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Title: Bariatric/Metabolic Surgery in Type 1 and Type 2 Diabetes Mellitus

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ABSTRACT: The prevalence of diabetes mellitus type-2 (T2DM) and obesity shows a gradual increase nowadays. Despite the introduction of multiagent treatment modalities, many patients with T2DM still do not have good results. Bariatric/metabolic surgery performed in the obese patients to attain weight loss have been shown to improve T2DM. Diabetes mellitus-type 1 (T1DM) is another type of diabetes which also shows an increase in prevalence. In this paper we aimed to evaluate the literature about the bariatric/metabolic surgical procedures performed in type 1 and type 2 diabetic patients.

Key Words: Bariatric surgery, metabolic surgery, diabetes mellitus type-1, diabetes mellitus type-2

INTRODUCTION:

T2DM is a chronic disease which causes many important medical complications and socioeconomic effects. In this disease, insulin is produced but is not a sufficient amount for body requirements or there is resistance to insulin. Obesity is one of the major causes for development of T2DM. Despite the introduction of multiagent treatment modalities, many patients still do not have good results (1-3).

T1DM is another type of diabetes in which there is absolute insulin deficiency; the body does not produce insulin or there is destruction in the insulin-producing beta cells in pancreas (4, 5).

Recent studies have shown the positive effects of bariatric surgery procedures in the treatment of obese and non-obese T2DM patients. Therefore, bariatric surgery is also referred to as metabolic surgery due to its effects ranging from weight loss to metabolic control, especially in T2DM patients. Currently, T2DM can be considered as a gastrointestinal disease that can be treated surgically (6-8). There is also evidence of such surgery improving the health of T1DM patients (9, 10).

In this paper we aimed to evaluate the literature about the bariatric/metabolic surgical procedures performed in type 1 and type 2 diabetic patients.

CLINICAL and RESEARCH CONSEQUENCES:

Diabetes mellitus is a metabolic disease that brings many economical and social problems to the affected patients. The number of people with T1DM and T2DM is expected to increase from 415 million in 2015 to 642 million in 2040 according to the International Diabetes Federation (11).

The incidence of obesity has showed an increase in the last years both in children and adults. It is associated with many comorbidities such as hypertension, dyslipidemia, cardiovascular disease,

diabetes, etc (12). So, we can say that obesity and diabetes are the twin epidemics of the twenty first century (6).

In the obese patients, the beta cells of the pancreas show a stress failure and it results to insulin resistance and T2DM. In addition, the adipose tissue which secretes different hormones such as leptin, estrogen, resistin, and adipocytokines is regarded as an immune tissue and plays important roles in the pathogenesis of obesity and diabetes mellitus (8).

In addition gastrointestinal tract has many important roles in diabesity and obesity via hormonal and neural pathways.

The feeding regulation system is located in the hypothalamus, and Neuropeptide Y (NPY) is a peptide found there. Disturbance of NPY system due to the changes of the levels of insulin, leptin, and ghrelin may cause to increased food intake and eventually obesity.

Incretins, gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1), are intestinal hormones that stimulate postprandial insulin secretion and have played important roles in the development of diabetes mellitus.

The gastric fundus secretes ghrelin and it stimulates satiety (2, 3, 8).

Current researchs have focused on host and environmental factors that may have a role in energy gain and loss. One of these factors is the gut microbiata. The gut microbiata composition is changed due to many factors, and it may cause to the development of obesity, T2DM and T1DM. These factors may increase gut permeability and cause metabolic inflammation, increase energy gain from the diet, impaire short-chain fatty acids synthesis, alter bile acids metabolism and FXR/TGR% signaling, and impaire glucose metabolism, resulting insulin resistance (13, 14).

Recent studies have revealed that bile acids not only facilitate lipid absorption but also affect diverse methabolic pathways including glucose methabolism, lipid metabolism and energy expenditure resulting to insulin resistance, diabetes, and metabolic syndrome (8, 15).

Gastrointestinal surgery performed for morbidly obese people are called as ‘’bariatric surgery’’ (baros=weight). It is accepted as the most effective treatment for morbid obesity and has been shown successful in treating T2DM in morbidly obese people. Bariatric surgical procedures are

classified as restrictive [laparoscopic sleeve gastrectomy (LSG) (Figure 1a), laparoscopic adjustable gastric banding(LAGB)] (Figure 1b), malabsorptive (intestinal bypass) and both restrictive and malabsorptive [Roux-en-Y gastric bypass (RYGB) (Figure 1c), biliopancreatic diversion with or without duodenal switch(BPD or BPD-DS)] (Figure 1d). Remission of T2DM has been reported as 66%, 45%, 80-85%, and 95% after LSG, LAGB, RYGB, and BPD-DS, respectively (2, 3).

