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## REMISSION OF DIABETES MELLITUS TYPE 2 IN OBESE PATIENTS

**Summary:** Diabetes is a disorder of carbohydrate metabolism that is characterized by the development of numerous complications and the deterioration of life quality. Remission of diabetes mellitus type 2 (T2DM) is defined as maintaining glycoregulation below the level used for diagnose: glycosylated hemoglobin (HbA1c) less than 6% (<42 mmol/mol) and glycemia less than 5.6 mmol/L, during the year, without using anti-diabetic medication. The key to remission of diabetes mellitus type 2 (T2DM) is weight loss, which can be the result of use hypocaloric diets and / or the result of surgical treatment with bariatric surgery. For remission of diabetes mellitus typ 2 in obese patients, who are the majority of patients, it is advised to lose a minimum of 15kg or an average of about 15% of body weight. Bariatric surgery leads to significant and sustained weight loss and diabetes remission up to 5 years after the intervention. Factors influencing the achievement of remission after bariatric surgery are: preoperative glycemic control, duration of disease, patient compliance, weight loss, type of diabetes mellitus and initial amounts of visceral adipose tissue. The SOS study found that operated patients had a significantly higher percentage of disease remission than a group of patients treated with classic lifestyle modification. There was more weight reduction for the remission of disease than baseline BMI. The Look AHEAD study failed to demonstrate a reduction in cardiovascular events by changing lifestyle habits, but clearly showed that intense lifestyle modification lead to more significant weight loss and better control of T2DM. A DiRECT study showed that 45.6% of patients with type 2 diabetes who were on a low-calorie diet entered T2DM remission after 12 months. This study found that 64% of patients who lost more than 10kg were in T2DM remission after two years. Given that bariatric surgery is an expensive method associated with complications and risks, researches need to be focused on less aggressive interventions to achieve remission

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of this disease, which would have significant benefits for both patients and the overall health system.

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Diabetes mellitus type 2 (T2DM) is a disorder of carbohydrate metabolism, defined by the American Diabetes Association (ADA) as a complex, chronic disease that requires continuous medical care and a multifactorial strategy to achieve optimal glycemic control. (1) In general, T2DM is considered to be a progressive, incurable and lifelong disease, and treatment has traditionally so far been aimed to achieving optimal glycemic control and prevention of complications resulting from hyperglycemia. (2)

The increase in the number of obese DM2 patients treated with bariatric surgery, the possibility of remission in some patients has been observed. The ADA defined T2DM remission as: "Achieving glycemia below the defined threshold for the diagnosis of diabetes in the absence of active pharmacological or surgical treatment." There is currently no consensus of the criteria for diabetes remission, but most studies rely on the recommendations of the American Diabetes Association (ADA). Defining disease remission as maintaining glycoregulation parameters below the level used to diagnose: glycosylated hemoglobin (HbA1c) less than 6% (<42 mmol/mol) and glycemia less than 5.6 mmol / L for one year without the use of anti-diabetic drugs.

This association classifies T2DM remission into three entities:

- Partial remission is defined as maintaining glycoregulation at a suboptimal level, that is, glycosylated hemoglobin is less than 6.5% and glycemia is listed between 5.6-6.9 mmol / L, without pharmacological therapy for more than one year.
- Complete remission is defined as maintaining glycoregulation parameters within the normal range, ie HbA1c less than 5.7%, glycemia less than 5.6 mmol/L, without pharmacological therapy, for a minimum of one year.
- Extended T2DM remission refers to the maintenance of complete remission for more than five years. (3)

Given that one of the major pathophysiological mechanisms in the onset of T2DM is obesity, accompanied by insulin resistance, it is thought that the key to achieving remission is weight reduction, which can be achieved through intensive lifestyle modification and / or surgical treatment of obesity. For remission of diabetes mellitus type 2 in obese patients, who make up the majority of patients, it is advised to lose a minimum of 15kg or an average of about 15% of body weight.

