

# An Overview of the Progress in Obesity, Diabetes and Bariatric Surgery

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**Abstract:** Under the backdrop of changing lifestyle and a sharp increase of aging population, the prevalence of diabetes and overweight/obesity is increasing rapidly. At present, the prevalence of obesity and diabetes in China ranks first in the world, leading to a significant economic burden to China's social development and public health. The association between obesity and diabetes was recognized as early as 50 years ago. Eighty to ninety percent of patients with diabetes are classified as obese. Obesity is considered an independent risk factor for diabetes mellitus. Obese patients often have abnormal glucose metabolism and other components of metabolic syndrome. Currently, bariatric surgery is recognized as the most effective and long-term method for weight loss. In addition to promoting effective weight loss, it can also enhance blood glucose levels and reduce cardiovascular risk. However, some obese patients fail to lose weight after weight loss surgery, and diabetes does not improve. This article reviews the latest epidemiological characteristics of obesity and diabetes, the internal association between obesity and diabetes, the mechanism of weight loss and diabetes relief after weight loss surgery, and the impact of diabetes on weight loss. The aim is to provide a comprehensive understanding of these two chronic metabolic diseases.

**Keywords:** Obesity, Diabetes Mellitus, Bariatric surgery

## 1. Definition of obesity and the latest epidemiological study of diabetes mellitus

Obesity is an abnormal or excessive fat deposition that can compromise health due to a complex etiology. Many familial clusters and twin studies have demonstrated that genetic factors are a primary contributor to obesity, accounting for 40% to 70% of the influencing factors of obesity. In addition, diet and exercise are also important influencing factors. Since 1984, the WHO has included obesity in the list of diseases, and it was officially defined as a disease in 1997. Obesity has received widespread attention. The classification of obesity is divided into primary obesity and secondary obesity based on different causes, central obesity and peripheral obesity based on different fat distribution, and metabolic normal obesity and abnormal obesity based on the presence of obesity-related diseases. Overweight or obesity was assessed using Body Mass Index (BMI) and waist circumference. Assessment of overweight or obesity with BMI is developed based on cardiovascular disease risk. BMI is currently commonly used to detect overweight or obesity in adults. The National Institutes of Health and WHO defined BMI of 25.0-29.9 kg/m<sup>2</sup> as overweight (China's standard for overweight is a BMI of 24.0-27.9 kg/m<sup>2</sup>), and a BMI of 30.0 kg/m<sup>2</sup> as obesity (China's standard for obesity is a BMI of 28.0 kg/m<sup>2</sup>)<sup>[1]</sup>. By 2030, one in five women and one in seven men will be obese (BMI 30 kg/m<sup>2</sup>), and obesity will affect over 1 billion people worldwide. Obesity rates are increasing across all age groups and genders, irrespective of geographical location, ethnicity, or socioeconomic status<sup>[2]</sup>. Obesity is one of the most prominent yet often overlooked public health issues. It is a well-recognized risk factor for various diseases, such as type 2 diabetes, cardiovascular disease, metabolic syndrome, chronic kidney disease, hyperlipidemia, high blood pressure, non-alcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, depression, and certain types of cancer, among others<sup>[3]</sup>. The high incidence of obesity and its complications seriously affects individuals, families, the healthcare system, and carries a huge burden on the entire economic society.

Type 2 diabetes, a slowly progressive chronic metabolic disease accounting for more than 90% of all diabetes types, is mainly characterized by hyperglycemia resulting from insulin resistance and relative insulin deficiency. Typical symptoms of diabetes are "three more and one less," namely polydipsia, hyperphagia, polyuria, and weight loss. The current diagnostic criteria for T2DM are based on the WHO 1999 criteria<sup>[4]</sup>. A comprehensive study of 204 countries and regions revealed that there were 529 million

people with diabetes worldwide in 2021, with an age-standardized prevalence of 6.1%. Moreover, the prevalence of diabetes was higher in men than in women (6.5% vs. 5.8%). By 2050, it is estimated that there will be around 1.31 billion people with diabetes worldwide. The increase in the prevalence of diabetes, 49.6%, was attributed to the changing trends in obesity<sup>[5]</sup>. According to the latest epidemiological survey of chronic diseases in China, over 50% of Chinese adults are overweight or obese. The overweight rate among adult residents is 34.3%, while the obesity rate is 16.4%. Additionally, 19% of children and adolescents are overweight or obese. In China, there are 121 million people with diabetes, ranking first in the world, and about 507 million overweight and obese individuals, also ranking first globally<sup>[6]</sup>. Two chronic diseases, such as obesity and diabetes, exert significant pressure on economic, social development, and public health. Therefore, they require urgent attention and action.