The mechanism of the remission of T2DM after bariatric surgery is still controversial. Weight loss due to calorie restriction after restrictive procedures achieve glycemic control. Weight loss reduces metabolically active sick fat. An increase in GLP-1 and PYY due to rapid gastric emptying and an decrease in ghrelin after sleeve gastrectomy have a role in the resolution of diabetes. The nutrients are delivered rapidly to the distal ileum stimulating GLP-1 and leading to increased insulin release. Malabsorptive procedures excludes the duodenum and upper part of the jejunum, and it results in the inhibition of anti-incretins (2, 3, 8) . It is known that the gut microbiome and bile acid levels are changed after metabolic surgery. Serum bile acid levels increase after bariatric surgery, and this fact results to decreased postprandial blood glucose levels but results to the maximal secretion of GLP-1. The intestinal micro-organism pattern changes after gastric and intestinal tract procedures (16, 17).

Bariatric surgery that aims to treat the comorbid conditions such as diabetes mellitus associated with obesity is generally called as metabolic surgery. In addition to the above mentioned most widely used bariatric procedures, various metabolic surgical procedures have been developed to treat T2DM. One of them is sleeve gastrectomy with duodenojejunal bypass (LSG-DJB) (Figure 2a). It has several advantages over the duodenal switch operation. In this operation the pylorus is preserved and the dumping syndrome and reactice hypoglycemia are seen less. The duodenojejunostomy is performed at 1-2 cm distal to the pylorus, so the anastomosis is wider. The complications of nutritional deficiencies are lower (18, 19). Seki Y et al (18) investigated the effects of LSG-DJB on weight loss and T2DM in 120 patients. The mean per cent of total body weight loss was 28.9, 28.6 and 63.6 at 1, 3 and 5 years, respectively. Remission of T2DM was in 63.6% at 1 year, 55.3% at 3 years, and 63.6% at 5 years.

In ileal transposition (IT) (Figure 2b), a segment of the ileum is translocated into the upper jejunum. It has been combined with sleeve gastrectomy or RYGB in several studies, and it has been

reported to change gut hormone secretion and host-microbial relations, have many positive effects in the bile acid metabolism, and decrease metabolic endotoxemia(20-25).

Çelik et al (26) investigated the metabolic results of laparoscopic diverted sleeve gastrectomy with ileal transposition in 159 obese patients with T2DM. In their study, mean BMI decreased from 39.33 to 25.51, mean fasting glucose level decreased from 189.9 to 123.5 mg/dl and mean HbA1c decresed from 9.24 to 6.14 % 1 year after surgery. Hypertension resolved in 94.2% of patients, and blood glucose levels decreased in most of the patients.

Sleeve gastrectomy with transit bipartition (Figure 2c) is another operation for diabetes and obesity. First a sleeve gastrectomy is performed, then transit bipartition is performed via a gastrointestinal anastomosis in the antrum. The stomach has 2 outflow pathways (27, 28).

Single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) (Figure 2d) is an operation in which a sleeve gastrectomy is followed by an end-to-side duodeno-ileal diversion at 250 cm proximal to the cecum. It is a modification of DS procedure. However, SADI-S procedure has many advantages. In DS, while approximately 80% of intestine is being bypassed, ,in SADI-S 50% of intestine is bypassed. So, protein, vitamin and mineral deficiencies are lower in SADI-S procedure (29, 30).

Another procedure similar to SADI-S procedure is stomach intestinal pylorus sparing surgery (SIPS) (Figure 2e), which is a modification of duodenal switch procedure. This procedure has 3 steps: creating a sleeve gastrectomy, transecting the duodenum just beyond the outlet valve of stomach (pylorus), and performing an end to side anastomosis between ileum 300 cm proximally to the ileocecal valve and duodenum. These modifications are expected to reduce the operative complications, diarrhea, and nutritional deficiences seen with the DS. In addition, this procedure provides a more effective metabolic effect and greater weight loss than LSG and RYGB (31, 32).

We tried to outline the most common surgical procedures that have been performed to improve T2DM beginning from the first report published in 1955 by Friedman (33). This paper reported that T2DM was improved after subtotal gastrectomy which was performed for peptic ulcer disease. In 1984, bariatric surgery was reported to have positive effects in diabetic patients (34), and in 1995, Porris et al (35) reported that it improved glucose abnormalities and resulted to T2DM

remission. A newer surgical technique is evolving every day , and a technique which is popular today might be accepted as ineffective in the future.

Now we want to define the comparisons of those techniques. Koliaki et al (36) investigated the effect of bariatric surgery to treat diabetes and showed that the value of those techniques for weight loss and T2DM remission was BPD>RFGB>SG>LAGB.

Colquitt et al (37) investigated 22 trials with 1798 participants. Weight loss and rates of remission of T2DM and hypertension did not show a difference between RYGB and SG, and both of these procedures had better results than LAGB. For people with very high body mass index (BMI), BPD-DS resulted in greater weight loss than RYGB.

