EC ENDOCRINOLOGY AND METABOLIC RESEARCH
Research Article

Metabolic Surgery and Type 2 Diabetes: Theoretical Analysis of the Possibilities and Results

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Abstract

Introduction: The manuscript discusses Metabolic Surgery as a therapeutic procedure for Type 2 Diabetes Mellitus (T2DM), a disease that currently affects around 400 million people worldwide. This theoretical review, carried out in the databases of SciELO and PubMed, discusses the possibility of performing the procedures characterized as Metabolic Surgery for the purpose of reducing glycemia in patients with T2DM and remission of the disease in patients who do not reach the expected goals in the treatment, since it is a chronic disease that arises when the metabolism is not able to meet the demand for insulin or has a resistance to it, causing glycemic levels to increase, which promotes endothelial vascular injury and a series of micro- and macrovascular complications.

Objectives: The purpose of this article is to demonstrate aspects of the use of Metabolic Surgery for the resolution of T2DM in patients who do not reach the expected results with conventional treatment.

Methods: A non-systematic bibliographic review was performed in the SciELO and PubMed databases.

Results: The effects of Metabolic Surgery in poorly controlled non-obese patients, due to the optimization of enteric hormonal functionality, have shown that minimally invasive techniques, especially video laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass can be effective in controlling or reversing T2DM.

Conclusion: Patients submitted to procedures such as the Gastric Sleeve and the Roux-en-Y Gastric Bypass benefit with the remission of T2DM. Patients with lower body mass index present a lower rate of postoperative complications. Further long-term studies in patients with BMI indices lower than 35 kg/m2 are necessary in order to properly establish efficacy.

Keywords: *Metabolic Surgery; Diabetes Mellitus; Clinical Evolution*

Introduction

Type 2 Diabetes Mellitus is a public health problem that has become an imminent pandemic, reaching over 400 million people worldwide. Estimates show that by 2040 there will be more than 600 million cases [1].

It is a chronic disease that develops when serum insulin levels become insufficient to meet the body's demand, initially due to an increased resistance to its action, which subsequently adds an absolute deficit in its synthesis [2]. This leads to a hyperglycemic state of the patient, which promotes vascular endothelial injury and a host of complications such as neuropathy, nephropathy, retinal and cardiovascular injuries [3].

Even with the advances made in recent years in drug and therapeutic interventions, a large number of patients fail to achieve treatment goals, which are HbA1c less than 7%, LDL less than 100 mg/dl, and blood pressure below 130/80 mmHg [1]. This failure is mainly due to the maintenance of an inadequate lifestyle and difficulties in adherence to optimal treatment (quantity of medications and respective administration schemes), consequently leading to the appearance of complications of the disease [3,4].

In the course of studies and several researches, it was observed that patients undergoing bariatric surgery had an improvement in glycemic, lipid and pressure parameters, as well as a reduction in body weight, both in those classified as obese and non-obese [1,3].

Since then, bariatric surgeries, which were initially indicated for weight loss in obese patients, has been regarded as potentially efficient in the treatment of Type 2 Diabetes Mellitus (T2DM). In this context, the benefits achieved seem to be related to adjustments in the neurohormonal mechanisms secondary to weight loss, such as decreased secretion of ghrelin (a hormone responsible for the sensation of hunger) and elevation of GLP-1 secretion (glucagon-like peptide 1) and PYY (peptide YY) - peptides involved in the control of glycemic homeostasis and gastric motility, respectively - changes in bile acid metabolism, detection of nutrients in the gastrointestinal tract, utilization of glucose, insulin resistance and maintenance of intestinal microbiomes. As a consequence of these bariatric surgery effects, the outcome of the intervention was the remission of T2DM in most cases, as well as the improvement of the metabolic control in other treated patients. In line with these results, when applied with the objective of T2DM control - not a simple reduction of body mass - the techniques used in bariatric surgery started to be called Metabolic Surgery [1,3,5].

Long-term studies have shown that Metabolic Surgery is also associated with reduced risk factors for cardiovascular complications. Similarly, recent randomized trials comparing the efficacy of surgical versus non-surgical interventions in patients with T2DM confirmed the improvement from surgery, with similar benefits being observed among type 2 diabetic subjects with preoperative Body Mass Index (BMI) between 30 and 35 kg/m^2 and individuals elected for traditional bariatric surgery (BMI greater than 35 kg/m^2) [1].