## BARIATRIC SURGERY

Surgical treatment of obesity, also known as metabolic or bariatric surgery. It is indicated in obese subjects with a BMI (body mass index BMI) greater than 40 kg / m<sup>2</sup>, or with a BMI greater than 35 kg / m<sup>2</sup> with comorbidities present, in persons older than 18 years and younger than 60 years. Surgery, primarily restrictive methods, may be considered in some patients with a BMI of 30-35 kg/m<sup>2</sup>. Bariatric surgery leads to significant and sustained weight loss and diabetes remission up to 5 years after the intervention. (4, 5)

These surgical interventions can be divided into restrictive procedures (procedures that reduce gastric volume), malabsorption procedures (which reduce nutrient absorption), and combination procedures. (5, 6) In terms of duration, these operations are divided into reversible and irreversible. (5) Reversible operations are usually used in the treatment of moderate obesity or as a preparation for performing an irreversible bariatric procedure.

Restrictive interventions are:

- The adjustable gastric band is the least invasive method that is purely restrictive. It reduces the intake of food by placing a strip on the stomach fundus, where a small pouch (size 10–15 cm<sup>3</sup>) into which the food reaches is formed.
- Gastric sleeve resection or left vertical gastrectomy is a method that vertically removes a portion of the stomach and reduces its volume to 20–25% of the original, thereby preventing excessive food intake. During the intervention, the pyloric valve is left, so that the digestion is unchanged. This intervention removes the gastric fundus, whose cells secrete ghrelin, thereby reducing appetite, and due to the rapid passage of food through the constricted stomach, the secretion of GLP1 (glucagone like peptide1) and the polypeptide YY (PYY) is induced which stimulates insulin secretion and causes a feeling of satiety. (7)
- “Gastric imbrication”, that is, a wrinkle, is a relatively new bariatric method by which a large curve of the stomach is plated, and it narrows to form a narrow tube, similar to a sleeve resection, except that it does not remove or cut the organ.

### Combined methods of bariatric surgery

An operation aimed at limiting food intake and reducing its absorption is a Roux-en-Y gastric bypass (RYGB). It is performed by surgically dividing the stomach into two parts, the proximal-smaller, so-called gastric reservoir and the second-blindly

closed gastric remnant continuing to the duodenum and proximal jejunum. This resection achieves a restrictive effect. Malabsorption is ensured by creating a long Roux swirl that connects the gastric reservoir to the rest of the jejunum.

### **Dominantly malabsorptive methods of bariatric surgery**

Biliopancreatic diversion and duodenal switch are primarily malabsorptive procedures that involve horizontal removal of the stomach, creating a sac that connects to the small intestine. The basic concept of malabsorptive surgery is to reduce the absorptive surface length of the small intestine, which leads to weight loss. The larger the intestinal segment is bridged, or the larger the stomach is removed, the more pronounced the weight loss.

## **MECHANISM OF T2DM REMISSION AFTER SURGICAL OBESITY TREATMENTS**

Metabolic surgery has the ability to induce and maintain significant weight loss through a variety of mechanisms, including calorie reduction resulting from the anatomical remodeling of the gastrointestinal tract, increased meal-induced thermogenesis, modulation of hypothalamic centers for regulating appetite and energy balance, changing eating habits, and by altering the gut-brain signaling pathways. (9)

Improvement in glycemic control occurs immediately, within a few hours to seven days after surgery and before weight loss, in response to enteroendocrine changes resulting from the altered intestinal flow. Caloric restriction contributes to the later maintenance of metabolic balance. (10,11)

The main pathophysiological mechanisms that mediate the positive effects of metabolic surgery are: increased insulin sensitivity (primarily at liver and muscle levels), repair of beta-cell function, changes in bile acid secretion (reduce hepatic gluconeogenesis and increase intestinal gluconeogenesis in parts without bile acids) the composition and modification of the intestinal microflora, an increase in glucose uptake at the level of the gastrointestinal tract (which is essential in postprandial glycemic control), and an increase in the amount of brown adipose tissue. (12)

The most significant mechanism of T2DM remission is weight loss after surgery (13). The rapid improvement of hepatic insulin sensitivity in the short term after surgery is the result of intensive reduction of caloric intake, while the repair of insulin sensitivity is a consequence of weight loss. The first phase of insulin secretion and the incretin effect, recover rapidly after metabolic surgery, especially after gastric bypass (RYGB). Establishing anastomosis and fast delivery of undigested foods from the stomach to the small intestine causes a rapid increase in circulating levels of incretin:

GLP-1 and GDIP (glucose-dependent insulinotropic peptide), which cause insulin release and improve beta-cell function. Increased secretion of GLP-1, PYY, GDIP and oxyntomodulin alters energy metabolism, as well as a consequent decrease in ghrelin suppressing hunger signals. (13,14)

