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## **Bariatric Surgery to Correct Morbid Obesity Also Ameliorates Atherosclerosis in Patients with Type 2 Diabetes Mellitus**

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### **Abstract**

Morbid obesity, a physiological dysfunction in humans associated with environmental, genetic and endocrinological origins, has significantly increased in the past few decades in the USA. Many methods have emerged for treating morbid obesity, such as diets, exercise, behavior modification, liposuction, drugs, and surgery; among these, bariatric surgery reduces weight and appears to have other curative effects. Roux-en-Y gastric bypass is the principal form of bariatric surgery, followed by laparoscopic adjustable gastric banding, gastric sleeve operation, duodenojejunal bypass and biliopancreatic diversion. This weight-loss surgery may also affect comorbidities of morbid obesity, such as type 2 diabetes mellitus (T2D), atherosclerosis, hypertension and steatohepatitis. Weight-loss surgery, for example, is associated with a more than 80% diabetes (data indicates > 80%) remission rate in severely obese persons. Empirical evidence also suggests that the use of bariatric surgery reduces atherosclerosis, and may ameliorate other comorbidities. This warrants closer examination.

**Keywords:** bariatric surgery, atherosclerosis, morbid obesity, diabetes mellitus

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### **1. Introduction**

Morbid obesity, particularly in the USA, is becoming a serious health problem. The incidence of obesity in the USA has increased from about 14% in the 1970s to 32% today [1,2]. The latest National Health and Nutrition Examination Surveys show that 127 million individuals are

overweight. Of these, 60 million are obese and 8-10 million have morbid obesity [BMI (body mass index=Body weight/square of height)  $\geq 40$  kg/m<sup>2</sup>] with serious medical comorbidities resulting in increased disability, morbidity and early mortality [1]. Obesity is now increasing in developing countries in South America, Asia, and Africa, as they adopt the more sedentary and

affluent lifestyles of developed countries [2].

## 2. Potential causes of morbid obesity

Medically defined, obesity is a physiological dysfunction in humans with environmental, genetic and endocrinological causes [3]. Obesity is characterized by excess body fat accumulation, which is associated with multiple organ-specific pathological consequences [4]. There are many underlying factors that contribute to obesity and morbid obesity. Metabolic disorder is a likely factor leading to morbid obesity. Surplus energy is stored as adipose tissue [5]. Anabolic metabolism in patients with metabolic disorders is much higher than catabolic metabolism. Obesity is becoming endemic, particularly because of an increase in nourishment and a decrease in physical exercise [6].

Some gastrointestinal hormones play important roles in morbid obesity. Peptide YY (PYY) is one such hormone produced by L cells of the distal gastrointestinal (GI) [7,8]. PYY is involved in the regulation of GI function by inhibiting gastric acid and pancreatic and intestinal secretions [8,9]. PYY also inhibits gastric emptying (GE) and GI motility [10-12]. PYY has strong anorectic effects and decreases plasma levels of ghrelin [13-15]. Ghrelin is produced in the cells of the gastric fundus [16]. Exogenous ghrelin exhibits potent orexigenic properties when administered peripherally or centrally and also enhances GI motility and GE [15,17]. Endogenous ghrelin levels also increase with weight loss and decrease with weight gain [15,18,19]. Ghrelin is associated with insulin sensitivity [20,21]. Total ghrelin includes acylated (10% of total ghrelin) and non-acylated (90% of total ghrelin) ghrelin, two distinct forms that were previously identified in circulation [20,21]. Furthermore, at pharmacological concentrations, acylated ghrelin increases the degree of insulin resistance, whereas co-administration of acylated ghrelin and non-acylated ghrelin improves insulin sensitivity [22]. Non-acylated ghrelin increased insulin release in vitro by insulinoma cell lines exposed to high glucose concentrations and over-expression of non-acylated ghrelin in pancreatic islets improved the insulin sensitivity to an intraperitoneal glucose load in mice [23-25]. Moreover, when co-

administered with acylated ghrelin, non-acylated ghrelin completely prevented the acylated ghrelin induced increase in circulating glucose levels and worsening of insulin sensitivity [26]. Thus, acylated ghrelin and non-acylated ghrelin forms may induce different physiological and/or metabolic effects. Leptin is an adipocyte-derived circulating hormone that provides information to the brain about energy stores [27,28]. The brain's response to leptin involves changes in energy expenditure and food intake [29]. Leptin-deficient mammals, including humans, are markedly hyperphagic, and leptin replacement reverses this [30]. Leptin acts on neural circuits governing food intake to diminish perception of food reward while enhancing the response to satiety signals generated during food consumption.