Objectives of the Study

The main objective of this article was to study the physiological modifications and results of the Metabolic Surgery in diabetic patients of different categories of BMI, aiming at the remission of the disease.

This article does not aim to exhaust the entire theme.

Methods

A bibliographic review was carried out through the reading of 21 articles and a Guideline, available in two databases - SciELO and PubMed.

The first search was carried out in the PubMed database with the following terms: Metabolic Surgery AND type 2 diabetes, with 5-year limiter, review type articles, free text available and restricted to humans. A total of 110 articles were identified, of which 35 abstracts were selected for reading. Based on the content of the abstracts, 10 articles were selected for the complete reading, since they presented information of relevance to the work, characterizing the types of metabolic surgeries, results, methods and neuroendocrine responses to the surgical procedures.

The second search was complementary to the first one in the database SciELO with the following terms: Metabolic Surgery AND type 2 diabetes AND glycemic control, with a limit of 5 years elapsed since publication. We identified 33 articles of which 19 abstracts were selected for reading. Based on the content of the abstracts, 11 articles was selected for full reading.

Metabolic surgery: Repercussions to type 2 diabetes mellitus

There are currently several techniques for performing metabolic surgeries, which are divided into three main groups: dysabsorptive surgeries, restrictive surgeries and mixed procedures [6,7]. These gastrointestinal (GI) procedures were developed in order to generate sustained long-term weight loss, especially in patients with severe obesity, in addition to physiological changes of the GI tract that may lead to the remission of related comorbidities, mainly through neuroendocrine mechanisms [3,6,7].

For more than 20 years, because of the 1991 consensus of the American National Institutes of Health (NIH), metabolic surgeries were indicated only for patients with BMI greater than or equal to 40 kg/m^2 or in those with a BMI greater than or equal to 35 kg/m^2 with the presence of significant comorbidities related to obesity [3]. However, subsequently, with the guidelines of the American College of Cardiology together with the American Heart Association, published in 2013, there was an expansion of the recommendations, suggesting surgical indication for patients with BMI of at least 35 kg/m^2 and Diabetes Mellitus. More recently, the guidelines issued in 2016 by the International Diabetes Organization supported the use of Metabolic Surgery as a specific treatment for T2DM [3]. Finally, a paper published in 2018 reported that Asian patients with a BMI between 25 and 35 kg/m^2, whose therapeutic goals had not yet been reached, characterizing treatment failure, presented a favorable response to minimally invasive laparoscopic procedure, both by the gastric sleeve (GS) and by Roux-en-Y gastric bypass (RYGB), achieving T2DM remission rates ranging from 52.9 to 96.2% in one to five years [3,6,8,9].

A meta-analysis has shown that different types of surgery produce different effects on glucose metabolism. In this sense, the efficiency in reducing serum glucose levels and remission of T2DM is greater in patients undergoing biliopancreatic diversion (BPD), with an efficacy of 95.1%, while RYGB is successful in 80.3% of the cases [7]. However, in a randomized controlled trial, patients submitted to GS had a lower remission rate than patients submitted to single anastomosis gastric bypass at 12 months (93%), 2 years (81%), and 5 years postoperatively (60%) [7].

In 2018, among 66 diabetic patients submitted to RYGB, the best results in terms of disease control were reached in the BMI group above 35 kg/m^2 compared to the BMI group between 30 and 35 kg/m^2, with higher reduction of glycated hemoglobin levels, which may be related to the finding of higher preoperatory glycemic levels in patients with higher BMI [10]. However, patients with a higher BMI had almost three times more surgical complications than patients with lower BMI, in addition to both groups having significant impacts on disease control with low morbidity [9].

Function of enteric hormones after the metabolic surgery

Metabolic Surgery plays a key role in the modulation of intestinal hormones (ghrelin, cholecystokinin, nesfatin-1, glucose-dependent insulinotropic peptide, GLP-1 and PYY), promoting an improvement in the digestive process, satiety and optimization of glucose homeostasis through feedback mechanisms [7].