Factors influencing the achievement of remission after bariatric surgery are: preoperative glycemic control, duration of disease, patient compliance, weight loss, type of diabetes mellitus, and initial amounts of visceral adipose tissue. In a recent meta-analysis of 15 studies (n = 1,753), Wang et al. showed that older life expectancy, longer diabetes duration, insulin use, and poorer disease control were associated with a lower likelihood of diabetes remission without having a gender or baseline body mass index (BMI). (15) Various models have been used to predict DM2 remission postoperatively: such as DiaRem score, ABCD score, etc. (16)

One of the most significant studies examining the impact of metabolic surgery on mortality was the SOS study (Swedish Obese Subjects study), which followed 3485 patients. The present study showed that the incidence of T2DM was significantly lower in the operated group than in the control group (on conventional therapy). Surgery patients had a significantly higher percentage of disease remission than the patient group treated with classic lifestyle modification. There was more weight reduction for the remission of disease than baseline BMI. (17) After 2 years of follow-up, 72% of patients treated with surgery were in remission. (18) Similar results were shown by studies that subsequently addressed a similar topic (19, 20) The most recent findings by Madsen in 2019, which monitored the impact of gastric bypass (RYGB) surgery on T2DM remission in a cohort of 1,111 T2DM patients indicated that remission of T2DM was achieved in 3/4 of the operated patients and that the negative predictors were: duration of T2DM longer than 2 years, life expectancy over 50 years, use of drugs other than metformin and HbA1c greater than 7%. (21)

## **T2DM REMISSION BY CHANGE OF LIFE HABITS**

Several studies have monitored the impact of lifestyle changes (low-calorie diet and dosed physical activity) of obese patients on T2DM remission.

Several studies have shown improvements in metabolic control in patients with T2DM, restriction of calorie intake using a very-low-calorie diet (VLCD) (22, 23)

In obese patients, improvement in insulin sensitivity is observed after seven days of a very low-calorie diet (VLCD), while insulin secretion recovers around the eighth week. (24) The rate of remission is higher for those who have lost more weight. (25)

Low-calorie diets have proven to be effective in achieving T2DM remission for up to two years through numerous studies. Diets are more effective in people who have a shorter duration of illness and need to have a significant reduction in caloric intake to achieve remission.

Studies have shown that over time, metabolic adaptation to caloric restriction occurs, and energy balance is re-directed to regaining weight loss. (26)

The Look AHEAD study published in 2003 (action for HEAalth in diabetes, Look AHEAD) failed to demonstrate a reduction in cardiovascular events by changing lifestyle habits (which was the primary goal), but clearly showed that intensive lifestyle modification leads to more significant weight reduction and better control of T2DM. This study showed that it is very difficult to control body weight just by modifying life habits. Average weight loss decreases over time: from 8.6% at the end of the first year to 4.7% at the end of the fourth year and over time the number of patients who achieved T2DM remission from 12% to 7% decreased. (27)

At the beginning of 2019, the results of the DiRECT study (Diabetes Remission Clinical Trial, DiRECT), which monitored 306 overweight subjects treated for T2DM for less than 6 years, were published. The study group had a special menu that changed through 3 phases, of which the introductory one was at 850 kCal and then continued with a restriction diet. The first results after one year showed T2DM remission in 45.6% of the patients who participated in the study. This study found that 64% of patients who lost more than 10kg were in T2DM remission after two years. (28)

The Carbohydrate-Restricted Diet (LC) is a type of diet that is based on a change in macronutrient intake – carbohydrate restriction and increased protein intake. There are two basic types of this diet: one with carbohydrate reduction to less than 130g and the other with very low carbohydrate levels of less than 20–30g daily. Proteins are represented by about 20% of daily calorie intake. These diets have been recommended for T2DM diet on the basis of the recommendations of the American Diabetes Association (ADA). (29)

## CONCLUSION

By intensive lifestyle modification in obese patients and surgical treatment of obesity, it is possible to achieve diabetes remission, and the duration of remission depends on the degree of weight reduction and the length of weight maintenance at the optimum level. To establish a good therapeutic response, it is necessary to educate patients about the importance of weight loss as a basic mechanism for achieving remission and accepting lifestyle modification as an integral part of treatment. Given that bariatric surgery is an expensive method associated with complications and risks, researches need to be focused on less aggressive interventions to achieve remission of this disease, which would have significant benefits for both patients and the overall health system.

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