There are also other gastrointestinal hormones such as cholecystokinin (CCK), glucagons, insulin, corticosteroid and glucagon like peptide 1 (GLP-1) that may play a role in morbid obesity [31,32] via a hormonal feedback loop involved in regulating body weight. The peripheral signals of hormones and vagal inputs from the gut, liver and fat provide information about the current nutritional state of the body. These signals are conveyed to the brainstem and hypothalamus where monoaminergic and peptidergic neurons integrate the information to modulate food intake [33,34].

## 3. Co-morbidities associated with morbid obesity

Obesity and T2D are emerging as the greatest public health problems of the coming decade [35]. The conditions are strongly linked, with the increased prevalence of T2D correlating with the increased prevalence of obesity [36]. Approximately half of those diagnosed with T2D are obese [37]. Early and intensive treatment of T2D is known to improve health and quality of life [35,38-40]. Weight control is the most important kind of T2D management, as weight loss reduces morbidity and mortality [41]. Recent evidence indicates that improvement in blood glucose level is related to degree of weight loss [42].

Insulin resistance refers to a decreased capacity of circulating insulin to regulate nutrient

metabolism. Individuals with insulin resistance are predisposed to developing T2D, with insulin resistance as an integral feature of its pathophysiology [43,44]. Chronic secretion of large amounts of insulin to overcome tissue insensitivity can lead, in predisposed individuals, to pancreatic  $\beta$  cell failure and concomitant defects in glucose and lipid metabolism [45]. Presently, few genetic causes have been identified. Insulin resistance is believed to be promoted by a sedentary lifestyle, obesity, fatty diet and increased age, and reversed by exercise and weight loss.

Overweight and obesity are associated with dyslipidemia, atherosclerosis, hypertension, cancer, osteoarthritis, etc [46-48]. Atherosclerosis involves a complex pathologic process thought to be initiated principally at sites of endothelial dysfunction by the retention, accumulation, and oxidative modification of lipoproteins in the arterial wall, especially the coronary arterial wall [49]. This comorbidity can result in myocardial infarction and sudden death. It accounts for over 500,000 deaths annually in the United States. Diseases related to atherosclerosis such as myocardial infarction and stroke account for the majority of death in industrialized countries. The proportion of mortality caused by cardiovascular complications is 44/2037, which is the major cause of death in obese patients [50,51]. Hypertension and dyslipidaemia often manifest concomitantly with obesity and insulin resistance. The activity of the renin-angiotensin system is elevated in obese patients, and such elevations may enhance vasoconstriction, thereby leading to an increase in blood pressure [52-55].

Accumulation of lipid in the liver often accompanies and parallels weight gain and obesity [56]. Pro-inflammatory substances activate Kupffer cells, which are abundant in the liver and account for over 5% of total cells. The activation state of Kupffer cells increases with obesity [57]. Additional immune cells in the liver may also be involved in inflammation-induced insulin resistance. Morbid obesity is a type of local or systemic state of pro- or subacute inflammation. Signals such as NF- $\kappa$ B, TNF- $\alpha$  and interleukins are found to be elevated in liver [57-62]. Obesity and lack of physical activity have been associated with many kinds of malignant tumors, including

pancreatic cancer, colon cancer, breast cancer, prostate cancer and ovarian tumor [63-65]. Tumors are reported to be the major non-cardiovascular cause of mortality in obese patients and the mortality proportion of tumor is 48/2037 [50]. Obesity is also associated with many other comorbidities, such as cholelithiasis, gastroesophageal reflux, obstructive sleep apnea, degenerative joint disease, gout, lower back pain, and polycystic ovary syndrome [66,67].