In procedures such as the GS, gastric tissue resection promotes a decrease in ghrelin levels [7]. In other studies, in addition to GS, RYGB promoted an increase in GLP-1 and PYY concentrations [7,11]. Furthermore, the immediate and independent glycemic effects of weight loss triggered by these surgeries are directly related to postprandial insulinemia due to a rapid passage of nutrients from the stomach to the intestinal absorption surface, which promotes the activation of secretagogues in the small intestine, probably related to the significantly increased secretion of GLP-1 by L cells. This phenomenon combined with preoperatory high glycemia leads to a hyperinsulinemic effect [11].

Physiological glucose homeostasis is tightly regulated by endogenous GLP-1. This was evidenced by experiments with continuous infusion of a potent GLP-1 antagonist, exendin 9, which was able to produce glucose intolerance by eliminating the effect of the GLP-1 peptide. In addition, it is known that GLP-1 secretion stimulates 30 to 40% secretion of insulin and reduces glucagon secretion, thereby promoting the reduction of blood glucose levels, through its dislocation to the interior of the cells [11].

Dong., *et al.* studied the responses in glycemic, insulin and GLP-1 levels after a liquid meal or oral glucose intake in patients undergoing three different types of Metabolic Surgery: Adjustable Gastric Bandage (AGB), GS and RYGB. They found out that patients submitted to GS and RYGB presented a more rapid and effective response to the stimulus [8].

Bile acids are directly related to endocrine functions associated with GLP-1. They regulate the metabolism of lipids and glucose, in addition to energy balance, promoting the improvement of carbohydrate metabolism and reduction of hepatic steatosis. Emerging evidence has suggested that bile acids also promote incretin secretion, fibroblast growth factor production, and regulate the intestinal microbiota. Moreover, new findings have shown that improved glycemic control following gastric bypass surgery can also be attributed to bile acid signaling in the bowel [10,12].

PYY, also called YY pancreatic peptide or tyrosine-tyrosine peptide, is also released by L cells into the mucosa of the gastrointestinal tract, mainly in the ileal portion of the small intestine, being a peptide that induces an anorexigenic food response. It promotes an increase in the absorption of nutrients in the ileum, retards gastric emptying and secretion, attenuates the action of the gallbladder and inhibits pancreatic secretion. In a significant number of studies, it was shown that, after GS and RYGB, there was an increase in PYY secretion [12].

Ghrelin is a neuropeptide synthesized mainly by the oxyntic cells of the gastric fundus and has an orexigenic function, hence generating hunger. It has, among its functions, the suppression of insulin secretion, thus having a diabetogenic effect [12]. It has already been shown, in 2012, that, after GS or RYGB, a reduction in serum ghrelin concentrations occurs, most evident in patients submitted to the first type of surgery, in which there is an excision of tissue from the gastric fundus. However, in experimental studies, the decline of ghrelin production could not be decisive, since a possible compensatory mechanism could exist in animals with this incretin deficiency; in this context, weight loss would lead to positive feedback in the body's attempt to recover lost mass [1,3,5,12].

T2DM is a disease that grows exponentially in Brazil and in the world. Therefore, it is extremely important to consider new modalities of treatment for T2DM, either pharmacological and/or surgical, aiming at more fruitful therapeutic results. Other pillars of treatment are adherence to appropriate dietary recommendations and changes in lifestyle, which includes the practice of physical activities.

According to the theoretical review here presented, in most studies, the use of GS and RYGB surgical techniques is related to long-term improvement and remission of T2DM, which highlights surgery as a viable treatment option for the disease.

Both GS and RYGB have been shown to be effective in reducing blood glucose levels and even remission of diabetes. However, it is necessary to consider the risks related to abdominal surgery, despite the advances of minimally invasive surgical techniques, mainly via videolaparoscopic approach. The advent of robotic surgery offers improved accuracy of anastomoses and decreased cavity manipulation, but this is also related to a higher cost of the procedures. Thus, among advantages and disadvantages, it is worth evaluating the cost-benefit of Metabolic Surgery.

Furthermore, there are no studies that separate the results across the different epidemiological profiles of diabetic patients in order to determine whether surgical therapy will be effective for all or only a subpopulation of diabetic individuals will benefit from it.

