Bariatric Surgery - Effects on Obesity and Related co-Morbidities

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**Abstract:** Laparoscopic adjustable gastric banding (LAGB), laparoscopic Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (SG) are the three most commonly performed bariatric procedures. Obesity responds well to bariatric surgery, with major long-lasting weight loss that is most pronounced after RYGB and SG, where the mean weight loss is about 40 kg or 15 body mass index (BMI) units. Some of the benefits after RYGB and SG are independent of weight loss, and the remission of type 2 diabetes is observed a few days after the operation; this depends on changes in insulin sensitivity and gut hormone responses, especially a 10-fold increase in glucagon-like peptide-1 (GLP-1), which improves insulin secretion. After gastric banding, the remission of diabetes depends more on weight loss. Bariatric surgery reduces cardiovascular risk factors including hypertension, lipid disturbances, non-alcoholic fatty liver, musculoskeletal pain and reduces mortality of diabetes, cardiovascular diseases and cancers. Bariatric surgery also improves quality of life. The acute complications of surgery are infection, bleeding and anastomotic leak. Long-term complications are nutritional deficiencies, including vitamins and minerals, and anemia. Some patients have dumping after meals, and a few patients will develop postprandial hypoglycemia after RYGB. About 25% of patients require plastic surgery to provide relief from excessive skin tissue.

**Keywords:** Bariatric surgery, comorbidities, type 2 diabetes, metabolic syndrome, cancer, mortality.

**INTRODUCTION**

Obesity is a growing worldwide epidemic, which has generated a secondary epidemic of metabolic syndrome, characterized by abdominal obesity, dyslipidemia, hypertension and glucose intolerance associated with increased risk of type 2 diabetes and cardiovascular disease [1,2]. Additional metabolic comorbidities include polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA) and several forms of cancers.

Lifestyle changes can lead to a weight reduction of 5-10%, but most individuals start to regain weight after three to six months, and about 90% return to or even exceed their initial weight, indicating that obesity in most cases is refractory to lifestyle therapy [3]. The recent LOOK-ahead trial [4], which randomized 5,145 overweight or obese patients with type 2 diabetes to either intensive lifestyle intervention or standard care, reported a 6% weight loss after 10 years in the intervention group vs. 3.5% in the control group. However, the study failed to demonstrate an effect on cardiovascular morbidity or mortality [4]. The use of anti-obesity agents may result in a further weight loss of 2-8 kg; thus, with the agents on the market or in development at present, the mean weight loss does not exceed 10 kg in clinical trials [5].

In contrast, in severely obese individuals, bariatric surgery results in major weight loss of 20-30% that is sustained for at least 15-20 years [6]. Some bariatric surgery procedures are furthermore regarded as “metabolic” surgery, due to their beneficial effects beyond weight loss on metabolic syndrome and type 2 diabetes [7,8]. The most commonly used bariatric operation is laparoscopic Roux-en-Y gastric bypass (RYGB), followed by laparoscopic sleeve gastrectomy (SG), and laparoscopic adjustable gastric banding (LABG) [9].

The aim of this review is to provide an update on the effects of RYGB, SG and LAGB on obesity and related comorbidities.

**EFFECT OF BARIATRIC SURGERY ON WEIGHT**

The Swedish Obese Subjects study (SOS) [6] consisted of a surgical group (n=2,010) and an obese control group (n=2,037). The groups were matched at 18 clinical variables. Patients in the surgical group underwent adjustable or non-adjustable gastric banding (n=376), vertical-banded gastroplasty (n=1,369) or RYGB (n=265), while those in the control group received customary non-surgical obesity treatment at their local health centers. In the control group, a maximal weight loss of 1-2% of basal weight was seen, compared to 20%, 25% and 32% for adjustable gastric banding, vertical-banded gastroplasty and RYGB, respectively. The maximal weight loss was achieved 1-2 years after surgery. Hereafter, some patients in all surgical subgroups showed a slight weight gain, which leveled off after 8-10 years. At the 15 year follow-up, the weight loss was 13%, 18% and 27% in the three surgical groups, respectively [10-12]. Another prospective cohort study, LABS-2, reported a mean weight-loss of 41 kg after 3 years in 1738 RYGB operated patients [13], and several studies have shown that weight loss usually peaks 1.5 to 2.0 years after surgery [6,14,15].

