ABCDDV/818

ABCD Arq Bras Cir Dig
2011;24(4): 312-317

Review Article

METABOLIC SURGERY - CURE FOR TYPE 2 DIABETES

Cirurgia metabólica - cura para diabete tipo 2

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ABSTRACT - ***Introduction*** - Type 2 diabetes is a metabolic disease characterized by chronic hyperglycemia associated with several organs damage and failure. It is the most common cause of blindness, amputation and kidney failure in western adults, besides increase the risk of coronary disease and stroke with high mortality of patients. The association of type 2 diabetes with obesity is really significant. Obese diabetic patients had a better glucose control after bariatric surgery even prior to weight loss. ***Methods*** - A systematic review in Pubmed, Bireme and Scielo research sites was made, using "Diabetes Mellitus", "Bariatric Surgery" and "Obesity" keywords. Were selected the studies related to surgical techniques in the treatment of obesity and type 2 diabetes. The papers presented at the 1st and 2nd World Congress of Interventional Therapies for Type 2 Diabetes was also included. ***Conclusion*** - Surgical treatment of patients with obesity and type 2 diabetes showed important initial results controling blood glucose. However, the procedures and techniques used must be more investigated in randomized controlled trials comparing the clinical and surgical treatments, in animals and in humans.

HEADINGS - Diabetes Mellitus, Bariatric Surgery, Obesity.

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Financial source: none
Conflicts of interest: none

Received for publication: 22/11/2010
Accepted for publication: 15/03/2011

RESUMO - ***Introdução*** - O diabete melito tipo 2 é doença metabólica caracterizada por hiperglicemia crônica que está associada com dano e insuficiência de vários órgãos. A evolução da doença é a causa mais comum de cegueira, amputações e insuficiência renal em adultos no ocidente, além de aumentar a incidência de infarto agudo do miocárdio e acidente vascular cerebral, com maior mortalidade dos pacientes. A associação dele com obesidade é relevante. Os pacientes obesos diabéticos quando submetidos ao tratamento cirúrgico da obesidade apresentam melhor controle da glicemia, mesmo antes de perderem peso. ***Método*** - Foi realizada revisão de literatura nos sites de pesquisa PubMed, Bireme e Scielo, com os descritores "Diabetes Mellitus", "Cirurgia Bariátrica" e "Obesidade". Selecionaram-se, principalmente, os estudos de aplicação de técnicas cirúrgicas nos tratamentos da obesidade e do diabete tipo 2. Adicionalmente foram revisados os trabalhos apresentados no 1st e 2nd World Congress of Interventional Therapies for Type 2 Diabetes. ***Conclusão*** - O tratamento cirúrgico de pacientes obesos e diabéticos tipo 2 tem mostrado bom resultado inicial, com controle clínico precoce da glicemia. Porém, os procedimentos e técnicas empregados devem ser melhor investigados em estudos randomizados e controlados, comparando os tratamentos cirúrgico e clinico, em animais de experimentação e em seres humanos.

DESCRITORES - Diabetes Mellitus. Cirurgia Bariátrica . Obesidade.

INTRODUCTION

Diabetes mellitus type 2 (DM2) is a metabolic disorder characterized by hyperglycemia triggered by deficient secretion of insulin from pancreatic β cells and/or increased peripheral resistance to its action. The chronic hyperglycemia is associated with damage and failure of various organs. The disease is the most common cause of blindness, amputation and kidney failure in adults in the West and as a coronary risk factor, increases the incidence of myocardial infarction and stroke[1].

The prevalence of the disease has been growing in scale. It is estimated that approximately 150 million people worldwide suffer from DM2, increasing to approximately 300 million in 2025, with the emergence of a new case every five seconds[14].

In Brazil, the eighth largest number of cases, the disease affected 4.5

million Brazilians in 2000, with the perspective of twice that number by 2030, according to the World Health Organization[30].

The association between obesity and diabetes is well defined. Mainly located in the abdominal region may increase the risk by 10 times, and for each 10% increase in body weight, thre is an increase of 2 mg/dL in fasting plasma glucose[15].

According to the World Health Organization[31], obesity increases morbidity and mortality related to cardiovascular disease, insulin resistance, DM2, dyslipidemia, sleep apnea, orthopedic problems, lung diseases and psychological disorders. As far as, losing weight contributes greatly to the success of therapy in diabetic patients, the fight against obesity has gained increasing importance.

