

## Metabolic Aspects of Bariatric Surgery

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The metabolic consequences of obesity are well known but incompletely understood. They include insulin resistance, type 2 diabetes mellitus (T2DM), the metabolic syndrome, and polycystic ovary syndrome (PCOS). Each disorder develops as a result of the poorly defined interaction between a genetic predisposition and other acquired and environmental factors such as age, gender, ethnicity, dietary choices, and level of physical activity. Taken together, these disorders have become an increasing source of morbidity worldwide as the obesity pandemic continues to spread. It is generally agreed that the global prevalence of insulin resistance is continuing to increase. In the United States, diabetes is the sixth leading cause of death and continues to be a major cause of blindness, renal failure, peripheral neuropathy, and amputation [1]. It is now estimated that 90% of all diabetes cases are T2DM [2]. The economic cost is already enormous and growing. In 2002, T2DM was responsible for at least \$132 billion in medical expenditures and lost productivity [3]. By 2020, the overall cost is projected to reach a staggering \$192 billion annually.

It is well documented that the metabolic problems associated with obesity can be partially or completely reversed, but only with early and aggressive therapy. Accordingly, a variety of medical and surgical treatments are now available and new ones continue to evolve. The time-honored approaches of diet, exercise, and behavioral modification can achieve a 10% to 15% reduction in body weight and significantly enhance insulin sensitivity and glycemic control in the short term [4]. Nonetheless, the extended

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results of nonoperative therapy continue to be disappointing because protracted compliance is difficult and weight loss tends to be unsustainable [5].

An important role for surgery in the management of these difficult problems was first suggested over a decade ago by the breakthrough work of Pories and colleagues [6] in which a rapid and durable resolution of T2DM was observed following gastric bypass operations. Since then, numerous other investigators have confirmed and extended these findings using a wide range of bariatric procedures. This cumulative experience has helped to promote a dramatic growth in the volume of bariatric surgery. In addition, it has stimulated multidisciplinary efforts to better understand the pathophysiology of obesity-specific metabolic diseases and to determine the most appropriate therapeutic targets. Some of the results are discussed herein.

### **Insulin resistance**

Insulin is a potent anabolic/pleiotropic hormone that is primarily responsible for glucose homeostasis but is also involved in fat and protein metabolism, endothelial nitric oxide synthesis, and cell differentiation and growth. It acts to maintain plasma glucose within a reasonably narrow range by a complex interaction primarily with insulin-sensitive cells of the liver, adipose tissue, and skeletal muscle. At a cellular level, insulin promotes the transport of glucose from the bloodstream into the cytoplasm by binding to a specific surface receptor and initiating an intracytoplasmic, multistep signaling pathway that leads to activation of glucose transporter 4 (GLUT4). This pathway involves phosphorylation of intracellular receptor substrates (proteins), which, in turn, activate several additional pathways, the most important of which is the PI-3 kinase/PDK-1-AKT pathway [7]. In vivo, the main effects of insulin on glucose metabolism are to suppress hepatic glucose production by inhibiting hepatic gluconeogenesis and glycogen breakdown and to promote the transport of glucose from the bloodstream into peripheral tissues, especially skeletal muscle.

Insulin resistance is defined as the inability of insulin to produce its usual biologic effects at circulating concentrations that are otherwise effective in normal subjects. It is the central metabolic abnormality associated with obesity and is present in the great majority of morbidly obese patients. In obese diabetic and nondiabetic subjects and in animal models, there is a reduction of insulin receptor number as well as decreased insulin receptor phosphorylation, IRS-1 and IRS-2 phosphorylation, and activation of PI-3 kinase. It is likely that other factors are affected as well [8,9].

Insulin resistance is heterogeneous in its expression. It is associated with impaired suppression of glucose output by the liver and reduced postprandial uptake of glucose, primarily by muscle. In addition, it is accompanied by increased triglyceride breakdown in adipose tissue with generation of free

fatty acids, which further interferes with insulin action and glucose metabolism. The specific pathogenesis of these molecular defects in humans is not yet clearly defined but important clues are beginning to emerge; all point to the participation of multiple factors (Fig. 1) [10].

The most common but still elusive factor is a genetic predisposition. In this regard, polymorphisms of certain genes (*IRS-1*, *IL-6*, *PPr $\gamma$* , *PC-1*, *UCP-2*) have previously been demonstrated to predispose to insulin resistance and T2DM in selected ethnic groups [11,12]. Furthermore, epidemiologic studies of affected twins, first-degree relatives, and American Indians suggest the importance of genetic factors [13,14].

Advanced age can also promote insulin resistance. This effect is explained in part by the changes in body composition that occur with aging, such as losses in muscle mass and gains in total and visceral fat content [15]. In addition, the reduction in physical activity that typically accompanies aging is a major independent risk factor for insulin resistance at whatever age [16,17]. At a subcellular level, the reduced ATP synthesis that occurs as