In a large meta-analysis by Buchwald et al. [8], weight loss, expressed as per cent of excess weight (EBWL), in a population of 34,000 patients, was 46% after gastric banding
and 60% after RYGB; a subgroup analysis (n= 14,000) showed a slightly higher weight loss at 2 years postoperatively with EBWL of 49% after gastric banding and 63% after RYGB.

In a recent small meta-analysis of randomized controlled studies, the total weight loss was 26 kg after bariatric surgery, but only 381 patients were included; the duration of the follow-up period varied and the heterogeneity between studies was very high [16].

SG has been reported to result in similar [17] or slightly lower weight loss than RYGB [18]. In a recent epidemiological study of 2,949 patients, weight loss (EBWL) after RYGB, SG and LAGB was 67%, 56% and 44%, respectively, 3 years after surgery [18]. Lastly, in a randomized controlled study (RCT) of SG (n=107) vs. RYGB (n=110), an excessive BMI loss (EBMIL) of 72% vs. 77% was reported at the 1 year follow-up [17].

The SOS-study, primarily using banding gastroplasty, reported that 20-25% of the weight lost after surgery was regained by the 10 year follow-up [10-12]. In the Utah-Obesity study following 418 patients for 6 years after RYGB, the weight loss at 2 years was higher than after 6 years, where a regain of 7% of the initial 35% weight-loss was reported [15].

### EFFECTS OF BARIATRIC SURGERY ON CO-MORBIDITIES

#### Effect on Blood Pressure

Bariatric surgery has been reported to ameliorate hypertension, with normalization of blood pressure in 30-50% of patients 1-2 years after RYGB [13,15,19] and a reduced need antihypertensive treatment in a further 20-30% of patients [19]. The remission of hypertension seems to be associated with the degree of weight reduction [19], and patients seem to have a higher remission rate after RYGB than after LAGB [13]. Remission of hypertension did not differ between RYGB and SG in a randomized study [17], but only a limited numbers of reports have included SG.

Interestingly, in the Utah- and SOS-studies, relapse of hypertension was seen at the 6 to 10 year follow-up [6,10,15].

The results from the epidemiological retrospective studies discussed here have not been confirmed in randomized clinical trials including type 2 diabetic patients: Mingrone et al. found no difference in systolic blood pressure between patients undergoing intensive medical treatment and RYGB-operated patients after 2 years [20], despite the antihypertensive treatment being reduced or discontinued in 70% of the medically treated group vs. 80% in the surgery group [20]. Ikramuddin et al. only found a modest effect on systolic blood pressure of RYGB after 1 year, but with less medications for comorbidities; however, these were not completely specified for hypertension [21].

#### Effect on Plasma Lipids

Weight loss is associated with an improved lipid profile [22]. In the Utah-Obesity study, dyslipidemia, characterized by high levels of low-density lipoprotein (LDL) and triglycerides and low levels of high-density lipoprotein (HDL), was resolved 6 years after RYGB in 57-69% of the patients [15], and the remission-rate of dyslipidemia 3 years after RYGB was 62% in the LABS-2 study [13]. The LABS-2 study also reported a remission-rate of 17% after LAGB. Similar results after LAGB have been described by Dixon et al., with favorable changes for fasting triglycerides and HDL-cholesterol [22].

In a 24-month follow-up of diabetic patients randomized to either intensive medical treatment, RYGB or SG, an increase in HDL and decrease in triglyceride were seen [23], and these results were sustained at 3 years [24]. The changes were equal for SG compared to RYGB, while no decrease was seen for LDL- or total cholesterol [23].

In the SOS-study, the triglycerides did not differ between the surgical and control group at the two and ten year follow-ups, but the reduction in triglycerides was greater in the subgroup treated with RYGB [10]. Buchwald et al. also described an overall improvement in dyslipidemia for all types of bariatric surgery in approximately 70% of the patients, but this improvement was not clearly defined [14]. In another meta-analysis of randomized controlled trials (RCT) [16], only triglyceride- and HDL-concentration changed beneficially after surgery in comparison to controls.