METHOD

Literature review was conducted on sites search PubMed, BIREME, SciELO, with the headings "Diabetes Mellitus", "Bariatric Surgery" and "Obesity". Were selected mainly studies with application on surgical techniques in the treatment of obesity and DM2. In addition was reviewed the papers presented at the 1st and 2nd World Congress of Interventional Therapies for Type 2 Diabetes held in New York in 2008 and 2011, respectively.

Observations obtained with surgical treatment

Patients with severe obesity, ie BMI greater than or equal to 40 kg/m^2, are at increased risk of comorbidities[28]. For these individuals, as well as those with a BMI equal to or greater than 35 and who already had associated diseases, bariatric surgery has proven effective in improving these diseases, including DM2.

The first bariatric operations began in the 50s and were disabsortive, decreasing the size of the small intestine to approximately 50 cm. These techniques led to diarrhea, excessive weight loss (60% to 70%) and severe malnutrition.

Friedman et al.[12] described improvement in diabetes mellitus after the completion of subtotal gastrectomy for peptic ulcer disease, demonstrating the influence of digestive operations in non-obese.

Cummings and Overduin[8] studies in 2007 demonstrated the action of intestinal peptides, called incretins, peripheral and centrally acting on glycemic control and regulation of food intake. They suggested that the change in anatomy and physiology, provided by the operation, influence their action. Currently, the researches are focused on enteroinsular axis of GLP-1, GIP, PYY, ghrelin and gastrin.

Glucagon-like peptide-1 (GLP-1) is shown in the central nervous system and in L cells of the small intestine and secreted after eating in proportion to the caloric intake, especially when the food reaches the most distal portions of the intestine. Rask et al.[20] evaluated the effect of GLP-1 in satiety and its influence on body weight in the long- term. Evidence suggests that the secretion and response to food stimulation of GLP-1 are reduced in obese and weight loss normalizes these levels. Besides the role in control of hunger, GLP-1 also increases insulin secretion by stimulating the expression of the insulin gene and enhance every step of their biosynthesis. The glucose-dependent insulinotropic polypeptide (GIP) is synthesized and secreted in the duodenum and proximal jejunum, mainly in response to glucose and fat, and influence the synthesis and secretion of insulin. Rubino et al.[24] observed reduction of GIP after bariatric surgery in obese patients, but not in the group obese nondiabetic; they identified gaps in the response of GIP on the degree of insulin resistance, suggesting that the state of insulin resistance is associated with a defect in the response to GIP. These authors also demonstrated that PYY participates in the mechanism of appetite and weight control. It is a counterpart to the incretin GLP1 produced in L cells of the digestive tract, along its entire length, being a polypeptide similar to GLP-1. Its production is stimulated by intraluminal nutrients, modulate and inhibit several functions of the gastrointestinal tract, including the pancreas, especially insulin.

Cummings et al.[8] says that gastrin is a unique orexigenic hormone produced primarily by the stomach and proximal small intestine, regulating appetite in several species. Increases gastrointestinal motility and decreases insulin secretion by action on receptors in the pancreatic islets. Circulates shortly before meals and is suppressed by nutrient intake, mainly carbohydrates.The secretion of preprandial ghrelin seems to be a response mediated by the sympathetic nervous system. Has a role in controlling food and body weight regulation by direct influence on the control of hunger; its levels are inversely proportional to body weight. Weight loss increases it.

Bariatric surgery interferes with the enteroinsular mechanism positively influencing the production of these and other hormones that somehow work in promoting pancreatic β cell insulin production[21].

Surgical techniques

Considering the mechanism that induces weight loss, surgical procedures are often classified as restrictive or disabsorptive. However, knowledge of other mechanisms, such as the action of incretins in the outcome of surgical procedures, makes this classification questioned because not only the restriction or malabsorption leads to weight control.

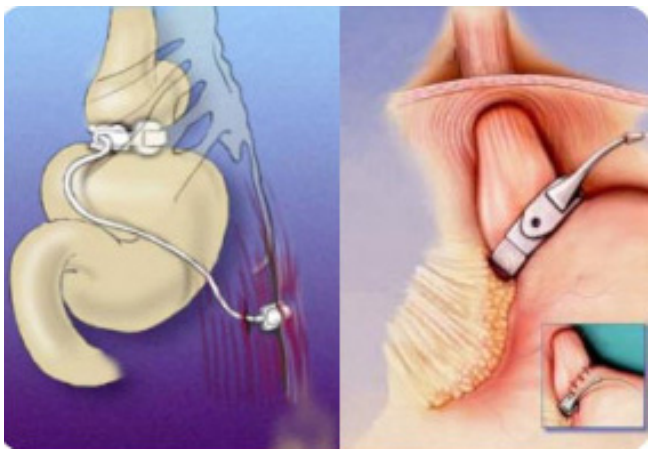
Restrictive operations

These procedures aim to reduce the gastric cavity. Examples are the adjustable gastric band and sleeve gastrectomy (sleeve). These procedures do not

involve exclusion of the intestinal tract.