#### **4. Bariatric surgery: A new method in body weight control**

Many methods are used to treat obesity and morbid obesity, such as diets, exercise, behavior modification, liposuction and drugs [68]. The US Center for Disease Control reports that obesity will increase to 39% by 2010, despite current attempts at preventative treatment [69-71]. There is thus an urgent need to address the status, cost and effectiveness of current healthcare options for treating morbid obesity. Three licensed drugs— orlistat (Xenical; Hoffman-LaRoche, USA), sibutramine (Meridia; Abbott Laboratories, USA) and rimonabant (Acomplia, France)—require a two year treatment regimen to achieve a 5-10% weight loss in 60-70% of obese patients [71]. Combining weight-loss drugs may provide some added benefit as well [69]. Reports show that abdominal liposuction does not significantly improve obesity-associated metabolic abnormalities [68,72]. Furthermore behavior modification and drug therapy in morbidly obese patients are ineffective in inducing major weight loss [70]; this suggests that surgery is the most effective and reliable option for treating the morbidly obese patient [73,74].

Observational evidence suggests that weight-loss surgery is associated with a 60% to 80% diabetes remission rate in severely obese persons and that earlier interventions are more likely to provide remission [75]. Concerns exist regarding the lack of evidence, as well as the safety, invasiveness, and cost-effectiveness of surgical weight loss procedures. Providing appropriate evidence has previously proved problematic, because the invasive nature of the surgery makes participant recruitment difficult. However, with the advent of safer, less invasive surgical weight-

loss procedures, randomized trials are now feasible, and it is possible to study the examining mild to moderate obesity, which is responsible for many cases of diabetes.

Of the 180,000–200,000 bariatric surgeries performed in 2006, about 80% were Roux-en-Y gastric bypass (RYGB). RYGB also reverses and ameliorates the major cardiovascular and metabolic risk factors, including T2D and hyperlipidemia and dyslipidemia. RYGB also reduces long-term mortality and morbidity associated with obesity, and decreases health care costs, although recidivism occurs in about 20% of patients who fail to sustain their weight loss [55,76-78]. Weight loss as a result of RYGB is probably due to two reasons. First is the small gastric pouch that limits caloric intake. Secondly, Roux-en-Y loop of hindgut short-circuits the remaining gastrointestinal tract, thereby decreasing nutrient absorption. However, evidence suggests that hormonal components play a major role in reducing food intake and decreasing weight after RYGB [78,79]. Other mechanisms are initiated in the creation of the gastric pouch because it divides vagal parasympathetic and sympathetic fibers, thereby influencing the afferent signals to the brain. Efferent signals can also be disrupted, which may play a role in the outcome of this operation [80].

Besides the body weight change, the fasting glucose and insulin resistance are also obviously decreased after bariatric surgery. And these changes come even earlier than weight change [81]. Edward Mason mentioned that gastric bypass was reported to reverse diabetes as far back as the 1950s. After operation, surgeons were aware of the fact that before the patients got out of the hospital, they no longer needed insulin [81]. Bypass surgery decreased fasting glucose to normal level [80]. As research expands, gastric bypass surgeries are beginning to be performed on less obese patients with diabetes although there can be severe complications, such as infection, gallstones and hernias. There's "huge demand, no regulation, everybody's got their own operation. Patients are willing to do whatever it takes to get it." Currently, U.S. National Institutes of Health guidelines recommend that gastric bypass surgery be considered only for people who have a body mass index (BMI) of at least 40. At a meeting in

Rome last year, 78% of attendees supported lowering the limit to a BMI of 30 for those with diabetes just because T2D contributes to more than 1 million deaths worldwide each year [50,81].