#### Effect on Type 2 Diabetes

Bariatric surgery has a marked effect on type 2 diabetes with rapidly normalized blood glucose concentrations in the majority of patients. In the meta-analysis by Buchwald et al. [8], including 4,973 patients with type 2 diabetes, remission of diabetes was found to occur in 80% after RYGB and in 57% after LAGB. However, subsequent studies have demonstrated that the remission rate of type 2 diabetes depends on the definition of remission applied. This was exemplified by Pournaras et al. in a recent study of 160 patients with type 2 diabetes, where diabetes remission was found to occur in 41% after RYGB [25] when applying the more strict criteria for remission from a recent consensus [26]. Preoperative treatment with insulin was associated with an even lower remission rate [25]. Nevertheless, overall glycemic control improved after RYGB, and glycosylated hemoglobin (HbA1c) decreased from 8.0% to 6.2% [25].

Recently, three randomized controlled trials proved RYGB superior to conventional pharmacological treatment in achieving glycemic control within 1-2 years after surgery, and demonstrated that lower HbA1c levels can be achieved without or with less medication after RYGB [20,21,27]. In one of the studies, a group of SG patients was included, and the results were comparable to the RYGB operated patients with respect to improvement in HbA1c and in percentage of patients achieving the primary end-point of HBa1c ≤ 6.0%: 42% for RYGB and 37% for SG [24,27]. The same researchers report a slightly smaller remission rate at the 3 year follow-up; 38% of patients after RYGB and 24% after SG, but the glycemic control was still superior to intensive medical therapy with only 5% of the patients achieving the HbA1c target [24]. After 3 years HbA1c declined from 9.3%, 9.5% and 9.0% at baseline to 6.7%, 7.0% and 8.4%; and the body weight change from baseline was 26.2 kg, -21.3 kg and -4.3 kg for RYGB, SG and the medically treated group, respec-
tively. Furthermore the use of glucose-lowering medications was lower in both surgical groups [24].

Also, LAGB has shown superiority in the treatment of type 2 diabetes when compared to intensive pharmacological and lifestyle intervention. In a randomized controlled study with a 2 year follow-up period, the remission rates were 73% for LAGB and 13% for the control group [28]. Diabetes remission was related to weight loss and lower baseline HbA1c levels [28]. Compared to RYGB, patients treated with LAGB appeared to experience a lower rate of diabetes remission.

The SOS-trial reported a higher remission rate of diabetes after 2 (OR 8.4, CI 5.7-12.5) and 10 years (OR 3.5, CI 1.6-7.3) compared with the control group, but a 50% relapse was observed at 10 years (remission rate 72% at 2 years and 36% at 10 years) [6]. In addition, bariatric surgery reduced the incidence of type 2 diabetes (hazard ratio (HR) 0.22, CI 0.18-0.27) in the follow-up period of up to 15 years (mean 10 years) compared with the control group; this was most efficient in patients at high risk due to impaired fasting glucose (IFG) at baseline (number needed to treat (NNT) in order to prevent one case of type 2 diabetes was 1.3 in patients with IFG and 7.0 in patients with normal fasting glucose) [6,29].

The remission rates seem to be associated with the duration [24] and degree of glycemic control before the operation [30]. Other predictors are C-peptide (beta-cell function), preoperative glucose-lowering treatment (insulin vs. oral), preoperative body mass index (BMI) and weight loss [31]. Relapse of diabetes is associated with failing beta-cell function. Recurrence rates of diabetes in recent epidemiological studies with long-term follow-up (> 5 years) were 13-35% after RYGB [15,30,32], and were associated with weight regain, longer duration of diabetes, poor preoperative glycemic control and insulin treatment before surgery [30].

The effect on diabetes seems to include the improvement or delayed progress of end-organ complications such as retinopathy and nephropathy in addition to improved glycemic control [33].

Effects on Metabolic Syndrome

Before surgery, most obese patients will display symptoms of metabolic syndrome, with components of high triglycerides, low HDL, hypertension, high plasma glucose and waist circumference. Batsis et al. found the prevalence of metabolic syndrome to be decreased after 3.4 years of follow-up from 87% to 29% in response to RYGB compared to a decrease from 85% to 75% in the conventional lifestyle-intervention control group [7]. The strongest predictor for resolution was loss of body weight [7]. Furthermore, the authors estimated that four deaths and 16 cardiovascular events per 100 patients would be prevented by bariatric surgery during a 10-year period.