## 2. Relationship and Mechanism of Obesity and Diabetes

Obesity and diabetes are closely related, and the term "diabesity" was proposed as early as 1973 to emphasize the pathophysiological link between type 2 diabetes and obesity. Sim et al. found that young men without a family history of diabetes, who increased their BMI to 28.0 kg/m<sup>2</sup> through overfeeding for 6 months, exhibited reversible increases in fasting insulin, glucose, and triglyceride concentrations, as well as impaired glucose tolerance<sup>[7]</sup>. Obesity has been reported in 80-90% of patients with type 2 diabetes<sup>[8-9]</sup>. The prevalence of diabetes among overweight and obese people in China was 12.8% and 18.5%, respectively<sup>[10]</sup>. Obesity is considered an independent and the most dominant risk factor in diabetic patients. The observed rise in the incidence and prevalence of diabetes reflects the increase in the prevalence of obesity<sup>[11]</sup>.

Obesity is strongly associated with the development of insulin resistance. Insulin resistance is characterized by a reduced responsiveness to insulin, commonly observed in obese patients. Although obesity is not always associated with insulin resistance, the vast majority of individuals with insulin resistance are obese or overweight<sup>[12]</sup>. The imbalance between energy intake and expenditure in obese patients can promote the expansion and deposition of adipose tissue. In chronic obese patients, adipose tissue can undergo remodeling, activating inflammatory factors that cause chronic inflammation throughout the body and tissue damage, which is one of the causes of insulin resistance<sup>[13]</sup>. In the past, adipose tissue was considered to be merely an energy storage depot. However, it has been discovered that adipose tissue is also an endocrine and immune organ with high metabolic activity. It can secrete adipokines to regulate metabolism and energy homeostasis, potentially leading to insulin resistance and chronic low-grade inflammation. Although the exact molecular interaction between obesity and insulin resistance has not been well explained, most studies suggest that obesity can promote endoplasmic reticulum (ER) stress, induce oxidative damage, impair insulin signal transduction elements, enhance inflammatory events, reduce islet  $\beta$ -cell function, and cause mitochondrial dysfunction, thereby damaging the insulin signaling pathway and leading to insulin resistance<sup>[14]</sup>. Obesity-related insulin resistance plays a key role in the development of abnormal glucose metabolism, coronary syndrome, metabolic syndrome, polycystic ovary syndrome, and non-alcoholic fatty liver disease. Insulin resistance primarily affects adipose tissue, skeletal muscle, and liver insulin sensitivity. In the liver, it reduces glycogen synthesis and inhibits gluconeogenesis. In adipose tissue, it hinders fat breakdown and promotes dysfunctional fat synthesis. In muscle tissue, it impairs glucose transport, resulting in reduced glucose utilization rates, ultimately leading to glucose metabolism disorders.

Type 2 diabetes mellitus is a slowly progressive chronic disease, and its natural course is often characterized by three stages: normal glucose tolerance stage, pre-diabetes stage, and diabetes mellitus stage. One of the main features of type 2 diabetes is insulin resistance. In the pre-diabetic stage, islet cells can compensate by secreting more insulin to overcome the lack of insulin sensitivity and maintain blood glucose homeostasis. As the disease progresses, the function of islet B cells gradually decreases and cannot compensate for insulin resistance, eventually leading to the development of diabetes. It is noteworthy that insulin resistance is a common and significant factor in the development of obesity and diabetes. This may help explain the high incidence of diabetes among obese patients.

## 3. Treatment of obesity combined with diabetes mellitus

### 3.1 Lifestyle Intervention

Lifestyle intervention should be utilized as a first-line treatment approach for obese patients with T2DM and should be sustained over the long term. It is recommended to control daily energy intake at

1500-1800 kcal/day for men, 1200-1500 kcal/day for women, or 500-700 kcal/day based on current energy intake levels, considering age, physical activity, and stress levels. Maintain a balanced diet by ensuring that carbohydrates make up 45% to 60% of total energy intake, while keeping fat consumption below 30% of total energy<sup>[15]</sup>. In addition, personalized and precise dietary intervention methods, such as energy restriction with a balanced diet, intermittent diet, Mediterranean diet, low-carb diet, and nutritional meal replacements, have certain effects on weight control. Obese patients should perform at least 150-300 minutes of moderate-intensity aerobic exercise per week, or 75-150 minutes of high-intensity aerobic exercise.

### **3.2 Drug Therapy**

Currently, FDA-approved drugs for the treatment of obesity include naltrexone, lorcaserin, phentermine/topiramate, orlistat, and GLP-1 receptor agonists (liraglutide and semaglutide). Patients with type 2 diabetes mellitus (T2DM) who are obese should consider both blood sugar control and weight management when selecting hypoglycemic medications. It is advisable to opt for hypoglycemic agents that have a positive effect on blood sugar levels without causing weight gain. GLP-1 receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors are recommended for diabetic patients who are obese or overweight<sup>[16]</sup>. In addition, metformin, dipeptidyl peptidase 4 (DPP-4) and glucosidase inhibitors can also effectively reduce body weight, with or without causing weight gain.

