects of liposuction and some of them are claiming beneficial metabolic effects of the procedure beyond its cosmetic utility. In this review, we examine studies that have determined the effect of large-volume abdominal liposuction on insulin sensitivity and on risks factors for cardiovascular disease.

Overview of Trials

The population and study characteristics of trials of abdominal liposuction and reduction of cardiovascular risk factors are presented in Table 2. The analysis is based on seven clinical trials published between 1996 and 2004, comprising 12 strata with a total of 167 subjects. The duration of intervention until the maximal effect (or, if not reported, the overall insulin effect) on insulin action was achieved varied between 3 and 52 weeks. All of the studies enrolled only female subjects. The mean age of trial populations ranged from 29 to 51 years. Four percent of the subjects were diagnosed with type 2 diabetes according to the American Diabetes Association's criteria. There were no dropouts from the only randomized control trial (62) included in the review.

Changes in Body Weight Induced by Abdominal Liposuction

Mean initial body weight and BMI were 79.4 kg and 33.6 kg/m^2, respectively. After abdominal liposuction, the mean net change in body weight of the populations was 4.1 kg (with a range of −3.0 to −7.1 kg). Most of the population considered by Klein et al. (82) was morbidly obese, with a BMI greater than 35 kg/m^2.

TABLE 2 Clinical trials of the metabolic effects of liposuction

Study	Year	N	Follow-up (weeks)	Age (year)	Level of evidence$^+$	BMI (kg/m^2)	Preop weight (kg)	ΔWeight (kg)
Klein et al. (82)	2004	15	12	42	II	37.3	103	−7.1
Giugliano et al. (60)	2004	30	26	34	II	34	88	−3.0
Robles-Cervantes (129)	2004	15	3	29	IV	26.3	70.1	−0.9
Gonzalez-Ortiz et al. (62)	2001	6	4	30	II	31.7	89.8	−3.2
Giese et al. (59)	2001	14	18	39	IV	29.1	N/A	−6.4
Berntorp et al. (15)	1998	53	13	51	II	34.3	90.7	−4.1
Cazes et al. (22)	1996	34	52	41	II	42.4	111	−11.1

BMI, body mass index; N, subject number, N/A, not available; $^+$ II, nonrandomized clinical trial; IV, case-series

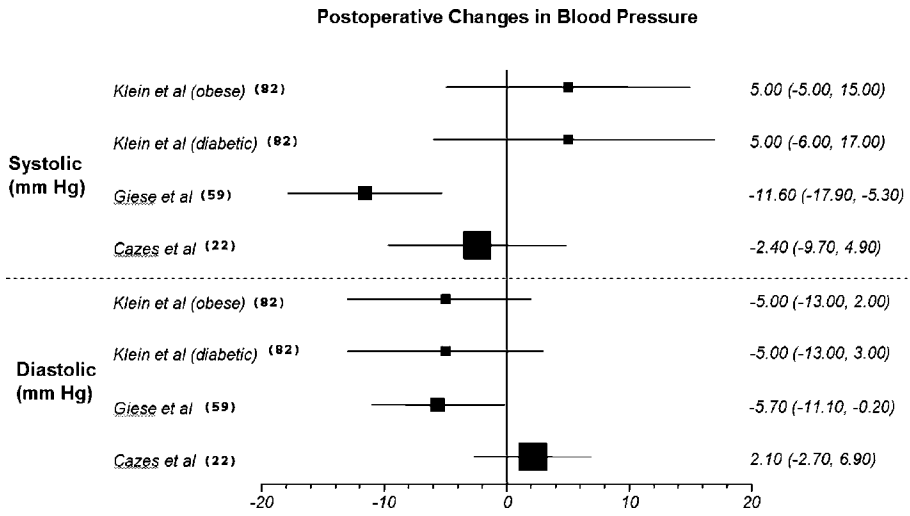

Figure 6 Forest plot of changes in blood pressure after liposuction. Boxes are weighted mean differences; bars are 95% confidence interval.

Effects on Blood Pressure

Net changes in systolic and diastolic blood pressure due to abdominal liposuction, with 95% confidence intervals (CI), are presented in Figure 6. Data were available from three studies. The only notable effect was demonstrated in the study by Giese et al. (59), in which the postoperative change was significant for both systolic and diastolic blood pressure ($P < 0.01$).

Effects on Inflammatory Mediators

Liposuction caused a significant decrease in plasma leptin levels in both groups considered by Klein et al. (82). Giugliano et al. (60) found that liposuction also significantly decreased plasma levels of TNF-α, adiponectin, IL-6, and CRP (Table 3).

Effects on Lipid Metabolism

Forest plots for net changes in total cholesterol, HDL cholesterol, and triglycerides due to abdominal liposuction, with 95% CI, are presented in Figure 7. Data were available from five studies, and none of them showed any statistically significant change.