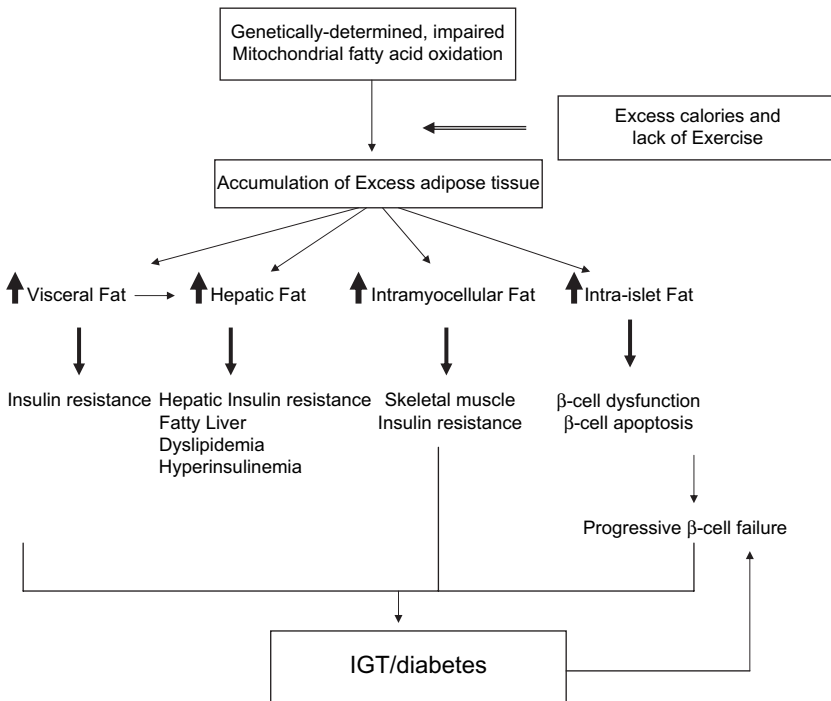


Fig. 1. Proposed effect of adipose tissue accumulation in the development of insulin resistance and type 2 diabetes. (From Rattarasarn C. Physiological and pathophysiological regulation of regional adipose tissue in the development of insulin resistance and type 2 diabetes. Acta Physiologica 2006;186:87–101).

a result of age-related mitochondrial degradation has been demonstrated to impair insulin function [18].

Obesity is linked to insulin resistance through a variety of injurious cellular events, most of which result from lipid oversupply, so-called “lipotoxicity.” In part, this is a manifestation of the chronic accumulation of excess fat within hepatocytes, myocytes, and adipocytes with resultant perturbation of the molecular mechanisms of insulin signaling.

In skeletal muscle, major defects occur in oxidative capacity secondary to elevated levels of long chain acyl CoA and the subsequent activation of protein kinase C isoforms with or without accumulation of ceramide [19,20]. Other unspecified mechanisms are undoubtedly involved. Parenthetically, accumulation of intramyocellular lipids is also observed in endurance athletes but, in this setting, is associated with increased rather than decreased insulin sensitivity. This “metabolic flexibility” is due to an essential shift of energy metabolism from glucose to lipid oxidation [21].

It is well known that excess fat also accumulates in adipose cells and contributes to insulin resistance, but many of the steps in this sequence remain undefined. It is generally accepted that the pattern of fat distribution is an important predictor of risk. Individuals with predominantly upper body fat (visceral/android obesity) are more likely to be insulin resistant and hyperinsulinemic than are people with a preponderance of lower body fat (gynoid obesity). This association of insulin resistance with visceral obesity has been attributed, in part, to the enhanced lipolytic activity of visceral fat cells, especially in the omentum, with increased delivery of free fatty acids into the portal and systemic circulations and chronic exposure of hepatocytes and myocytes to high free fatty acid levels. Several mechanistic studies performed in rodents support the concept that increased free fatty acids have an important role in the pathogenesis of insulin resistance [22].

Chronic, low-grade inflammation in adipose tissue has also been implicated in insulin resistance and has been cited as an important cause of the extraordinary risk of cardiovascular disease observed in patients with obesity and T2DM [23].

Excess fat in adipose cells can induce increased secretion of monocyte chemoattractant protein-1 (MCP-1), which is a mediator for macrophage recruitment. The infiltrating inflammatory cells may, in turn, secrete a variety of chemokines and cytokines (eg, interleukin-6 [IL-6], interferon- $\gamma$ ) that further promote the local inflammatory response and secondarily affect gene expression in adipocytes, resulting in systemic insulin resistance [24].

Individual adipocytes are now recognized to have a central role in the pathogenesis of obesity-related insulin resistance. They are highly specialized cells that not only store triglyceride but also serve as a source of various regulatory peptides (adipokines) that can trigger a wide range of metabolic and inflammatory processes. The specific signals that initiate adipokine secretion remain to be completely determined, but the mechanical stress

of adipocyte swelling, intracellular oxidative stress, and endoplasmic reticulum stress are well-recognized candidates [25,26].

Adiponectin (Acrp30 or adipoQ) is the most abundant known adipokine and has several unique characteristics. It is expressed only in adipocytes and is secreted directly into the circulation, and it is the only known adipocyte-secreted factor that increases tissue sensitivity to insulin. This increased sensitivity is accomplished, in part, by the promotion of lipid uptake and oxidation in muscle and by the inhibition of triglyceride synthesis in hepatocytes [27]. Accordingly, plasma adiponectin levels are inversely related to visceral obesity, T2DM, hypertension, and coronary artery disease [28,29].