### **3.3 Surgical Treatment**

The effectiveness of lifestyle intervention and drug-based weight loss is limited, making it challenging for patients to adhere to. Weight loss surgery is considered the most effective and long-term method for weight reduction, with its safety and effectiveness being widely acknowledged<sup>[17]</sup>. Laparoscopic sleeve gastrectomy and laparoscopic RYGB (Roux-en-Y gastric bypass) are two types of weight loss surgeries recommended in China. In addition to promoting effective weight loss, weight loss surgery can also enhance glucose metabolism. Surgical treatment can be considered for obese patients with T2DM who experience weight loss or unsatisfactory glycemic control following non-surgical treatment.

## **4. The Effect and Potential Mechanism of Weight Loss Surgery on Diabetes**

Weight loss surgery was originally used for weight reduction. However, in the 1980s, researchers discovered that weight loss surgery can not only relieve type 2 diabetes and various coexisting metabolic syndromes. This approach is also known as metabolic surgery for weight loss. Several studies have confirmed that bariatric surgery is significantly more effective than medication in reversing type 2 diabetes mellitus, reducing the onset of T2DM, and lowering the risk of complications. It is reported that the remission rate of T2DM is 50-75% at 2-3 years after weight loss.

### **4.1 Weight Loss**

Weight loss surgery can lead to significant weight loss, with 51-79% excess weight loss at 1-2 years after the procedure, and 54-72% excess weight loss at 5-7 years post-surgery. Weight loss can enhance insulin resistance and boost insulin sensitivity. Insulin resistance plays a crucial role in the pathogenesis of diabetes in obese patients, and bariatric surgery can help alleviate diabetes. In fact, improvements in blood glucose levels often appear within days to weeks after weight loss, even before weight loss occurs<sup>[18]</sup>. Some studies have found that surgical weight loss is significantly more effective than drug therapy. For this reason, the mechanistic basis of the improvement effect of weight loss surgery on T2D is complex and is known to be at least partially independent of its effect on weight loss.

### **4.2 Reduction of energy intake and absorption**

At present, two mainstream weight-loss procedures in China—laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass surgery (LRYGB)—are considered restrictive energy surgeries. LSG restricts gastric volume by creating a sleeve or tubular stomach along the lesser curvature of the stomach, thereby limiting food intake to regulate energy consumption. LRYGB limits food intake and reduces absorption in the small intestine by decreasing stomach volume and altering food pathways. Previous studies suggest that the anatomical changes in the gastrointestinal tract resulting from weight

loss surgery, which can lead to inadequate calorie absorption and nutrient deficiencies, are the primary factors contributing to weight loss and metabolic improvements in patients. However, some studies have shown that RYGB does not change the length of the functional small intestine and the residence time of food in the small intestine<sup>[19]</sup>. Additionally, the absorption of sugars did not decrease<sup>[20]</sup>. Insufficient energy absorption may contribute less than 10% to postoperative efficacy<sup>[21]</sup>. It is believed that reduced energy intake and absorption are not the main mechanisms.

#### **4.3 Changes in intestinal hormones**

After weight-loss surgery, the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) has been confirmed by many studies<sup>[22-24]</sup>. The commonly used hindgut theory suggests that RYGB alters gastrointestinal anatomy, speeding up food passage through the gastrointestinal tract. This leads to a high concentration of intestinal nutrients that stimulate the secretion of GLP-1 and PYY intestinal hormones in the distal intestine and colon. GLP-1 and PYY can inhibit gastric emptying, decrease intestinal peristalsis, suppress appetite, and ultimately aid in weight reduction. In addition, GLP-1 can also promote glucose-dependent insulin secretion and inhibit glucagon secretion to improve glucose metabolism<sup>[22]</sup>. RYGB surgery can alleviate pressure on the anterior small intestine, leading to a reduction in the secretion of gastric peptides (GIP) associated with insulin resistance. This, in turn, can enhance glycemic control. This hypothesis is called the foregut hypothesis<sup>[25]</sup>. Some studies suggest that the decrease in ghrelin and leptin levels after bariatric surgery may also be associated with weight loss and metabolic improvements<sup>[26-27]</sup>.