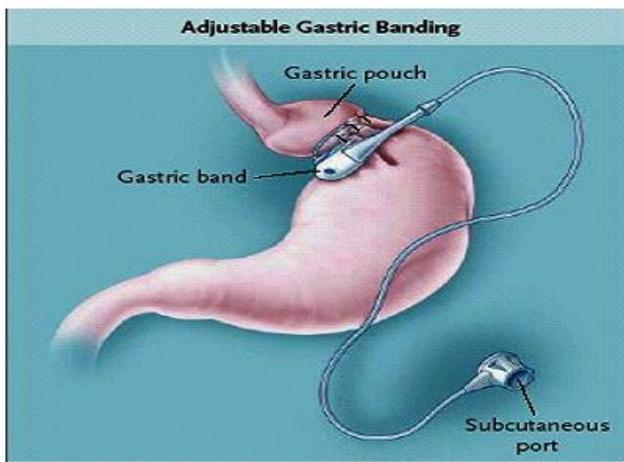
However, these mechanisms do not sufficiently account for the maintenance of body weight loss or regain after RYGB. Perhaps the hypothalamus, which regulates GI hormone secretion via efferent vagal and sympathetic fibers to the GI tract and via hypothalamic neuropituitary secretions of hormone precursor, contributes to a decrease of food intake after RYGB [82-84]. Experimental data from both human and rat consistently show resolution of T2D after RYGB. After RYGB, most T2D patients no longer need insulin, even before they have lost much weight. Some patients even suffer from hypoglycemia [81]. The data strongly suggest that a hormonal component(s) plays a contributory role in reducing food intake and in facilitating protracted weight loss after RYGB [85] due to the rearranged anatomy created by the RYGB to provide direct entry of food into the jejunum and hindgut. Food bypasses the remaining neuroendocrine and physiologically functional stomach as well as the duodenum and proximal jejunum, thereby circumventing their hormonal secreting, digestive, and absorptive functions [81]. Several studies have shown a positive association between obesity and an increased rate of death, with an even greater risk of death among persons with a BMI of 35 or more, as compared with those with a BMI of 30 to 34 [51]. Sjöström L and Ted D. Adams compared the mortality of patients who received bariatric surgery in 20 years and summarized the probable reasons for mortality in morbid obese patients [50,51].

Cardiovascular diseases and hypertension are important co-morbidities in morbidly obese patients (19.3/10000), which are believed to be the main contributors to mortality [50]. Cancer (15/10000) and diabetes (3.5/10000) are believed to be the other two major reasons for mortality in obese patients. After bariatric surgery, the mortality rate for cardiovascular disease is 8.5/10000, and for cancer and diabetes are 5.4/10000 and 0.3/10000, respectively [50,51]. Bariatric surgery can increase the survival rate in patients whose BMI are larger than 45kg/m<sup>2</sup>. This is reported to be the most effective option for

weight loss in the severely obese. Obesity is prevalent and associated with multiple medical comorbidities, including early death from heart disease and cancer [51,86]. Weight loss yields improvement of these co-morbidities and decreases mortality [50,55,76,77].

### Laparoscopic lap band operation (LAGB)

Laparoscopic adjustable gastric banding, gastric sleeve operation, duodenojejunal bypass and biliopancreatic diversion are also widely used in the treatment of morbid obesity [87-89]. Gastric fundus and small curve are isolated and one adjustable gastric band is fitted around the uppermost part of the stomach with golden finger, forming a 15cc small pouch [73]. This can be inflated or deflated at any time after the operation and helps the patient continually lose weight until they reach their goals. The restriction takes place in the radiology suite and normally takes 15 minutes. This simple procedure is painless. Saline is injected into a port placed under the skin in the wall of the stomach. A tube connects the band to the port.



**Figure 1.** Laparoscopic adjustable lap band surgery is depicted. Adjustable gastric banding is a kind of restrictive bariatric surgery that produces a small pouch at the cardium of the stomach and thus restricts the volume and velocity of food intake. It is much smaller for the first pouch and makes patients feel full quickly while eating. Thus food intake decreases. A lap band is placed around cardium of the stomach and fixed with a suture. The band is connected with a subcutaneous port.

After surgery, saline is injected into the port to decrease the pouch diameter, and thus decrease food intake.