Effects on Glucose Metabolism and Insulin Sensitivity

Data on postliposuction glucose and insulin levels could be extracted from six studies. A forest plot for net changes in fasting blood glucose due to abdominal

TABLE 3 Effects of liposuction on mediators of inflammation

Mediator	Obese (Reference 82)	Diabetic (Reference 82)	(Reference 60)
Leptin	+	+	N/A
Adiponectin	↔	↔	+
TNF-α	↔	↔	+
IL-6	↔	↔	+
CRP	↔	↔	+

↔, no difference; +, improvement after liposuction; N/A, not available; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

liposuction, with 95% CI, is presented in Figure 8. With the exclusion of the study by Giugliano et al. (60), none of the trials showed any statistically significant postoperative change in glucose levels.

Two studies showed a small but significant variation in insulin levels after liposuction (Figure 9). In the Giugliano et al. study (60), the mean change in insulin levels was −4 μU/ml (95% CI −7.8 to −0.2; $P < 0.05$). Giese et al. (59) reported the highest change in insulin levels: −5.4 μU/ml (95% CI −8.3 to −2.5; $P < 0.01$).

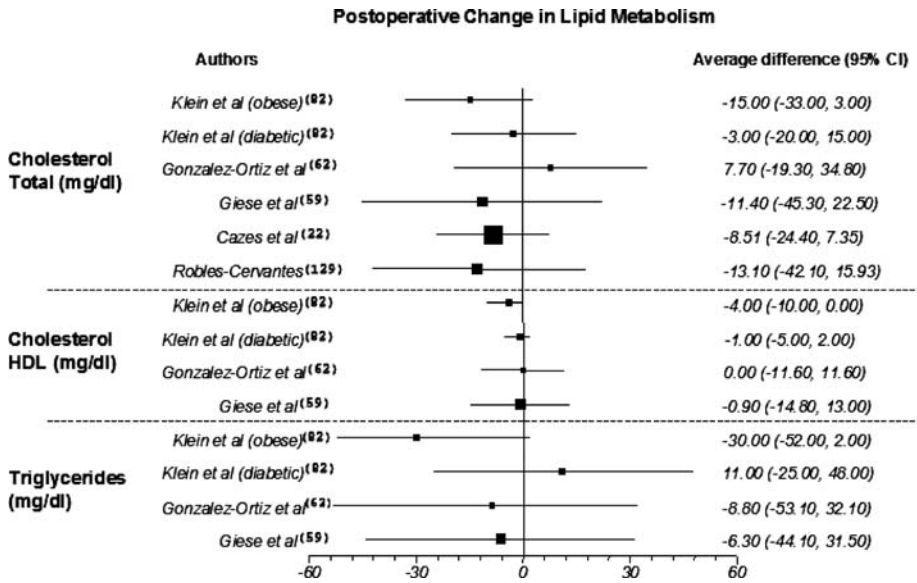

Figure 7 Differences in total cholesterol, high-density lipoprotein cholesterol, and triglycerides after abdominal liposuction. Boxes are weighted mean differences; bars are 95% confidence interval.

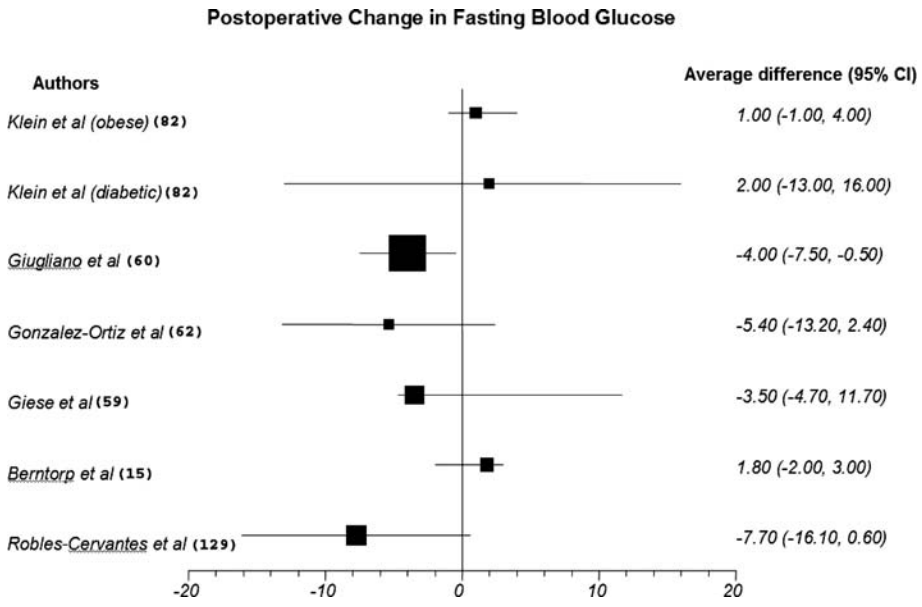

Figure 8 Differences in fasting blood glucose (mg/dL) after abdominal liposuction. Boxes are weighted mean differences; bars are 95% confidence interval.