Leptin, another potent adipokine, acts primarily through hypothalamic receptors to regulate food intake and energy homeostasis [30]. It is considered an independent risk factor for cardiovascular diseases and is released in proportion to excess body weight. Significant molecular cross-talk has been demonstrated between leptin- and insulin- signaling networks, especially in the liver, but no clear relationship to insulin resistance has been established [31,32]. Other insulin-resistant adipokines, such as resistin, retinol-binding protein 4, tumor necrosis factor alpha, IL-6, plasminogen activator inhibitor, and MCP-1, can be increased in obesity but are less well understood [33].

### **Insulin resistance syndrome**

In his 1988 Banting lecture, Reaven [34] first introduced the concept of Syndrome X as a cluster of related physiologic disorders that could predict an increased risk of cardiovascular disease. The specific disorders in his syndrome were insulin resistance, central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL), arterial hypertension, and altered glucose metabolism. Since that initial description, the World Health Organization, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII), and the International Diabetes Federation have all modified the original criteria. Nevertheless, in each case, the intent has remained the same, that is, to have a tool that will reliably identify high-risk individuals and prevent the long-term progression of metabolic and cardiovascular disease (Table 1) [35].

The name of the syndrome has been changed several times (insulin resistance syndrome [IRS], metabolic syndrome, dysmetabolic syndrome), and a specific ICD9 code (277.7) has been assigned. Patients affected by the IRS have a twofold increase in the risk of cardiovascular disease and a fivefold increase in the risk of T2DM when compared with unaffected individuals [36].

Ischemic and non-ischemic mechanisms may be involved in the elevated risk of cardiovascular disease. In Sweden, Hulthe and colleagues [37] performed carotid and femoral artery ultrasound studies on 818 asymptomatic,

Table 1  
Abnormalities of the insulin resistance syndrome

Parameter	Abnormal value
Triglycerides	> 150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	< 50 mg/dL
Blood pressure	> 130/85 mm Hg
Glucose	
Fasting	110–125 mg/dL
120-min post glucose challenge	140–200 mg/dL

nondiabetic, 58-year-old men. The IRS was diagnosed in 62 subjects (16%) and was associated with a significant increase in the rate of preclinical atherosclerosis and the presence of a small low-density lipoprotein (LDL) particle size pattern. Depres and colleagues [38] studied patients from the Quebec Cardiovascular Study cohort and noted that fasting hyperinsulinemia was an independent predictor for ischemic heart disease in nondiabetic men. In another study of 700 subjects undergoing coronary angiography, Saely and colleagues [39] noted that the IRS was an independent predictor of new vascular events within several years. Similarly, studies of coronary artery calcification using electron beam tomography have demonstrated a significant and independent association between such calcification and the IRS and insulin resistance [40]. The mechanisms responsible for the increased risk of atherosclerosis are complex and not firmly established. As summarized by DeFronzo and Ferrannini [41], increased insulin concentrations enhance very low-density lipoprotein (VLDL) synthesis by the liver leading to hypertriglyceridemia. Moreover, elimination of lipid and lipoproteins from the VLDL particle results in the formation of further intermediate- and low-density lipoproteins. All of these processes are atherogenic.

Indirect evidence also indicates that ectopic lipid accumulation in the human myocardium may lead to non-ischemic, functional alterations. In the Strong Heart study of American Indians, an ethnic group known to have a higher prevalence of insulin resistance, impaired glucose tolerance and T2DM were found to be associated with myocardial hypertrophy and systolic and diastolic dysfunction [42]. Similarly, in the Framingham Heart Study, a direct correlation was observed between insulin resistance and echocardiographically determined left ventricular mass, with significant ventricular hypertrophy found in insulin-resistant patients [43]. In a pathologic study, Sharma and colleagues [44] found that intramyocellular lipid overload was present in 30% of non-ischemic failing hearts in biopsy specimens. The excess lipid accumulation was particularly notable in patients with obesity (body mass index [BMI] > 30) and diabetes. Collectively, these and other data suggest that cardiac lipotoxicity is an entity that may contribute to the risk of cardiovascular disease in the IRS.

The therapeutic implications of the IRS are being vigorously debated. Its clinical relevance and utility as a stand-alone syndrome have recently been questioned by its original proponent and by the American Diabetes Association and the European Association for the Study of Diabetes [45,46]. Variations in the philosophical approach to, and the diagnostic criteria of, the three different versions of the IRS have been cited as major concerns. Conversely, the American Association of Clinical Endocrinologists and the American Heart Association have strongly endorsed the IRS concept. Grundy [47] has noted that diagnosis of the IRS imposes a cardiovascular disease risk that is greater than the sum of its parts. He has also suggested that certain metabolic risk factors such as a proinflammatory state and a prothrombotic state, which are not included in standard risk algorithms, become accessible for treatment based on a diagnosis of IRS. Using the recent clinical guidelines proposed by the American Heart Association/National Heart, Lung, and Blood Institute, the diagnosis of IRS can be conferred by the presence of three or more abnormalities from the following list: central obesity (increased waist circumference), elevated triglycerides, reduced HDL cholesterol, hypertension, and elevated fasting glucose [48].

The therapeutic strategy advocated for patients with multiple risk factors, whether labeled as the IRS or not, is to target the individual risk factors with appropriate medications using available guidelines [49]. The problems associated with polypharmacy, such as poor compliance and adverse drug interactions, require special attention. Lifestyle modification is a critically important but generally underused aspect of therapy. It can reduce medication use, control risk factors, and decrease the long-term risk of cardiovascular disease. In the aggregate, these difficulties suggest a potential role for bariatric surgery [50].