### Laparoscopic sleeve gastrectomy (LSG)

A gastric tube is created using repeated firing with linear staplers from the distal antrum to the Hiss angle, with complete removal of the greater curvature and fundus. During the operation, a gastroscop is maintained in the gastric cavity to prevent a complete closure of the gastric cavity by the linear stapling procedure (Fig. 2).

### Laparoscopic gastric bypass

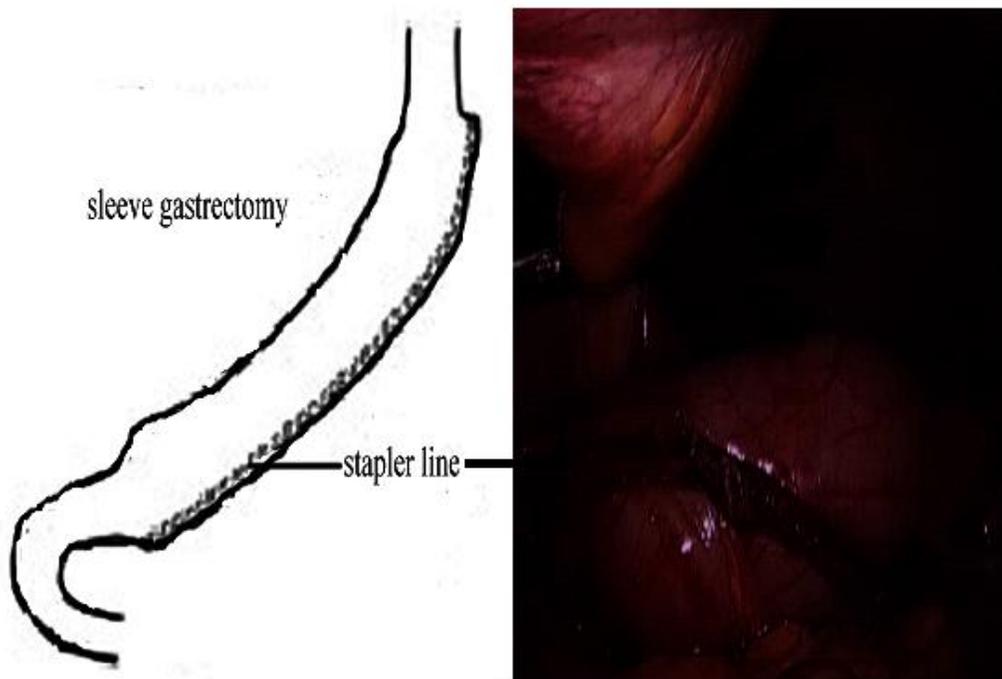
RYGB, the common bariatric surgery performed in the United States, combines a restrictive and a malabsorptive procedure [51]. A small gastric pouch (15-30 ml) is created to restrict food intake and a Roux-en-Y gastrojejunostomy provides the mild malabsorptive component. Superior weight loss including excellent long-term weight reduction and elimination of co-morbidities occurs in 95 % T2D patients and 80% of T2D were cured after Roux-en-Y gastric bypass surgery compared to vertical banded gastroplasty2D) [51]. Early and late complication rates are reasonably low, and operative mortality ranges from 0.2 to 1 percent [51] (Fig. 3).

### The Biliopancreatic Diversion - Duodenal Switch

In the Biliopancreatic Diversion-Duodenal switch (BPD/DS), roughly half of the stomach is permanently removed. The stomach goes from the shape of a small pineapple to the size and shape of a banana. The pylorus, which is the valve at the outlet of the stomach, remains intact. The stomach is then connected to the last 250 centimeters (8 feet) of small intestine. The remainder of the small intestine is connected 100 centimeters from the end of the small bowel, forming the common channel, where food mixes with the digestive enzymes.

