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ABCD Arq Bras Cir Dig
2016
DOI: /10.1590/0102-67202016nahead0001

Review Article

THE ROLE OF METABOLIC SURGERY FOR PATIENTS WITH OBESITY GRADE I ANDCLINICALLY UNCONTROLLED TYPE 2 DIABETES

O papel da cirurgia metabólica para tratamento de pacientes com obesidade grau I e diabetes tipo 2 não controlados clinicamente

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Inter Societary guideline bythe Brazilian Society for Bariatric and Metabolic Surgery (SBCBM), Brazilian College of Surgeons (CBC) and Brazilian College of Digestive Surgery (CBCD), São Paulo, SP, Brazil

ABSTRACT - ***Introduction***: Even considering the advance of the medical treatment in the last 20 years with new and more effective drugs, the outcomes are still disappointing as the control of obesity and type 2 Diabetes Mellitus (T2DM) with a large number of patients under the medical treatment still not reaching the desired outcomes.***Objective***: To present a Metabolic Risk Score to better guide the surgical indication for T2DM patients with body mass index (BMI) where surgery for obesity is still controversial.***Method***: Research was conducted in PubMed, Medline, PubMed Central, Scielo and Lilacs between 2003-2015 correlating headings: metabolic surgery, obesity and type 2 diabetesmellitus. In addition, representatives of the societiesinvolved, as an expert panel, issued opinions. ***Results***: Forty-five related articles were analyzed by evidence-based medicine criteria. Grouped opinions sought to answer the following questions: Why metabolic and not bariatric surgery?; Mechanisms involved in glycemic control; BMI as a single criterion for surgical indication for uncontrolled T2DM; Results of metabolic surgery studies in BMI<35 kg/m^2; Safety of metabolic surgery in patients with BMI<35 kg/m^2; Long-term effects of surgery in patients with baseline BMI<35 kg/m^2 and Proposal for a Metabolic Risk Score. ***Conclusion***: Metabolic surgery has well-defined mechanisms of action both in experimental and human studies. Gastrointestinal interventions in T2DM patients with IMC≤35 kg/m^2 has similar safety and efficacy when compared to groups with greater BMIs, leading to the improvement of diabetes in a superior manner than clinical treatment and lifestyle changes, in part through weight loss independent mechanisms . There is no correlation between baseline BMI and weight loss in the long term with the success rate after any surgical treatment. Gastrointestinal surgery treatment may be an option for patients with T2DM without adequate clinical control, with a BMI between 30 and 35, after thorough evaluation following the parameters detailed in Metabolic Risk Score defined by the surgical societies. Roux-en-Y gastric bypass (RYGB), because of its well known safety and efficacy and longer follow-up studies, is the main surgical technique indicated for patients eligible for surgery through the Metabolic Risk Score. The vertical sleeve gastrectomy may be considered if there is an absolute contraindication for the RYGB. T2DM patients should be evaluated by the multiprofessional team that will assess surgical eligibility, preoperative work up, follow up and long term monitoring for micro and macrovascular complications.

HEADINGS - Metabolic surgery. Obesity. Type 2 Diabetes Mellitus. Bariatric surgery.

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Fonte de financiamento: não há
Conflito de interesses: não há