The adjustable gastric band (Figure 1) developed in 1982 in Austria, had greater popularity with the diffusion of laparoscopic surgery of the 90's, with the adjustable system being applied in the surgical treatment of obesity.

Dixon et al.[10] observed significant improvement of diabetes in patients undergoing adjustable gastric band with a BMI between 30 and 40 in follow-up period of two years. The author observed remission in 73% of cases compared to 13% in a group that underwent clinical treatment. This operation has a restrictive and not metabolic effect. The success with respect to weight loss and control of diseases is not as effective when compared to other techniques[3,4]. Due to high rates of weight regained, many surgeons have sought other alternatives[31].



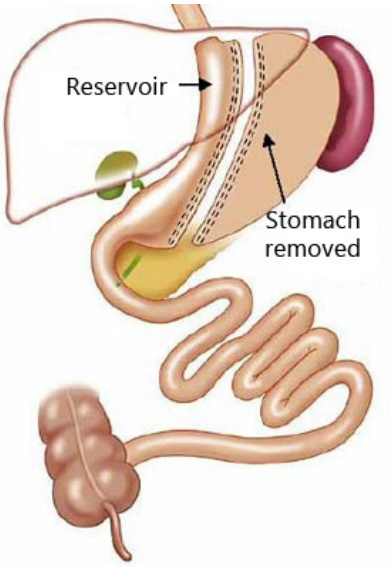
Fonte: (http://www.sbcbm.org.br/pacientes_duvidas_frequentes.php)

FIGURE 1 - Adjustable gastric band

The vertical gastrectomy (sleeve) is one of the new procedures that have been accepted worldwide (Figure 2). In it, the surgeon performs up to 80% removal of the stomach, leaving a vertical cavity. Besides being restrictive procedure takes action to reduce ghrelin. Initially it was first proposed as a two-step procedure, associated in a second time to one malabsorptive procedure for patients at high surgical risk. In addition to the restrictive effect, authors have suggested an incretin effect increasing gastric emptying which could lead to more effective release of GLP-1, showing similar results when compared with malabsorptive procedures[2].

Disabsortive operations

Gastroplasty with gastrointestinal Roux-en-Y bypass (RYGB) (Figure 3) is the most commonly performed bariatric surgical procedure in the world and is considered the "gold standard" treatment for morbid obesity. In this operation, most of the stomach, duodenum and proximal jejunum are no longer part



Fonte: (http://www.ifso.com/index.aspx?id=SleeveGastrectomy1)

FIGURE 2 - Vertical gastrectomy

of the circuit passage of food, reducing the length of the path of common limb to food and biliopancreatic juice to about 450 cm[5].

Pories[18] has published a paper describing the effects of surgical treatment by RYGB. This study included 515 morbidly obese patients and that 288 (55.95%) were diabetic or had glucose intolerance. They were assessed preoperatively weekly during the first month and monthly until the sixth month postoperatively. After surgery only 30 (5.8%) patients remained diabetic. Patients that did not normalize glucose levels after surgery had diabetes during a longer time than those who improved in the postoperative evaluations.

These data have been reproduced in several studies and meta-analysis[3,4].

Schauer et al.[27] studied obese DM2 patients undergoing RYGB. The assessment of diabetes control was performed with the fasting plasma glucose and HbA1c dosage, as well as evaluating the need for medication. They achieved a reduction in fasting plasma glucose and glycosylated hemoglobin in 83%, reduction of oral medication in 80%, and 79% in insulin. Patients with shorter disease duration (<5 years) and with great weight loss showed complete resolution of diabetes.

The concept of biliopancreatic diversion (BPD) (Figure 4) was first described by Nicola Scopinaro of Genova, Italy in 1979. It consists of operation with greater restriction and malabsorption effect and leads to significant greater weight loss compared to RYGB, but can cause complications such as protein malnutrition, hypocalcemia, bone demineralization, diarrhea, gastric ulcer, iron deficiency, vitamin B12 and fat soluble vitamins and excessive flatulence. The author working with 312 patients and 10 years of follow-up had 97% resolution of diabetes (26,27). Other

Fonte: (http://www.sbcbm.org.br/pacientes_duvidas_frequentes.php)

FIGURE 3 - Gastroplasty with gastrointestinal bypass Roux-en-Y

authors have added some modifications in the original technique with good results[31].