Vidal et al. retrospectively compared diabetic patients after RYGB and SG and found comparable resolution rates of both diabetes (85% in each group) and metabolic syndrome (67% vs. 62%) [34].

In a recent study using the Bariatric Outcome Longitudinal Database, 23,106 patients were identified to have metabolic syndrome before surgery [35]. The 1 year resolution of hypertension, diabetes and dyslipidemia after LAGB was 19%, 28% and 17%, respectively, compared to 45%, 62% and 45%, respectively, after RYGB, and 35%, 52% and 34%, respectively, after SG [35].

Effect on Non-alcoholic Fatty Liver Disease

After bariatric surgery, a reduction in liver steatosis, inflammation and fibrosis was observed 15 months after RYGB, SG or LAGB [36]. Thus, inflammation and fibrosis were completely resolved in 37% and 20% of the patients, respectively. In another study, NAFLD resolved in 89% of RYGB-operated patients [37].

Effects on Cardiovascular Disease and Cardiovascular Mortality

Bariatric surgery has beneficial effects on cardiovascular risk factors such as left ventricular hypertrophy [38], carotis intima thickness, and flow-mediated vessel dilatation [39].

Moreover, the resolution of diabetes, hypertension and hyperlipidemia postoperatively results in an overall 10 year reduction in the coronary heart disease Framingham risk score from 6% to 3% [38], and other researchers have found an even better improvement in the risk score [40], which was most pronounced in men.

In the SOS-study, the number of cardiovascular events was 234 in the control group vs. 199 in the surgery group (HR 0.83, CI 0.69-1.00), and the number of cardiovascular deaths was 49 vs. 28 (HR 0.56, CI 0.35-0.88), respectively [12]. Surgery was also associated with a reduced number of fatal myocardial infarctions [12]. Insulin resistance at baseline rather than BMI predicted the beneficial effects of surgery [12]. In type 2 diabetes patients, bariatric surgery also reduced the incidence of cardiovascular events after a follow-up period of 13 years (adjusted HR 0.56, CI 0.34-0.93) [41] compared with the control group. NNT to prevent one myocardial infarction in a 15 year period among the obese diabetic population was 16 [41].

In the retrospective study by Christou and co-workers, which compared 1035 patients after bariatric surgery (81% RYGB, 19% vertical banded gastroplasty) with 5,746 matched control subjects during a five year follow-up, the risk reduction in cardiovascular disorders was 82% in favor of surgery [42]. Likewise, in the study by Adams et al., which compared 7,925 patients after RYGB with the same number of matched controls, the reduction in mortality of coronary artery disease was 56% [43].

Effect on Obstructive Sleep Apnea

A meta-analysis of 69 studies including 13,900 patients indicated that bariatric surgery resolves or improves OSA in more than 75% of patients with this condition, with the most pronounced effect being reported after RYGB, followed by SG and LAGB, probably reflecting the degree of weight loss achieved by patients following these procedures [44]. Other investigators have presented similar results [14,45,46]. Interestingly, a randomized study of conventional weight loss
therapy vs. LAGB found no difference in OSA resolution despite major differences in weight loss [47].

**Effect on Musculoskeletal Pain**

Obesity is associated with musculoskeletal pain [48]. Results from the SOS-study report an increased recovery as well as a reduced incidence of work-restricting musculoskeletal pain after bariatric surgery; furthermore, the recovery-rate was related to the degree of weight loss following surgery [48].

**Effects on Cancers**

After a 10.9 year follow-up period in the SOS-study, the number of first time cancers in the surgery group was reduced compared with the control group (HR 0.67, CI 0.53-0.85; p=0.0009) [6]. In women, the number was 79 vs. 130 patients, respectively (HR 0.58, CI 0.44-0.77; p=0.0001), whereas there was no effect of surgery reported in men.

Christou et al. reported 21 cancers in the surgery group (n=1,035, 82% RYGB) compared with 487 cancers in the control group (n= 5,746), with a Relative Risk (RR) of 0.22 (CI 0.14-0.35 p=0.001) after a maximum follow-up of five years [49]. Adams et al. found that the reduction in cancer-caused mortality was 61% after a mean follow-up of 7.1 years [43]. In a later follow-up, after a mean of 12.5 years, a 24% reduction in cancers was found in the surgical group compared with the control group, whereas the overall cancer mortality was reduced by 46% [50]. In particular, the incidence of uterine cancer was significantly lower among surgical patients.