Recebido para publicação: 28/01/2016
Aceito para publicação: 19/04/2016

RESUMO – ***Introdução:*** Mesmo considerando o avanço do tratamento clínico ocorrido nos últimos 20 anos, com novos e mais eficientes medicamentos, os dados ainda são desanimadores quanto ao controle da obesidade e da diabete melito tipo 2(DMT2),com grande parcela de doentes em tratamento clínico ficando fora da meta desejada de controle. ***Objetivo:*** Apresentar proposta de Escore de Risco Metabólico para melhor orientar a indicação cirúrgica do diabete em pacientes com índice de massa corpórea (IMC) mais baixo nos quais o uso de procedimento cirúrgico para obesidade ainda é controverso. ***Método:***Foi realizada pesquisa nas bases de dados PubMed, Medline, PubMed Central, Scielo e Lilacs entre 2003-2015 correlacionando os descritores:cirurgia metabólica, obesidade e diabete melito tipo 2. Adicionalmente, representantes das sociedades envolvidas emitiram opiniões em pontos nos quais não existia na literatura trabalhos com graus de evidência elevados. ***Resultados:*** Foram encontrados 45 artigos relacionadosque foram analisados pelos critérios da medicina baseada em evidências.As opiniões agrupadas procuraram responder as seguintes questões: Porque cirurgia metabólica e não bariátrica?;Mecanismos envolvidos no controle glicêmico; IMC como critério isolado de indicação cirúrgica para o DMT2 não controlado; Resultados de estudos de cirurgia metabólica em IMC<35 kg/m^2; Segurança da cirurgia metabólica em pacientes com IMC<35 kg/m^2; Efeitos em longo prazo da cirurgia em pacientes com IMC inicial <35 kg/m^2; Proposta de Escore de Risco Metabólico. ***Conclusão:***A cirurgia metabólica tem mecanismos de ação bem definidos tanto em estudos experimentais quanto em seres humanos. As intervenções gastrointestinais em diabéticos com IMC≤35 kg/m^2 possuem segurança e eficácia semelhantes aos grupos com IMCs maiores, levando a melhora do diabete de forma superior aos tratamentos clínicos e mudanças de estilo de vida, em parte através de mecanismos independentes da perda ponderal. Não há correlação entre o IMC inicial e perda ponderal em longo prazo com os índices de sucesso do tratamento cirúrgico. O tratamento cirúrgico é opção para os pacientes portadores de DMT2 sem adequado controle clínico, com IMC entre 30 e 35, após minuciosa avaliação seguindo os parâmetros dispostos no Escore de Risco Metabólico aqui proposto. DGYR é a técnica indicada para os pacientes selecionados no Escore, existindo a possibilidade de indicação da gastrectomia vertical para os casos em que exista contraindicação para ela. O paciente deve ser avaliado por equipe multiprofissional envolvida na indicação, preparo e acompanhamento após as operações e acompanhados com monitorização de complicações micro e macrovasculares.

DESCRITORES: Cirurgia metabólica. Obesidade. Diabete melito tipo 2.

INTRODUCTION

The type 2 diabetes mellitus (T2DM) is characterized by defects in insulin secretion and sensitivity. Increased insulin resistance is the initial phenomenon of the disease, gradually leading to beta-cell functiondecline and finally emerging clinically detectedhyperglycemia[2]. Data released in 2015 by the International Diabetes Federationestimated that there are about 415 million T2DM patients worldwide, with a potentialgrowth to 642 million by 2040. Diabetes has been associated with 5 million deaths in 2015, surpassing the deaths from HIV, tuberculosis and malaria together for the same year. Brazil occupies the fourth position worldwide in number of T2DM, with 14.3 million recorded in 2015[21].

Many clinical studies have shown the importance ofT2DMcontrol to prevent complications and improving quality of life and reducing mortality[25,27]. However, the clinical endpoints are generally not achieved. In a Brazilian study, only 27% of T2DM patients reach glycosylated hemoglobin (HbA1c) levels below 7%[42].

In a recent North American publication, considering the three main goals of clinical control (HbA1c < 7%, LDL cholesterol < 100 mg/dl and blood pressure below 130x80 mmHg), only 18.8% were able to achieve the recommended values[43].

Even considering the advance of the medical treatment that occurred within the last 20 years with newer and more effective drugs, data is still discouraging with a large portion of patients outside the desired control targets. In addition, changes in lifestyle with adequate eating habits, regular physical activity and weight loss are essential to achieve the disease control targets, but may bedifficult to be maintained in the long run[7].In this scenario, metabolic surgery comes asan effective tool to achieve durable control of metabolic risk factors and promote proper weight loss, contributing to improved results in obesity grade I and T2DM[1]. It is noteworthy that for patients with uncontrolled T2DM andobesity grade II and III, all medical societies involved in the treatment of diabetes and obesity have recognized bariatric surgery as the best alternative to achieve control of the disease.