## Diabetes mellitus

Diabetes is the prototypical insulin-resistant state. In its earliest phase, muscle, liver, and adipose tissue all become progressively insulin resistant but plasma glucose levels and glucose tolerance remain normal because of a compensatory increase in circulating insulin. Histologically, this phase is associated with hypertrophy and hyperplasia of the beta cells in the pancreatic islets of Langerhans. Over time, impaired glucose tolerance develops and gradually progresses to overt T2DM as beta cells become incapable of increasing their secretion of insulin to compensate for the defect in insulin action (Fig. 2) [51].

In large clinical series, obesity is the single most important predictor of T2DM [52]. The risk of developing T2DM is exponentially related to the BMI, with approximately 40% of morbidly obese patients (BMI > 40) having either impaired fasting glucose or impaired glucose tolerance and nearly 20% developing T2DM [53]. This close association is so prevalent

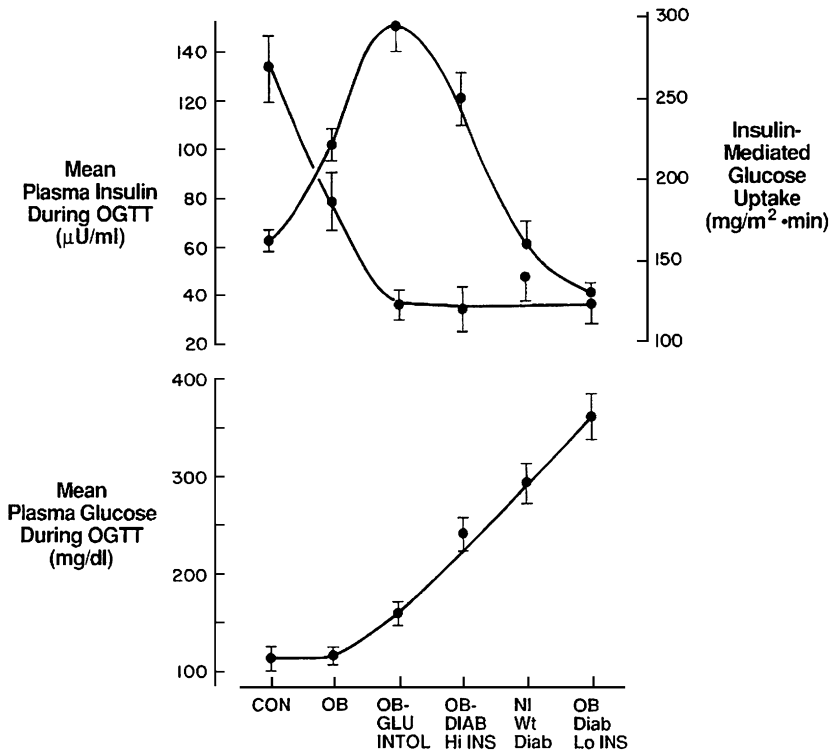


Fig. 2. Plasma glucose (*bottom*) and insulin (*top*) response during 100-g oral glucose tolerance test (OGTT) and tissue sensitivity to insulin (*top*) in control (CON), obese nondiabetic (OB), obese glucose-intolerant (OB-GLU INTOL), obese hyperinsulinemic diabetic (OB-DIAB Hi INS), normal weight diabetic (NI Wt Diab), and obese hypoinsulinemic diabetic subjects (OB Diab Lo INS). (From DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 1988;37:667-87. Copyright © 1988 American Diabetes Association; reprinted with permission.)

that it has been termed *diabetes* [54]. It has been documented to affect both genders, all races, and all ages, although the risk is clearly higher in women, non-Hispanic blacks, American Indians/Alaska natives, and Mexican Americans. Particularly alarming is the recent increase in the prevalence of obesity and T2DM in adolescents, especially in minority populations [55]. Overall, diabetes is associated with significant disability, a poorer quality of life, an increased malignancy risk, and premature death. In a follow-up of the first National Health and Nutrition Examination Survey, at least 70% of T2DM patients died of cardiovascular disease [56]. In 2000, the excess global mortality attributable to diabetes was estimated to be 2.9 million deaths or 5.9% of all deaths worldwide [57].

Because of the chronic, progressive, and heterogeneous nature of diabetes, its management is complex and must be long term. If successful, the treatment plan can ameliorate the symptoms of the involved disease processes

and control their complications. As described in comprehensive reviews by Scheen [58] and by Campbell and Rossner [59], therapy is based on a multimodal strategy: (1) weight reduction through lifestyle modification together with the selective use of anti-obesity drugs (orlistat, sibutramine); (2) improved blood glucose control with agents from one or more of the following groups: biguanides (metformin), which suppress hepatic glucose production and improve insulin sensitivity; sulfonylureas (glimepiride, glipizide, glyburide, acetohexamide, chlorpropamide), which increase pancreatic insulin secretion; thiazolidinediones (pioglitazone, rosiglitazone), which increase sensitivity to insulin;  $\alpha$ -glucosidase inhibitors (acarbose and miglitol), which decrease postprandial hyperglycemia by reducing gastrointestinal carbohydrate absorption; and meglitinides (repaglinide and nateglinide), which increase pancreatic secretion of insulin through a different receptor than that employed by sulfonylureas; and (3) control of common associated risk factors such as arterial hypertension and dyslipidemia.