## 5. Prospects for bariatric surgery eliminating atherosclerosis in morbid obesity

Atherosclerosis accounts for over 500,000 deaths annually in the United States [90]. Diseases



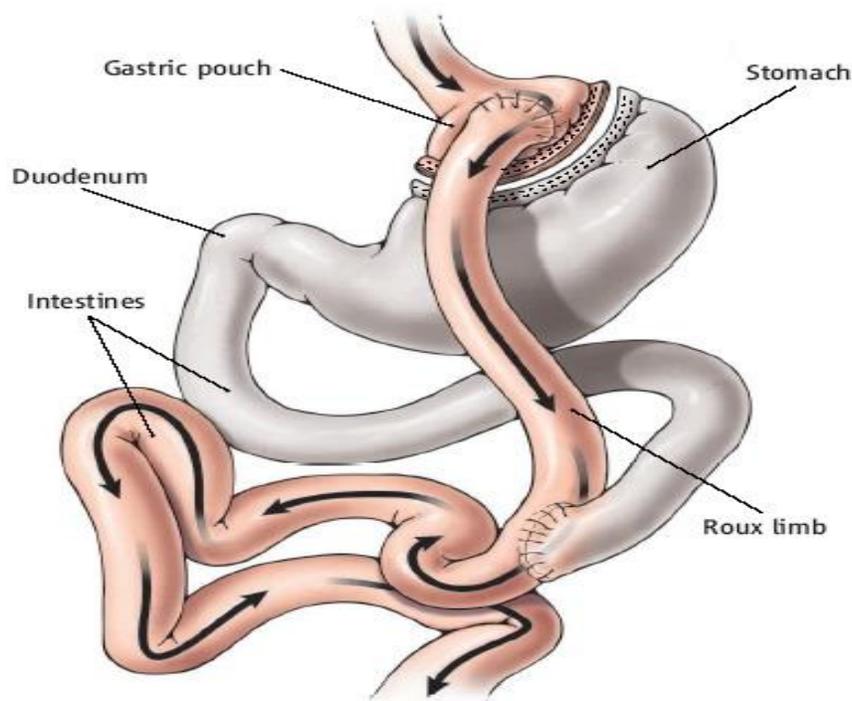
**Figure 2.** Laparoscopic sleeve gastrectomy is depicted. Sleeve gastrectomy is also a kind of restrictive bariatric surgery. Using a laparoscope, an 80-90% reduction in the stomach volume is achieved with a liner stapler along the small curve. Initially, the larger omentum is moved away with LigaSure, then the liner staplers are used to reduce all of the larger curve and gastric fundus, leaving about 10-20% of the stomach in the small curve. In this way, food passes through a smaller volume of the stomach. The serum ghrelin (a major orexigenic hormone in the gastrointestinal tract) level decreases significantly after surgery.

related to atherosclerosis such as myocardial infarction and stroke account for the majority of deaths in industrialized countries [91,92]. Atherosclerosis is a complex, multifactorial disease with both genetic and environmental determinants. Despite extensive research, the link between dietary habits, traditional risk factors such as hypertension, smoking, diabetes, and obesity, and the development of atherosclerosis has not been fully elucidated [93]. In some trials on atherosclerosis and hypertension, researchers have found a direct association between the amount of weight loss and blood pressure reduction at 36 months [92,93]. Prospective cohort studies have also found that atherosclerosis and hypertension prevalence decreases with weight loss [94-96]. In addition, several researchers have found positive associations between weight gain and obesity with atherosclerosis and hypertension [94,97-100].

Epidemiologic evidence for links between obesity and inflammation have existed for decades,

although it has not been detailed in terms of its importance to the pathophysiologic conditions associated with obesity [101,102]. Epidemiologists have found elevations in markers and potential mediators of inflammation, suggesting that low-grade inflammation precedes and predicts the development of atherosclerosis. Proinflammatory cytokines may cause insulin resistance, and anti-inflammatory medications may reverse it, suggesting that inflammation may be directly involved in the pathogenesis of cytokines. Evidence suggests that both macronutrient intake and obesity may activate inflammatory signaling pathways in cells [103]. Glucose and fat intake have both been shown to induce inflammation, potentially through increases in oxidative stress and the activities of transcription factors such as nuclear factor NF- $\kappa$ B, activating protein-1, and early growth response-1 [104,105]. Intravenous lipid infusion (triglyceride plus heparin) in normal subjects can be used to raise levels of free fatty acids (FFA) to those

found in obese subjects, which leads to an inflammatory response [106].