METHODS

A comprehensive search was conducted in PubMed, Medline, PubMed Central, Scielo and Lilacs between 2003 and 2015 correlating the headings: metabolic surgery, obesity and type 2diabetes mellitus. In addition, experts that represented the involvedSocieties have issued opinions on points where there were nohigh degreeevidencesin literature.

RESULTS

Forty five related articles were analyzed following evidence-based medicine criteria

Why metabolic instead ofbariatric surgery?

Bariatric surgery is indicated for the treatment of patients with body mass index (BMI) greater than 40 kg/m^2 or for those with BMI above 35 kg/m^{2}with comorbidities, as T2DM, hypertension, dyslipidemia, sleep apnea, osteoarthritis, among others. Metabolic surgery can be defined as any surgical intervention involving an anatomical modification of the gastrointestinal tract resulting in better metabolic control (such as T2DM)through weight independent mechanisms and weight loss.

A large number of publications asprospective case series and randomized controlled trials with long term follow-up showed good results in T2DM remission, even in patients with BMI less than 35 kg/m^2 [1]. T2DM remission rates vary according to the surgical technique employed, being the best results observed afteroperationsthat are associatedfood rereouting, when compared with the purely restrictivetechniques[35].Thus, a large number of those procedures are being perfomed each year in the world and gradually are incorporated as part of the diabetes treatment algorithms, alongside with changes in lifestyle and pharmacotherapy. Using the name "metabolic surgery" is not just semantics; however, it has the main objective to make clear that the surgical indication is not related to BMI as a sole criterion, but mainly in the normalization of metabolic disorders with improved quality of life. The main goals of metabolic surgery, in addition to weight loss, are metabolic control with consequent cardiovascular risk reduction.

Mechanisms involved in glycemic control

Several studies have shown that insulin sensitivity in severely obese patients, with or without T2DM, improves with weight loss after anyoperation[3,28]. Initially, the most widely accepted hypothesis to explain the metabolic effects were only related to weight loss.However, it has been shown that glycemic control could be achieved early in the postoperative period even before significant weight loss, which showed clearly the involvement of other mechanisms beyond weight change by itself[7,34,39]. Furthermore, when comparing a purely restrictive surgical technique (adjustable gastric band) and Roux-en-Ygastic bypass(RYGB) even after similar weight loss, the percentage of T2DM remission is significantly higher with the second technique (17%vs.72%, p<0.001)[3,22].Some studies compared different strategies of weight loss through low calorie diet versus RYGB. It was reported better glycemic control (at the same weight loss) in the RYGB arm, with reduced antidiabetic medication and lower postprandial glycemic excursions[3,22].

Studies have shown that more than just calorie restriction and weight loss, intestinal rearrangement after some surgical techniques, asRYGBand biliopancreatic diversion are involved in rapid improvement of T2DM. Two hypotheses have emerged to explain these results: the "distal and the proximal intestine" mechanisms.The first suggests that the swifter delivery of less digested nutrients to the distal intestine may stimulate the production of hormones that may help glycemic control[36]. The more frequently described mediators that play an important role in the "distal hypothesis" are the *incretins*, that stimulate insulin secretion and reducefood intake[17,24]. In the secondhypothesis, the duodenal and proximal jejunum exclusion from food transit prevents the secretion of a supposed peptide that promotes insulin resistance and T2DM. Recently, a study in mice demonstrated that jejunal proteins hinder the signaling of insulin in muscles, worsening insulin resistance[37].

Ghrelin is a hormone produced in the stomach and duodenum and stimulates the secretion of other counter-regulatory insulinhormones, which is changed afterRYGB. Despite the decreased production of this hormone seem be a plausible explanation for thepostoperative improvement of T2DM, studies are controversial and many of them did not show any measurable effect[15,44].

Recent discussions also involve changes in the intestinal microbiota as a key regulator of metabolic pathways and theimunoinflammatory axis connecting physiologically the intestine, liver, muscles and the brain[30]. Studies in rats and humans have shown differences in gut microbiota of obese and non-obese subjects,and some changes before and after RYGB. The studies suggest that changes in intestinal microbiota play a role in the pathophysiology of obesity and metabolic /bariatric surgery outcomes[19,45]. However, more studies are needed.