#### **4.4 Increasing bile acid levels**

After Roux-en-Y gastric bypass (RYGB), the route of enterohepatic circulation is shortened. This accelerates the contact between bile acids in the intestinal lumen and the ileum, the primary site of bile acid reabsorption. Consequently, postoperative bile acid reabsorption becomes earlier and more active. Bile acids, key factors in lipid absorption, also play an important role in regulating metabolism. Bile acid function is mediated by two major intestinal receptors, the Farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor (TGR5). Bile acids can activate FXR in ileal cells and promote increased production of FGF-19, ANG1, iNOS, and IL-18 downstream<sup>[28]</sup>. All of these factors are closely related to improved metabolism. Moreover, bile acids can bind to TGR5 in ileal L cells to promote the secretion of GLP-1. Increased serum total bile acids were reported after both RYGB and SG bariatric surgery<sup>[29-30]</sup>.

#### **4.5 Intestinal Microecology Changes**

In healthy adults, 90% of gut microbes are Bacteroidetes and Firmicutes. Obese patients had higher levels of intestinal Firmicutes, lower levels of Bacteroidetes, and generally reduced biodiversity compared to the normal population<sup>[31]</sup>. The intestinal microecology has been documented in obesity and diabetes, and changes in the Firmicutes/Bacteroidetes ratio are associated with obesity and insulin resistance. The number of Firmicutes decreased and Bacteroidetes increased after bariatric surgery, and flora diversity changed after metabolic surgery<sup>[32-33]</sup>. By transplanting the microbiota of patients after weight loss surgery into obese mice, researchers observed faster energy consumption, significant changes in gut microbiota composition, and weight loss. This suggests that the modified microbiota following weight loss could potentially aid in improving obesity<sup>[34]</sup>. At present, the specific mechanism of intestinal microecological changes after weight loss is not clear. This lack of clarity may be associated with postoperative alterations in dietary habits, gastrointestinal anatomy, and levels of gastrointestinal hormones.

### **5. The Impact of Diabetes Mellitus on Weight Loss**

Although weight loss surgery is considered the most durable and effective method for weight loss, some obese patients experience poor postoperative weight loss outcomes, leading to weight loss failure. Therefore, it is crucial to identify the factors that influence weight loss outcomes after weight loss surgery. There is no consensus on the assessment of weight loss after bariatric surgery, and most surgical literature commonly describes weight loss as % EWL (percentage excess weight loss)<sup>[35]</sup>. The reported studies have shown that there is an inverse association between preoperative age and BMI level, and the weight loss effect appears to be a consensus among the predictors of weight loss surgery<sup>[35-38]</sup>. There is no

definitive conclusion on the impact of gender on weight loss, but some studies suggest that women may have an advantage in achieving weight loss<sup>[39]</sup>. However, other studies indicate that men have better postoperative weight loss outcomes than female obese patients<sup>[36]</sup>.

Multiple studies have shown that obese patients with diabetes are associated with smaller weight loss<sup>[38-40]</sup>. Eleni Rebelos et al. followed 312 obese patients undergoing LSG and LRYGB surgeries for 1-5 years. They found that preoperative weight loss and weight loss in patients with T2D were more significant compared to those without T2DM<sup>[38]</sup>. Yunsheng Ma and Emilio Ortega followed up with 494 obese patients who underwent RYGB and 407 who underwent RYGB and SG, respectively. They found that obese patients with T2DM were still associated with smaller weight loss. The mechanism by which diabetes is a risk factor for weight-loss surgery may be related to the preoperative use of insulin. The body may require frequent "protective" calories to prevent hypoglycemic symptoms and reduce urinary glucose loss after surgery. Among the factors influencing the remission of diabetes mellitus after weight loss, preoperative BMI, age, fasting glucose, fasting C-peptide, HbA1c, and receiving insulin treatment can be used to predict diabetes remission<sup>[41-42]</sup>. However, the specific mechanism of the effect of diabetes on weight loss and the impact of weight loss on the remission of diabetes are still unknown. The pathogenesis of the two metabolic diseases, diabetes and obesity, intersect and appear to influence each other's outcomes, highlighting the need for further exploration of their pathogenesis.

## 6. Conclusion

Obesity and diabetes exert significant pressure on economic, social development, and public health. The global prevalence of diabetes and obesity is on the rise. Excessive fat deposition in obesity leads to insulin resistance, release of inflammatory factors from adipose tissue, fibrosis of the extracellular matrix, and systemic low-grade inflammation, which may be the underlying mechanism linking obesity to diabetes. Lifestyle interventions and drug treatments for obesity have limited efficacy, while weight loss surgery is currently recognized as the most effective and long-term method for weight loss. In addition to promoting effective weight loss, it can also enhance metabolic conditions such as blood sugar levels. Compared with non-T2DM patients, patients with diabetes experience poor weight loss effects, which may be associated with preoperative insulin use and frequent postoperative intake of energy. However, the underlying mechanism linking obesity and diabetes remains unclear and requires further exploration to address the economic and health burden of these two chronic diseases on society

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