**Figure 3.** Laparoscopic Roux-en-Y gastric bypass is depicted. Roux-en-Y gastric bypass is the most widely used bariatric surgery in the clinic. The cardium is separated from the major part of the stomach and anastomized with the jejunum. The total volume of the small pouch is about 50ml. The total stomach and duodenum and about 100-150 cm of the jejunum is bypassed. Food passes through the small pouch and goes to the jejunum directly. In this way, the gastric fundus and the duodenum are bypassed. The small intestine is also partly bypassed. As a result, the fasting glucose and insulin resistance decrease to normal right after surgery. Of the 180,000–200,000 bariatric surgeries performed in 2006, about 80% were Roux-en-Y gastric bypass.

NF- $\kappa$ B pathway and c-Jun NH<sub>2</sub>-terminal kinase (JNK) pathway are activated by many of the same proinflammatory stimuli including cytokines such as TNF- $\alpha$ , which in addition to being activators of NF- $\kappa$ B are also NF- $\kappa$ B-regulated products. This suggests a potential link between elevated circulating or tissue lipid concentrations and the immune system. Reactive oxygen species, endoplasmic reticulum stress, and ceramides are increased by adiposity, and all have been shown to activate both JNK and NF- $\kappa$ B. As previously mentioned, circulating ghrelin participates in long-term regulation of body weight, its plasma level increases with weight loss as part of the compensatory response to an energy deficit [20,107,108]. Recently, ghrelin and its receptors were detected in cardiovascular tissues, indicating that the peptide may play a role in

cardiovascular regulation [109]. Stimulation of growth hormone secretagogue receptor (GHSR) has been shown to prevent cardiac damage after ischemia/reperfusion in hypophysectomized rats [110]. Moreover, administration of ghrelin improved left ventricular function and attenuated the development of cardiac cachexia in a heart failure model [111]. Furthermore, ghrelin improved mortality and corrected the hemodynamic and metabolic abnormalities associated with endotoxic shock in rats [112]. The endocrine activity of ghrelin is dependent on its acylation and subsequent interaction with GHSR-1a [20]. However, both ghrelin and des-acyl ghrelin inhibit apoptosis in cardiomyocytes and endothelial cells, suggesting that ghrelin may also act through a novel, yet to be identified receptor, which is distinct from GHSR-1a [113]. Some

reports show that ghrelin inhibits basal and TNF- $\alpha$  induced chemotactic cytokine production and mononuclear cell adhesion in human vascular endothelial cells [109]. In contrast, gastric bypass may disrupt ghrelin secretion by isolating ghrelin-producing cells from direct contact with ingested nutrients, which normally regulate ghrelin levels, and this effect may contribute to the efficacy of the procedure in reducing weight [18,107,114-116].

## 6. Concluding Remarks

Morbid obesity and T2D mellitus are major contributors to the morbidity and mortality in our society. The percentage of patients with these diseases is rising rapidly and now is even affecting the very young. Cardiovascular comorbidities, such as myocardial infarction, hypertension, heart failure and so on, are the major reasons for mortality. Cancer is another major contributor, along with other complications, such as hyperlipidemia, steatohepatitis and renal dysfunction. Bariatric surgery controls comorbidities and decreases the mortality rate for the morbidly obese better than other methods, Bariatric surgeries, especially gastric bypass, are

proven to decrease fasting glucose and insulin resistance right after surgery. More and more surgeons are using this kind of technique in treating obese patients. Some others even use this technique in treating diabetes patients with or without obesity. While the modes of action are not completely understood at present, especially regarding effects in treating cardiovascular comorbidities, cancer and so on, current results are promising and further research is warranted. Gastric bypass surgery appears to have significant increased therapeutic potential for treating morbid obesity and T2D.

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