Metabolic surgery and the control of diabetes mellitus

Postoperative improvements in metabolic control occur rapidly and out of proportion to weight loss [13]. Studies have not reached an agreement regarding the target glycemic levels for post-surgical control. Ramos-Levi and Rubino (2017) have suggested using "optimal metabolic control" rather than the stricter "diabetes remission" for the long-term for evaluation. Their paper considered that diabetes remission solely regarded as biochemical normality underestimates the true overall value of Metabolic Surgery for patients who suffered long-term and poorly controlled T2D [14].

The scarcity of randomized controlled trials (RCT) and long-term analyses remain a limitation to the evaluation of the effects of the Bariatric/Metabolic Surgery in patients with T2DM. Moreover, RCT have been using a variety of protocols, including different pre-operatory (severity of the disease) and target pos-operatory glucose and hbA1c levels, a variety of operation techniques, and additional lifestyle interventions. Despite the variability in study design, there has been significant consistency in terms of major outcomes, including disease remission or improvement of HbA1c, favoring surgery when compared with medical therapy [15].

In a study that examined end-of-trial health outcomes in participants in the Action for Health in Diabetes (Look AHEAD) trial who had bariatric surgery during the approximately 10-year randomized intervention, surgically treated participants lost 19.3% of baseline weight, compared with 5.8% and 3.3% for the intensive lifestyle intervention and diabetes support and education groups, respectively, and were more likely to achieve partial or full remission of their diabetes [16].

The effect of Metabolic Surgery on the micro- and macrovascular complications of T2DM has been the object of study of observational prospective cohort trials. In addition, most RCT have shown the superiority of surgery over medical management at achieving remission or glycemic improvement [15]. The STAMPEDE trial, a 3-year RCT that reports on renal outcomes of patients with uncontrolled DM submitted to surgical treatment and compared them to controls, found higher improvement of urinary albumin-to-creatinine ratio in RYGB (62%) and SG (80%), with normalization of the results [17]. Moreover, the STAMPEDE trial demonstrated that bariatric surgery (RYGB or SG) did not appear to interfere with the course of retinopathy at 2 years compared with intensive medical management, and a majority (86.5% of patients within all treatment groups) had no change in retinopathy scoring [15].

Other secondary end points favoring surgery over medical treatment were weight loss and increase in HDL levels [18] and reduction of the number of medications and favorable changes in the Quality of life measures [17]. Furthermore, an RCT on fecal microbiota profile reported that duodenal-jejunal bypass surgery with minimal gastric resection increases the concentrations of Akkermansia bacteria, which are linked with better weight loss and metabolic control [19].

To this date, data regarding long-term mortality in Metabolic Surgery patients has been limited. A very interesting study which included exclusively patients with established cardiovascular disease (myocardial infarct or stroke) showed a 40% reduction in all-cause mortality [20]. Another long-term study reported a 56% drop in the coronary artery disease among RYGB compared to control subjects [21].

The 2nd Diabetes Surgery Summit (DSS-II) recommended that, based on such evidence, Metabolic Surgery should be recommended to treat T2DM in patients with class III obesity (BMI ≥40 kg/m^2) and in those with class II obesity (BMI 35.0 - 39.9 kg/m^2), when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy. According to the authors, surgery should also be considered for patients with T2DM and BMI 30.0-34.9 kg/m^2 if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications. These BMI thresholds should be reduced by 2.5 kg/m^2 for Asian patients [22].

Conclusion

With the progressive increase in the number of cases of T2D in the world, with the estimation of half a billion cases predicted for 2040, the search for methods and improvement of effective modalities of treatment for T2DM becomes inestimable.

The effects of Metabolic Surgery in poorly controlled non-obese diabetic patients have shown results capable of establishing, mainly due to the optimization of the intestinal hormonal functions, that the practice of minimally invasive surgical techniques is beneficial to the majority of patients submitted to such procedures, especially GS and RYGB.

Thus, it is concluded that despite the need for further studies of the surgical practice in diabetic patients with lower BMI and long-term studies to evaluate possible comorbidities, Metabolic Surgery is a procedure that can be considered a definitive treatment modality to a disease that, until recently, was considered incurable and that leads to a decrease in the quality of life and to a significant economic burden to the Health System.

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