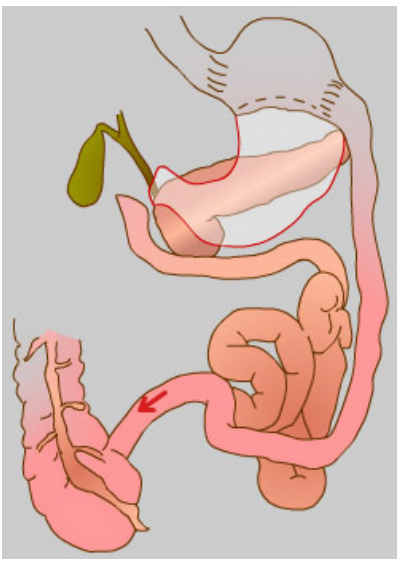


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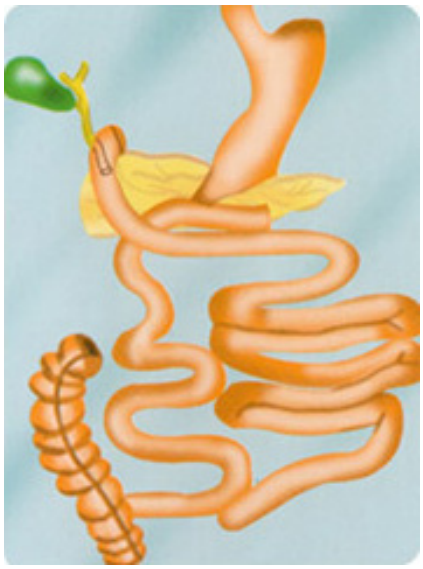
FIGURE 4 - Biliopancreatic diversion (Scopinaro)

Another operation on the same principles, is the one proposed by Hess and Hess and Marceau, variant of "duodenal switch" (Figure 5). It is a vertical gastrectomy and differs from Scopinaro operation by keeping the pylorus. This would maintain the benefits of biliopancretic bypass in weight loss and control of comorbidities, decreasing some complications such as dumping and marginal ulcer[13].

The control of diabetes would not be a secondary response to the treatment of obesity, but the exclusion of duodenojejunal segment. This idea is corroborated by several studies that show the improvement of



Fonte:(http://www.sbcbm.org.br/pacientes_duvidas_frequentes.php)

FIGURE 5 - Duodenal switch

diabetes a few days after surgery in obese and also the resolution of it in non-obese patients underwent duodenojejunal bypass, not associated with gastric restrictive operation[16].

The procedures (RYGB and BPD) include the diversion of part of the duodenum and jejunum. Peptides are released in this part of the digestive tract, functioning in the regulation of pancreatic beta cells that produce insulin in physiological state, and in diabetes. Enteroinsular changes induced by the operation may explain the anti-diabetogenic effect of the procedure. Thus, the improvement of diabetes would not effect the treatment of obesity, but rather a direct effect on duodenojejunal exclusion, and it can be achieved in individuals without obesity. To test this hypothesis Rubino and Marescaux[24] studied the effect of duodenojejunal bypass in Goto-Kakizaki rats (GK) - most widely used model for studying diabetes in animals without obesity. The operation has kept intact the volume of the stomach, with maintenance of caloric intake and weight maintenance of the animals. The result of this study was the change of severe diabetes, independently from dietary changes and weight of animals. The authors concluded that this procedure should be implemented in humans with diabetes to reverse the disease, without causing potential nutritional damage, common in bariatric procedures, such as vitamin deficiency and iron deficiency anemia.

This procedure was performed clinically by Cohen et al.[6], resulting in euglycemia and reduction of glycosylated hemoglobin to normal levels, evident even before hospital discharge in some cases.

De Paula et al.[9] evaluated the applicability of a technique that consists in performing sleeve gastrectomy and ileal interposition in the proximal jejunum. The physiological explanation is based on early contact of food with the distal ileum with

consequent earlier release of incretin. In analysis of 21 patients who underwent this operation with an average BMI of 39.2 kg/m^2 and median follow-up of 11 months, resulted in weight loss of 42.4% in 16 months and an average BMI of 23.1 kg/m^2. In an assessment of six months all patients with DM2 and sleep apnea were cured.

Despite these arguments to defend the use of surgery in the treatment of diabetes, this concept inevitably suffers resistance from experts who consider the disease as a clinical treatment. They use the argument of higher morbimortality with the procedure, despite knowing that diabetes is associated with severe clinical complications, reduction of life expectancy and quality of life.