Yormaz et al (38) compared the glycemic regulation in patients that have undergone the laparoscopic ileal interposition with diverted sleeve gastrectomy (II-DSG), laparoscopic transit bipartition with sleeve gastrectomy (TB-SG), and LSG. The purpose was to reach a long lasting fasting blood glucose <126 mg/dl. Their results showed that II-DSG and TB-SG had important regression rates during the follow up period. Since the TB-SG had finite anastomoses and intervening segments, it was considered to be a superior procedure over II-DSG and LSG procedures.

Torres et al (30) investigated the results of weight loss and improvement of blood pressure, lipid profile, and insulin resistance in the obese diabetic patients, and after a follow-up of 3 years, the outcomes were better in the SADI-S procedure than RYGB.

Lee et al (39) investigated T2DM remission, triglyceride improvement, and weight loss between 89 patients who received a DJB-SG surgery and the patiends who received SG. They reported better results in the patients with DJB-SG.

Metabolic surgery have been found to be effective in the non-obese diabetic patients as well as it is in the obese diabetics in several studies. Seki et al (40) investigated 72 patients with T2DM with a BMI of <35 kg/m² who underwent DJB-SG and had moderate weight loss and a superior improvement of glycemic control and cardiovascular risk.

Ramirez et al (41) investigated the effect of preoperative BMI (obesity class I, II, and III) on the patients undergoing laparoscopic gastric bypass, and reported that diabetes remission was 57.9%

in class I, 61.1% in Class II, and 60% in Class III, and the other metabolic and clinical profiles presented similar improvement.

Huang et al (42) aimed to investigate the effect of metabolic surgery on nonobese patients (BMI<30 kg/m²) with type 2 diabetes. After investigating 21 studies including 921 patients, they concluded that nonobese patients can attain normalisation in glucose and lipid levels after metabolic surgery.

Age, body mass index, duration and severity of diabetes, C-peptide levels and drug usage have been examined to calculate the improvement of glycemic control following bariatric procedures (1). Up to date, various scoring systems have been developed. These are DiaRem score, DSS score, and the ABCD score(1, 2, 7). ABCD score is the most widely used score based on age, BMI, C-peptide and duration od T2DM. Scores range from 0 to 10 with higher scores predicting higher remission rates. Remission of T2DM was defined as reaching a HbA1c level <6.5% without use of oral hypoglycemic drugs or insulin (1, 2).

Nowadays, obesity also affects T1DM patients. Thirteen per cent of young T1DM patients have obesity and approximately fifty per cent of the patients are overweight or obese (43, 44). Czupryniak et al reported the first observation of T1DM improvement in a severely obese patient who underwent gastric bypass in 2004 (9, 45).

Moreno-Fernandez and Chico (44) investigated 6 T1DM patients undergone bariatric surgery (3 RYGB, 3 SG). Total follow-up from surgery was 4.5±1.4 years. They could not observe significant HbA1c improvement after surgery, but daily insulin requirement decreased after surgery. They concluded that bariatric surgery induces weight loss but does not improve glycemic control in T1DM patients.

Hussain A (9) reviewed 9 studies involving 75 patients with T1DM undergone metabolic surgery (LAGB 2, vertical sleeve gastrectomy 11, LRYGB 52, BPD 7 and BPD-DS 3 patients). They reported that there was improvement in HbA1c, insulin dose and BMI after surgery. However, there was not any statistical significance in the improvement of HbA1c levels. The relation between postoperative insulin dose and BMI change was weak, and the relation between HbA1c and BMI change was negligible after surgery. So, they concluded that improvement of T1DM in obese patients

is not related to loss of excess weight. There may be a role for other factors such as reduction of insulin resistance, satiety/dietary change and possible neuroendocrine/hormonal or incretins influence.

In Conclusion; bariatric/metabolic surgery in obese and non-obese T2DM patients have been found to be effective in the improvement of glycemic control. However, the role of bariatric/metabolic surgery in T1DM patients will require larger and longer studies.

FIGURE LEGENDS

Figure 1 a)- Laparascopic Sleeve Gastrectomy

Figure 1 b)- Adjustable Gastric Banding

Figure 1 c)- Laparascopic Ruox-en-Y Gastric Bypass

Figure 1 d)- Laparascopic Biliopancreatic Diversion with Duodenal Switch

Figure 2 a)- Laparascopic Sleeve Gastrectomy With Duodeno-Jejunal Baypass (LSG-DJB)

Figure 2 b)- Laparascopic İleal İnterposition With Diverted Sleeve Gastrectomy (II-DSG)

Figure 2 c)- Laparascopic Transit Bipartition With Sleeve Gastrectomy (TB-SG)

Figure 2 d)- Laparascopic Single Anastomosis Duodeno- İleal Bypass With Sleeve Gastrectomy (SADI-S)

Figure 2 e)- Laparascopic Stomach İntestinal Pylorus -Sparing Surgery (SIPS)

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