The quality of the studies, except for the SOS-studies, is poor and randomized controlled studies with long-term follow-up are needed to obtain robust data on the effects of bariatric surgery on the risk of developing cancer.

**Effects on Mortality**

In the SOS-study, after an average of 11 years follow-up, the cumulative overall mortality was 129 subjects (6.3%) in the control group compared with 101 (5.0%) in the surgery group, indicating a relative risk reduction of 24% (HR 0.76, p= 0.04) [11]. The reduction in mortality was more pronounced in subjects with a higher BMI, with a reduction in the risk of death of about 30% in subjects with a BMI above the median of 40.8 kg/m² and 20% in subjects below the median [11].

Adams et al. retrospectively followed 7,925 people for seven years and found a 40% reduction of total mortality in the surgical group compared with a control group of subjects matched for age, sex and BMI [43]. In a third study, the reduction in all-cause mortality was 89% in the surgical group compared with a control group after at least five years of follow-up [42]. A limitation of all three studies is that the designs were not randomized and controlled and no information on baseline morbidity was presented.

A meta-analysis from 2011 reported an overall reduction in all-cause mortality of 45% (OR 0.55, CI 0.49-0.63), but the included studies were not randomized and the heterogeneity of the studies was very high [51].

**Effects on Quality-of-Life**

The substantial and long-term weight loss following bariatric surgery has a beneficial effect on the quality-of-life in most patients [52-54]. Furthermore, the degree of weight-loss appears to affect the quality-of-life improvements [52-54], and health-related quality-of-life over a 10 year period followed phases of weight loss, weight gain and weight stability, and was related to the magnitude of weight loss and weight regain in the SOS-study [53]. In contrast, Adams et al. found no improvement in a mental component score after bariatric surgery compared with two obese control groups [15], and other authors have suggested an increased risk of suicide after RYGB [43].

**RISKS OF BARIATRIC SURGERY**

In the best centers, the 30 day mortality is about 0.2-0.4% after laparoscopic RYGB [55,56] and below 0.1% after gastric banding [14,56]. The acute complications are bleeding, infections, anastomotic leak, arrhythmias and venous embolism. The risk of serious complications is reported to be 4.8% for laparoscopic RYGB and 1.0% for LAGB [55], and the total complication rate is about 17% [56]. Long-term complications after RYGB include internal hernias and anastomotic stenosis with vomiting, stoma ulceration erosions and nutritional deficiencies [57] and the patients need to be supplemented with vitamins and minerals. Some of the long-term risks are not seen after SG; instead, there is a longer stable-line of the stomach with associated risk of leakage. SG in general seems to cause fewer minor complications than RYGB [58] but the published data include only a small number of patients and further studies are needed.

Some patients will develop dumping, with symptoms such as abdominal pain and cramping, sweating, dizziness, nausea, tachycardia and diarrhea. Dumping symptoms become less prominent over time [57]. Few patients will develop postprandial symptomatic hypoglycemia, presumably because of an imbalance of excessive insulin secretion due to an exaggerated GLP-1 response and improved insulin sensitivity [59].

In summary, RYGB seem to have the highest rates of complication, followed by SG and LAGB, but the overall mortality is low.

**DISCUSSION**

Obesity is accompanied by comorbidities, making obesity a major threat to health. Treating obesity has been proven to be difficult and ineffective, and it is often considered to be a self-induced behavioral problem of the patients themselves instead of a physiological dysregulation. Many people often overestimate the benefits of lifestyle and pharmacological interventions, but unfortunately, lifestyle and pharmacological treatments rarely result in sustained weight loss, and many physicians consider obesity an intractable disease.

The only effective treatment for obesity is bariatric surgery, providing substantial long-term weight loss, which is most pronounced following RYGB and SG. The weight loss after LAGB is slower and less pronounced.
Obesity is associated with accelerated atherosclerosis and improvements in the CVD risk factor profile, including metabolic syndrome; a lower risk of ischemic heart disease and mortality has been demonstrated after bariatric surgery. Thus, improvements in hypertension and especially the lipid profile associated with metabolic syndrome, which is characterized by high triglycerides and low HDL cholesterol, have been reported. The effect on LDL cholesterol seems to be minimal. The weight loss after bariatric surgery also improves NAFLD, OSA, musculoskeletal pains and quality-of-life.