Although these approaches may be reasonably successful in well-motivated overweight and obese patients, they have little efficacy in the subset of morbid obesity. In large part, this is related to the high rates of recidivism that are observed in nonsurgical weight loss programs [60]. It is also a reflection of the difficulty experienced in medically managing the severe degrees of insulin resistance that are usually present. These challenges provide a strong rationale for the selective use of surgical methods.

### **Polycystic ovary syndrome**

PCOS is a common but complex female endocrinopathy affecting 5% to 10% of women of reproductive age [61]. The primary abnormality is an increase in ovarian androgen production, predominantly testosterone, which results in various combinations of anovulation, menstrual irregularities, infertility, hirsutism, and acne. The etiology of PCOS is not well understood but appears to be multifactorial, with genetic predisposition being a crucial component. It has reproductive and metabolic phenotypes.

Obesity, especially when visceral in distribution, also appears to be an important etiologic factor, occurring in approximately 30% to 75% of all women with PCOS. Moreover, nearly two thirds of affected individuals are insulin resistant, with the degree of insulin resistance showing a strong positive correlation with the hyperandrogenemia [62]. In this regard, the associated hyperinsulinemia is thought to promote androgen hypersecretion both directly by stimulation of specific ovarian insulin receptors and indirectly by the stimulation of pituitary luteinizing hormone secretion [63].

In addition to the reproductive and cosmetic aspects of PCOS, significant metabolic consequences are increasingly being identified. Notably, impaired glucose tolerance or T2DM has been reported in 40% to 45% of all PCOS patients, with the rate of conversion from normal glucose tolerance to

impaired tolerance being significantly increased [64]. Dyslipidemia is also common, with a prevalence of up to 70%. Noninvasive morphologic studies of carotid and coronary arteries have generally demonstrated evidence of early atherosclerosis. Available epidemiologic studies of fatal and nonfatal coronary and cerebrovascular disease have demonstrated at least modest increases in relative risk related to PCOS [65,66]. Definitive conclusions about outcomes will require larger studies with longer follow-up.

The medical and surgical management of PCOS is complex and beyond the scope of this article. Excellent reviews are available [67,68]. Treatment of insulin resistance has become increasingly important. Even a modest level of diet-induced weight loss in obese PCOS patients results in improved insulin sensitivity and lower androgen levels and can ameliorate many of the clinical signs and symptoms of PCOS, including oligomenorrhea, amenorrhea, and anovulation [69]. In patients who are not overweight or who do not respond to diet and exercise, pharmacologic therapy with insulin-sensitizing agents such as metformin (a biguanide) and the thiazolidinediones (pioglitazone and rosiglitazone) is effective and safe. In a recent systematic review, metformin was shown to be better than placebo in achieving ovulation in women with PCOS [70]. In addition, it has been found to correct the associated dyslipidemias and to improve health-related quality of life [71,72].

### **Surgical management**

The role of bariatric surgery in the management of the metabolic problems associated with morbid obesity continues to evolve. The NIH Consensus Development Conference on Gastrointestinal Surgery for Obesity (1991) recognized the importance of certain high-risk comorbid conditions including T2DM and proposed that the BMI threshold for surgical therapy could be dropped from 40 to 35 in appropriate patients [73]. A more recent nongovernmental Consensus Panel co-sponsored by the American Society for Bariatric Surgery (ASBS) and the ASBS Foundation suggested that further liberalization of the operative BMI threshold to 30 may be warranted in the presence of severe comorbidities [74]. This viewpoint has gained increased tenability as minimally invasive techniques have gained more widespread acceptance and as our understanding of the pathobiology of T2DM has improved [75,76]. More randomized clinical studies will be necessary to help determine the need for, and appropriateness of, further changes in the guidelines for bariatric surgical practice [77,78].

The bariatric procedures that are currently available can be divided into three general categories: malabsorptive, restrictive, and combined. Their history and the specific characteristics of each procedure are well discussed in other sources [79,80]. Efficacy and safety profiles differ slightly among the procedural categories, presumably because of the differences in surgical techniques and the variations in physiologic mechanisms.

Malabsorptive techniques induce weight loss by diverting nutrients away from the majority of the small bowel and directly into the distal ileum. Two procedures are now used, biliopancreatic diversion (BPD) and the duodenal switch (DS). For both techniques, general acceptance has been limited because of the relatively frequent side effects of diarrhea, flatulence, anemia, and bone demineralization.

Purely restrictive procedures induce weight loss by combining a small gastric pouch with a narrow outlet, thereby limiting oral intake and producing early satiety. Examples include the vertical banded gastroplasty (VBG), which was used extensively during the 1990s, and its contemporary replacement, the laparoscopic adjustable gastric band (LAGB). The LAGB consists of a water-filled Silastic cuff that is placed around the upper stomach and attached to a subcutaneous port to allow regular adjustments in the size of the gastric outlet.

The Roux-en-Y gastric bypass (RYGB) is the current gold standard of bariatric procedures in the United States and has restrictive and malabsorptive effects. This duality is accomplished by combining a small pouch with a 70- to 150-cm long jejunoileal limb that is excluded from bile and digestive enzymes. Moreover, because nutrients enter directly from the gastric pouch into the jejunum, injudicious carbohydrate intake may cause symptoms of the “dumping syndrome,” such as diaphoresis, tachycardia, nausea, and weakness, which provides a strong disincentive for most “sweet-eaters.”