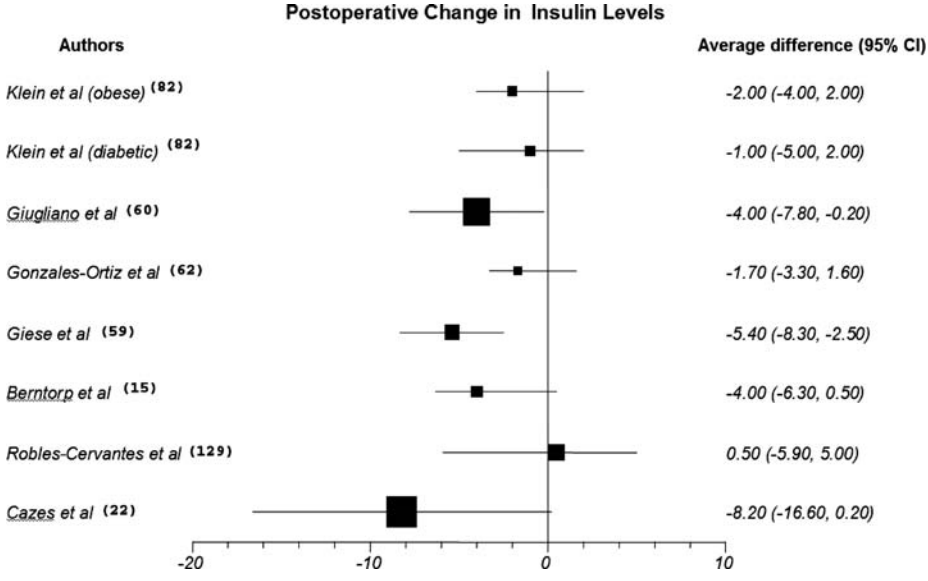

Figure 9 Differences in fasting insulin (μU/mL) after abdominal liposuction. Boxes are weighted mean differences (μU/mL); bars are 95% confidence interval.

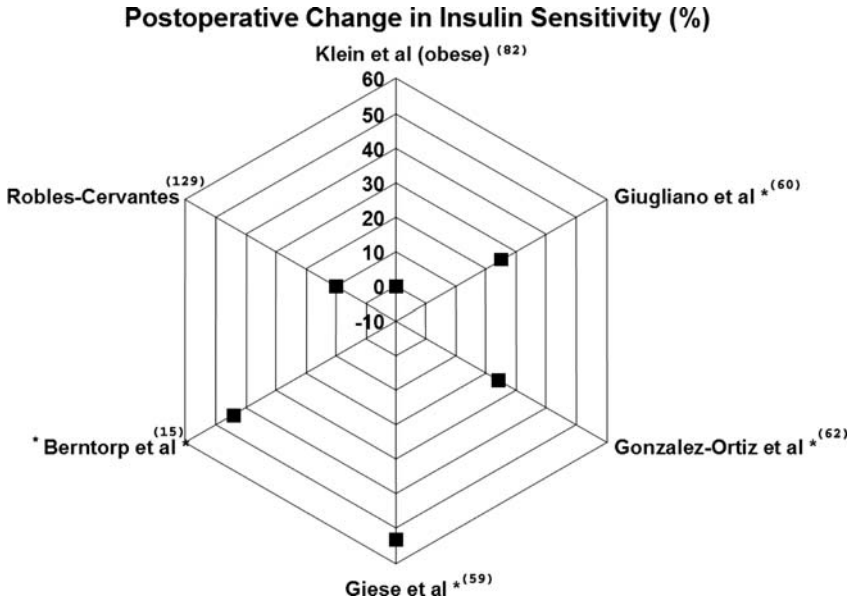

Figure 10 Change (%) in insulin sensitivity after abdominal liposuction. $^{*}p < 0.05$.

In the studies considered for this review, changes in insulin sensitivity were assessed using different methodology. The gold standard for an insulin sensitivity test is represented by the euglycemic hyperinsulinemic clamp. This technique was used only in two trials (15, 82). Therefore, the data presented in Figure 10 represent the mean changes in insulin sensitivity expressed in percent. With the exclusion of the study by Klein et al. (82), all of the trials showed statistically significant postoperative change in insulin sensitivity. The most notable effect was demonstrated in the study by Giugliano et al. (60), in which the HOMA index change was -2.08 ($P < 0.01$).