The control of diabetes by operations was initially thought to occur due by weight control; however, the rapid improvement of diabetes even before significant weight loss have shown different ways of action. Papers by Rubino[21] and Scopinaro[26] showed that the improvement of diabetes usually occurs in the first week after surgery and the patients who underwent the Scopinaro biliopancreatic diversion or duodenal switch were those with the highest rates of improvement with normal diet, including carbohydrates. The normalization of blood glucose occurs in the early postoperative period, even before a significant weight loss to explain this improvement[18]. This suggests that the anatomical and functional changes caused by the operation are the factors that contributed most to the improvement and, in most cases, normalization of parameters related to metabolic syndrome.

Two theories have been proposed to explain the beneficial effect of DJB (and RYGB and BPD) in DM2. One claims to be the result of disease control the discharge of nutrients from the chyme directly in the distal intestine, increasing the release of incretin and GLP-1. Another is based on the exclusion of the duodenum and proximal jejunum from food transit, possibly preventing the secretion of a specific signal that promotes insulin resistance and DM2. This second theory was proven in animals and subsequently in humans[21,24].

In meta-analysis, Buchwald et al.[3,4] included bariatric surgery studies published from January 1990 until April 2006. Were reviewed the cases of patients in whom there was resolution of clinical manifestations and improvement in short-term (<2 years after bariatric surgery) and long-term, based on metabolic data of insulin levels, glycosylated hemoglobin (HbA1c) and fasting glucose levels. In the 621 studies included in this systematic review, 78% of diabetic patients had resolution of clinical manifestations of DM2, and about 86.6% improved. The resolution was greater for patients undergoing BPD (95.1%), followed by the subject to RYGB (80.3%) and after adjustable gastric banding (56.7%). The proportion of patients with resolution or improvement of diabetes was similar in both, short (<2 years) and long-term (> 2 years).

Laferrere et al.[14] compared a group of obese DM2 patients undergoing RYGB (n = 9) with another (n = 10) in which was offered low-calorie diet and drugs for treatment of diabetes. The first was analyzed before and one month after the procedure, and medical therapy before and after loss of 10 kg. Besides the analysis of glucose, insulin, proinsulin, glucagon levels were measured GLP-1 and GIP, fasting and after stimulation with glucose. GLP-1 after oral glucose increased six times, the effect of incretins increased fivefold after RYGB, but not following the diet, the level of postprandial glucose also decreased more after the operation. In addition to the improved quality of life of patients undergoing bariatric surgery[17], it was observed that diabetics have an clinical improvement before a large weight loss. This has opened avenues for research of several factors as responsible for the return to euglycemia and reduction of medications in 80% to 100% of these patients[11]. But there is no data on the impact on chronic micro and macrovascular complications; therefore, there are doubts if will happen an increase on longevity of patients.

Patients with DM2 can be operated regardless of their BMI?

Besides the difficulty with diabetic control with lower obesity or only overweight and racial differences, studies are looking for scientific based criteria for surgical indication in these situations, nowadays well defined for obese grade 2 and 3.

Diabetes Surgery Summit held in April 2007 in Rome, set the criteria for use of this form of treatment in DM2. Obese patients (BMI ≥ 30 kg/m^2) are candidates for surgical treatment with duodenojejunal bypass with or without a gastric restrictive procedure. Was approved by consensus the use of RYGB as a technique of choice[21].

Considering the evidence that most patients who underwent RYGB or BPD remains in remission of diabetes without the need for medication on several years of monitoring, there is a definite reason for operation. Clinical experience with bariatric surgery and data from investigations in animals suggest now that the operation in patients with DM2 should not be based on current BMI of 35 kg/m^2, but on the assessment of risk/benefit, often faced by individuals with BMI less than 35 with diabetes and other comorbidities that affect quality of life. There is need to set other parameters to define the ideal candidate and the most appropriate type of operation. This was observed in the study of de Sa et al.[28] where 27 patients with uncontrolled DM2 who underwent RYGB with observation of 20 months, found complete resolution of diabetes, blood glucose below 100 mg/dL and glycosylated hemoglobin below 6%; in postoperative evaluation 100% glucose and 48% resolution of diabetes was found.

CONCLUSION

The procedures and results of operations to treat DM2 need to be better evaluated in further randomized controlled trials comparing surgical treatment with medical therapy. Only then, in the future, there may be better conclusions that can establish the best care that should be offered to patients with the possibility of permanent cure of the disease.

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