To date, most outcome-based studies pertain to T2DM in which the effect is often dramatic and usually rapid, being apparent within days of the operation. This level of improvement cannot be approximated using any currently available nonoperative methods. In the initial Greenville cohort of 608 gastric bypass patients first reported in 1995, a subset of 165 patients was found to have T2DM while another 165 patients demonstrated impaired glucose tolerance. In both groups, it was reported that postoperative glucose metabolism normalized with “surprising speed” [6]. Importantly, during a follow-up period of up to 14 years, euglycemia persisted in 88.5% of the T2DM group and 92.1% of the impaired glucose tolerance group. In a subsequent nonrandomized study from the same center, 154 surgical patients were compared with 78 patients who were managed without operation because of personal preference or insurance difficulties [81]. In the surgical group, the prevalence of T2DM decreased from 31.8% in the pre-study period to 8.6% at the last postoperative follow-up. In the nonoperative group, the prevalence actually increased from 56.4% to 87.5%.

In the largest prospective series reported to date, the Swedish Obese Subjects study, 1402 surgical patients were compared with 1489 contemporaneously matched controls who had declined an operation [82]. After 2 years, the mean body weight in the surgery group had dropped by 23.4% while in the control group it had increased by 0.1%. These changes were accompanied by a dramatic decrease in the incidence of T2DM in the surgical patients at 2 years (odds ratio, 0.14; 95% confidence interval [CI],

0.08–0.24) and at 10 years (odds ratio, 0.25; 95% CI, 0.17–0.38), confirming that bariatric surgery could prevent new-onset T2DM as well as reverse pre-existing disease. Schauer and colleagues [83] studied the preoperative predictors of T2DM resolution and confirmed that resolution was most likely to occur in patients with the mildest disease (oral medications; duration < 5 years) and the greatest weight loss. These findings have been confirmed by Torquati and colleagues [84] who also found peripheral fat distribution (small waist circumference) to be an independent predictor of T2DM resolution. Interestingly, the experience in adults is paralleled by the more limited studies available in adolescents. Complete resolution of T2DM has been reported in relatively small series by Sugerman and colleagues [85] and Fielding and Duncombe [86].

Other metabolic abnormalities are also responsive to bariatric procedures. Madan and colleagues [87] recently used NCEP-ATPIII criteria to identify 32 patients with the IRS and noted resolution in 31 patients following laparoscopic RYGB (96.8%). In two other studies, BPD was also shown to dramatically reverse IRS [88,89]. In addition, several other groups have evaluated patients with PCOS and documented significant improvements in the reproductive, metabolic, and cosmetic problems associated with this syndrome after bariatric procedures [90,91].

Similar benefits have been demonstrated using the LAGB, with T2DM remission rates reported to range from 64% to 71% within the first year [92,93]. Pontiroli and colleagues [94,95] studied a variety of clinical and metabolic factors in 143 morbidly obese patients treated by LAGB and compared them with a nonrandomized cohort of 120 equally obese control subjects. Following surgery, body fat distribution changed significantly, mostly due to the loss of visceral adiposity. This loss was accompanied by a rapid and sustained improvement in insulin resistance as measured by decreases in serum insulin levels and in the homeostasis model assessment (HOMA). During the same time, mean plasma glucose and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels normalized and dyslipidemias improved (Fig. 3). These postoperative changes were more evident in patients who had T2DM than in the impaired glucose tolerance group. Similarly, O'Brien and colleagues [75] reported a randomized, controlled study of 80 obese patients (BMI, 30–35) comparing LAGB with intensive medical therapy. The IRS was initially diagnosed in 15 patients in each group (38%). After 2 years, evidence for the IRS was still present in eight of the control patients (24%) but only one surgical patient (3%), and the quality of life was significantly better in the surgical group.

The cumulative experience with various operative techniques has been summarized in a recent meta-analysis of 22,094 morbidly obese patients by Buchwald and colleagues (Table 2) [96]. T2DM was diagnosed in 15.3% of the evaluable patients, and impaired glucose tolerance was diagnosed in 25.8%. Overall, T2DM resolved in 76.8% of all documented cases, with glycemic improvement observed in all types of bariatric surgery. Long-term survival was not addressed in this analysis and is not commonly