SUMMARY

Adipose tissue is a complex organ whose significance is only now becoming understood. By improving the components of the metabolic syndrome (dyslipidemia, hypertension, insulin resistance, and central obesity), bariatric surgery alters the cardiovascular risk profile of morbidly obese patients. The evidence for the benefit of liposuction in this regard is not as clear. The only studies on liposuction (22, 82) that investigated patients with a BMI greater than 35 kg/m^2 showed no difference in cardiovascular risk factors, whereas malabsorptive bariatric procedures (with or without restrictive components) universally result in improvements in the metabolic syndrome. Bariatric surgery rapidly corrects insulin and glucose metabolism long before significant weight loss has occurred, which is vital in the diabetic component of obesity; it also improves or cures hypertension and

corrects dyslipidemia. In light of this marked amelioration of the components of the metabolic syndrome accompanied by the reliable maintenance of weight loss, malabsorptive bariatric procedures are understandably the treatment of choice for morbid obesity and its comorbidities.

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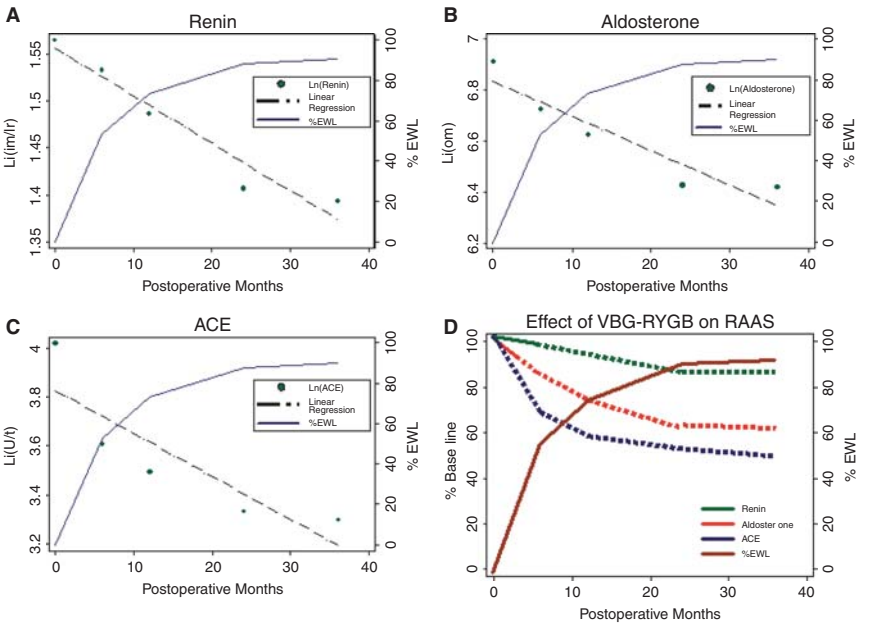

Figure 2 Changes in (*A*) renin, (*B*) aldosterone, (*C*) ACE, and (*D*) overall changes from baseline. ACE, angiotensin-converting-enzyme; EWL, excess weight loss; RAAS, renin-angiotensin-aldosterone system; VBG-RYGB, vertical-banded gastroplasty-Roux-en-Y gastric bypass. Lines in *D* are fractional polynomial fits; dashed lines correspond to values within the reference range. Based on Ruano et al. (132).

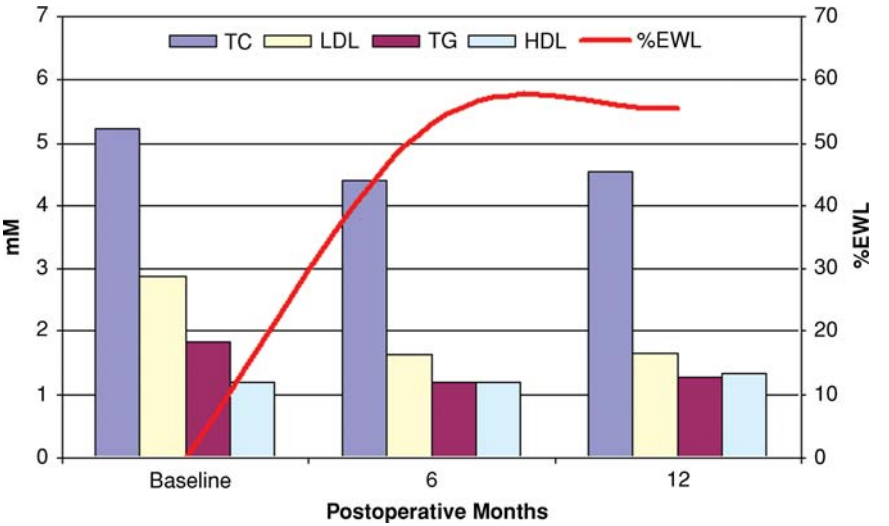

Figure 3 Lipid changes after bariatric surgery. TC, total cholesterol; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein; %EWL, percent excess weight loss.

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