Increased body adiposity is an established risk factor for the development of cancer. Although the studies may be criticized, several have provided evidence that weight reduction in obese individuals is associated with a subsequent reduction in cancer incidence. The effect seems limited to women, and the reductions are most robust for breast cancer and endometrial cancers, which are both hormone-sensitive. It is unknown whether different bariatric procedures may have different effects on the incidence of cancer.

Bariatric surgery also prevents new cases of diabetes compared with lifestyle treatment. A robust finding in many studies, independent of bariatric procedure, has been improvements or remission of type 2 diabetes already a few days after surgery, before any significant weight loss. This observation has introduced the term “metabolic surgery”, because of the marked modification of type 2 diabetes pathophysiology for the better without any weight loss. Randomized studies have shown the superiority of bariatric surgery compared to an intensive lifestyle and medical management in relation to both weight loss and remission of diabetes, but all of the studies have been of short duration and have included only few patients. Larger and longer trials are needed to estimate the benefit of bariatric surgery compared with the conventional treatment of type 2 diabetes. The remission rate of diabetes is higher and faster after RYGB and SG than after LAGB, but for all procedures, diabetes remission trended downwards over time.

The effects of all three procedures on glucose metabolism are explained by an increase in hepatic insulin sensitivity, which is induced at least in part by calorie restriction, and can be observed only a few days after surgery [60,61]. No hormonal changes explain the weight loss and remission of type 2 diabetes after LAGB. After RYGB and SG, an improved postprandial insulin secretion, associated with an exaggerated postprandial glucagon-like peptide-1 (GLP-1) secretion due to altered transit time of nutrients to the terminal ilium, is seen [60]. Thus, the physiological explanation of the remission of type 2 diabetes relies on GLP-1 and improved beta-cell function after RYGB and SG, which can also explain the lower diabetes remission rate in patients with advanced disease and longer duration and thus failing beta-cell function. Later, a weight loss-induced improvement in peripheral skeletal muscle insulin sensitivity is the final determinant of glucose tolerance after all three procedures [61].

The explanation of weight loss also differs between the three procedures. After LAGB distension, stimuli from the small pouch above the band may be transmitted via afferent vagal nerves to areas of the central nervous system that are implicated in satiety and reducing food intake [62]. The changes in food texture and eating small volumes to preserve digestive comfort may also explain modified eating behaviors and thereby part of the weight loss. Following RYGB and SG, increased postprandial responses of GLP-1, peptide YY (PYY) and oxyntomodulin seem to stimulate anorectic pathways in the hypothalamus and brain stem, leading to reduced appetite and food intake.

In a position statement from 2011, the International Diabetes Federation (IDF) recognized bariatric surgery as an appropriate treatment for type 2 diabetes if recommended glycemic targets are not reached with the available medical therapies, especially if hypertension and dyslipidemia also exist.

CONCLUSION

Thus, bariatric surgery results in substantial weight loss with excellent beneficial effects on comorbidities to obesity, but with the cost of surgical and medical complications, i.e. from micronutrient deficiencies, which require life-long monitoring. Many patients will also need to undergo plastic surgery to provide relief from excessive skin tissue, and this is expensive and may induce new complications.

This review has also revealed the shortcomings of many studies. Studies with long-term follow-up periods are limited and often report poor retention of participants. Another main limitation in many studies is their lack of randomization; the quality of studies varied from very few randomized studies to retrospective cohort studies without a control group. Standardized definitions for the resolution of co-morbidities are also needed for comparisons of the results of future studies. Longer and larger clinical trials comparing lifestyle and pharmacological treatments with bariatric surgery are an unmet need. Although RYGB and SG are more effective than LAGB for the reversal of obesity and diabetes, they also confer greater surgical risks; therefore, long-term studies comparing the different procedures are warranted.

The effects of bariatric surgery are intriguing and have created a new understanding of the pathogenesis of obesity and type 2 diabetes; however, it is impractical to perform surgery in all obese people. A goal must be to develop less-invasive methods, and ultimately, understand the effects of bariatric surgery on metabolism beyond that expected of weight loss, which may enable the development of new effective therapeutic strategies for weight loss and the treatment of diabetes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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