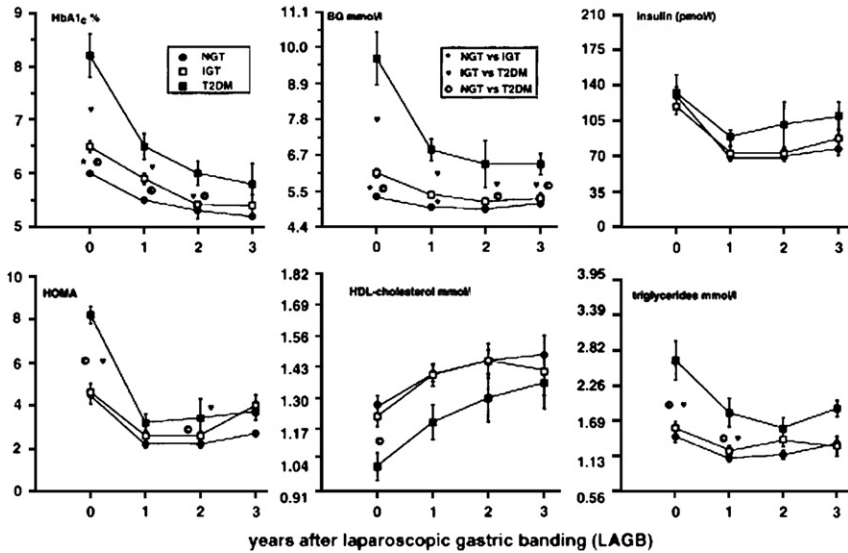


Fig. 3. Three-year behavior of HbA<sub>1c</sub>, fasting blood glucose (BG) (mmol/L), fasting insulin (pmol/L), HOMA, HDL cholesterol (mmol/L), and triglycerides (mmol/L) in grade 3 obese patients with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and T2DM undergoing LAGB. Means ± SE. (From Pontiroli AE, Pizzocri P, Librenti MC, et al. Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: a three-year study. *J Clin Endocrinol Metab* 2002;87:3560; used with permission. Copyright © 2002, The Endocrine Society.)

reported. Nevertheless, an 89% reduction in the relative risk of death was noted in a 5-year study performed at McGill University in which 1035 RYGB patients were compared with 5746 age- and gender-matched, nonoperated, severely obese patients [97].

The mechanisms responsible for the postoperative reversal of insulin resistance and its related disorders remain controversial. Most available

Table 2

Results of different types of bariatric surgery expressed as mean values from meta-analysis of 22,094 patients

	Malabsorptive (DS, BDP)	Restrictive (band, VBG)	Combined (RYGB)
Weight loss (% excess)	72	50–69	68
Abnormality resolved			
T2DM	98%	48%–68%	84%
Hypertension	81%	38%–73%	75%
Dyslipidemia improved	100%	71%–81%	94%
Operative mortality	1.10%	0.1%	0.5%

Data from Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–37.

evidence suggests that the extreme reduction in calorie intake induced by restrictive and malabsorptive procedures is the major factor. Nonetheless, because most of the metabolic effects of surgery are observed long before substantial weight loss occurs, it has been suggested that changes in regulatory peptides must also contribute [98,99].

The most commonly proposed mechanism involves alterations in the enteroinsular axis, the signaling pathway between the gut and the pancreas that serves to enhance insulin secretion in response to a meal [100]. The most important of the insulin secretagogues (incretins) are glucose-dependent insulinotropic peptide (GIP) and glucose-like peptide 1 (GLP-1) (Table 3). Both peptides are secreted by specialized cells in the gut, GIP by K cells in the duodenum and GLP-1 by L cells in the terminal ileum and colon. Together, they are responsible for 40% to 50% of postprandial insulin secretion, and both exhibit trophic effects by stimulating beta-cell proliferation and inhibiting apoptosis [101]. Overactivity of the enteroinsular axis has been cited as one potential cause of hyperinsulinism and T2DM [102].

Peptide YY (PYY) is another insulin-sensitizing peptide that is secreted by L cells in the hindgut. It is primarily involved in appetite regulation by stimulation of specific receptors in the hypothalamus. Together with GLP-1, it functions as an “ileal brake” by slowing gastric emptying and prolonging intestinal transit. Ghrelin is a novel gastric peptide with receptors in the hypothalamus. It is released principally in the preprandial state and serves as a stimulant of appetite and intestinal motility. It has also

Table 3  
Gastrointestinal hormone changes after bariatric surgery and their effect on insulin secretion

Hormone	Cell type and their location in the gastrointestinal tract	Effect on insulin secretion	Changes induced by surgery			Other actions
			BPD	RYGB	LAGB	
Ghrelin	X/A-like cells, stomach	↓	↑	↓ ↑	NC	Orexigenic, stimulates GH
GIP	K cells, foregut	↑	↓	↓	UNK	
GLP-1	L cells, hindgut	↑	↑	↑	UNK	Anorectic “ileal break”
PYY	L cells, hindgut	UNK	UNK	↑	UNK	Anorectic “ileal break”

Abbreviations: NC, no change; PYY, peptide YY; UNK, unknown.

been shown to inhibit insulin secretion, impair insulin sensitivity, block adiponectin release, and stimulate the secretion of growth hormone.

Changes in enteroinsular signaling following RYGB or BPD are thought to occur for two reasons: (1) the secretory mucosa of the excluded stomach, duodenum, and jejunum remains unstimulated because of the absence of food; and (2) the secretory mucosa of the terminal ileum is excessively stimulated because of the increased presence of incompletely digested food.

The role of foregut exclusion has been studied extensively by Rubino and Marescaux [103] using nonobese diabetic Goto-Kakizaki rats. They bypassed the duodenum and jejunum with a Roux-en-Y gastrojejunal anastomosis and found significant improvement in fasting glycemia and glucose tolerance within 3 weeks. Because this model was not associated with weight loss, unidentified humoral or neural factors independent of weight loss were suspected. Numerous other investigators have studied specific peptides, but the available data are inconclusive. Because ghrelin and GIP are primarily secreted by foregut mucosa, they are the peptides most likely to decrease after a bypass operation. In fact, ghrelin levels have been reported to increase, decrease, or remain unaltered following RYGB, an inconsistency that precludes assigning a mechanistic role [104–106]. Alternatively, GIP values are generally decreased following RYGB, especially in the presence of T2DM, but the significance of this finding remains to be determined [107,108].

In the hind gut, the normal responses of PYY and GLP-1 to a meal are clearly exaggerated following RYGB [109,110]. It seems likely that these increases contribute to the enhanced satiety that is characteristic of RYGB, but their precise relationship to the observed change in insulin sensitivity remains speculative. In this regard, Strader and colleagues [111] studied rats in which a short segment of ileum was surgically transposed to jejunum to rapidly expose the ileal endocrine cells to undigested nutrients. They confirmed a marked increase in the synthesis and secretion of PYY and GLP-1 and found improved insulin sensitivity in a comparison with sham-operated controls. These investigators and others have concluded that gastrointestinal peptides have a crucial role in glucose homeostasis and recommend that further evaluation should continue.

### **Metabolic complications**

The potential for metabolic/endocrine complications to develop as a result of weight loss surgery has only recently become evident. Endogenous hyperinsulinemic hypoglycemia with nesidioblastosis has been described in nine patients at variable time intervals after gastric bypass surgery. In one patient, multiple insulinomas were also found. All patients presented with symptoms of neuroglycopenia associated with hyperinsulinemia. Nesidioblastosis is a rare condition in which hypertrophy, hyperplasia of pancreatic islets, and neodifferentiation of islet of Langerhans cells from pancreatic exocrine duct epithelium are observed. It has been hypothesized

that this phenomenon could be caused by hypersecretion of GLP-1, a known beta-cell trophic factor, as a result of the gastric bypass (Fig. 4) [111,112].

Asymptomatic hyperinsulinemic hypoglycemia can also occur after gastric banding and is reported in 3% to 4% of LAGB patients [112,113]. It has been hypothesized that the substantial weight loss after this procedure markedly reduces insulin resistance in the context of beta-cell hypertrophy and hyperfunction that are characteristic of obesity, and that this effect may cause asymptomatic hypoglycemia. No patient undergoing gastric banding has been diagnosed with nesidioblastosis, pointing to a different pathogenesis of the hypoglycemia after the two different bariatric surgeries.

### Practical considerations

Bariatric surgery is always elective. Indeed, the best metabolic results are achieved when patients have been fully prepared and are adequately followed. In the preoperative period, most morbidly obese patients are already insulin resistant even though only a minority have T2DM. Accordingly, each patient should be assessed carefully for the presence of the IRS, and individual risk factors should be treated aggressively to minimize the risk of intraoperative and postoperative complications. In particular, if T2DM is present, good glycemic control should be achieved before the operation ( $HbA_{1c} < 7.0$ ) because infectious complications are more likely to occur in patients who are poorly controlled [114].

In the immediate postoperative period, most T2DM patients can expect a rapid reduction in or even termination of their diabetic medications; however, there are no specific guidelines for exact dosage changes. Oral diabetic medications can usually be withheld immediately after operation, but the

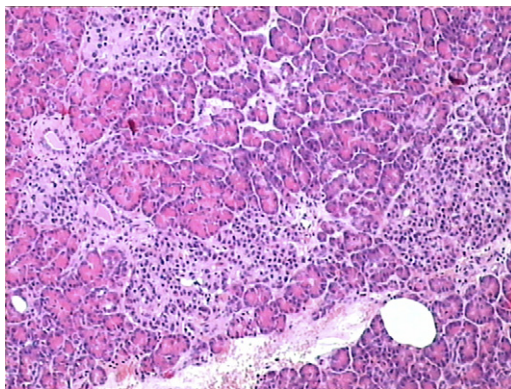


Fig. 4. Nesidioblastosis after gastric bypass surgery. There are several islets, some of which appear to be irregular and increased in size. Occasionally, groups of islets appear back-to-back close to small duct-forming structures resembling the ductuloinsular complexes. (Hematoxylin-eosin staining, final magnification  $\times 200$ ).

blood glucose levels should be carefully monitored and an insulin sliding scale initiated as necessary. Similarly, in patients who have more severe disease, such as those requiring insulin before surgery, a significant downward adjustment in medication dose is often possible before hospital discharge because considerable residual beta-cell function is usually present. In these patients, insulin needs should be managed initially with a sliding scale.

Following hospital discharge, caution is advisable in the use of anti-diabetic medications because daily oral intake usually does not exceed 500 calories for the first 2 weeks. As intake gradually increases, efforts should be made to optimize protein intake and limit carbohydrate and fat calories. In addition, because insulin sensitivity is markedly influenced by physical activity, patients should be encouraged to begin an exercise regimen that is tailored to their individual abilities. A program of 30 minutes of moderate-intensity exercise 5 days each week will help to maximize weight loss, tone muscles, improve attitude, and avoid depression.

## Summary

Insulin resistance is a nearly universal finding in morbid obesity. It may be compensated and latent or uncompensated with single or multiple clinical abnormalities, such as in the IRS, impaired glucose tolerance/T2DM, or PCOS. Although lifestyle interventions and medical measures alone may control most metabolic problems in the short term, the ultimate benefits of such an approach are usually limited by the complexity of available therapeutic regimens and the difficulty of maintaining full patient compliance. Many studies now document that bariatric surgery can effectively and safely control these complications in the short term and long term or even prevent their occurrence. Further investigations are needed to better understand the mechanisms involved and to define more clearly the appropriate indications and contraindications of the treatments proposed.

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