BMI as a single criterion for surgical indication for uncontrolled T2DM

The indications for bariatric surgery in Brazil are based on the recently published Federal Council of Medicine Clinical recommendation number 2131/15, which hasan expanded list of comorbidities accepted to support surgical indication[13]. Based on that recommendation,bariatric surgery is indicated

for patients with BMI above 40 kg/m^2 or above 35 kg/m^2 with obesity-related comorbidities. However, these standards do not specifically emphasize the treatment of T2DM.

BMI alone is not a good tool for choosing the best treatment for T2DM, since it does not reflect body composition and it is not able by itself to consider the differences related to race, gender, age and fitness status[32]. Because there are known weight independent antidiabetic mechanisms and baseline BMI does not predict T2DM control, surgery forT2DM patients is being considered by several medical and surgicalSocieties worldwide, mainly because over 50% of T2DM patients in the world have BMI below 35 kg/m^2 [5,6,9].Persistence of high rates of morbidity and mortality in T2DM patients is a sign that the outcomes following current treatments have not been satisfactory. Faced with this reality, the surgical option should be considered in selected cases. The Swedish Obesity Subjects study showed that metabolic surgery has a preventive effect on the incidence of T2DM, particularly in patients with impaired fasting glucose and initial BMI did not influence this preventive effect[10].

Isolated anthropometric data do not seem to be the best criterion for metabolic surgery indication in T2DM patients, as the best candidate would be the individual with increased insulin resistance, increased visceral and liver fat and high cardiovascular risk associated with BMI. For this reason, there is a worldwide motion between experts in the field to change the surgical indication guidelines, putting metabolic surgery inserted in the T2DMtreatment algorithms.

In 2011, the International Federation of Diabetesfirst introduced metabolic surgery in T2DM treatment flowcharts. Also, treatment algorithms were introduced asan alternative to patients with BMI between 30 and 35 kg/m^2 with uncontrolled diabetesdespite optimal drug regimens, especially in the presence of other major risk factors for cardiovascular disease[16]. In 2014, the regulatory agency of medical practice in the United Kingdom - National Institute for Health and Care Excellence- published its guidelines for the treatment of T2DM, and metabolic surgery was considered as part of the algorithm treatment for those with uncontrolled disease and BMI>30 kg/ m^2 [29].

Results of metabolic studies in surgery in BMI<35 kg/m2

Müller-Stich et al.[26] published a systematic review from studies that compared surgical vs clinical interventions over T2DM covering 818 participants. Each study concluded that several surgical procedures had superior outcomeswhen compared to a variety of non-surgical interventions on T2DMremission. The overall relative risk of superiority of the operations was 14.1 among all studies, and 22 among those who examined only patients with preoperative BMI<35 kg/m^2. The overall mean HbA1c (%) fell by 1.5 points inthe surgical arms compared to clinical treatment, and the surgery group used less medications for diabetes in comparison to themedical group.

A meta-analysis also recently published by Rao et al.[33] examined the effects of RYGBon T2DM in nine publications, with a total of 343 subjects (BMI of 19-35 kg/m^2, 1-7 years of follow-up). There was no mortality and the rates of surgical complications ranged from 6 to 20%, similar to the numbers reported in patients with BMI ≥35 kg/m^2. All nine publications reported significant reductions in HbA1c after surgery with 2.8 points average reduction. In general, the procedure decreased fasting glucose levels by approximately 60 mg/dl greater than the values of non-surgical interventions. T2DMremission rate ranged from 65 to 93%, which is at least as high as the historically outcomes reported in patients with BMI≥35 kg/m^2.

In a systematic review of T2DM remission predictors after metabolic surgery it was observed that the overall remission rate was equivalent between 60 studies with mean preoperative BMI ≥35 kg/m^2 as compared to 34 studies with mean preoperative BMI<35 kg/m^2 (71% vs 72% respectively). T2DM remission rates were also similar in each operation among patients with BMI higher vs lower than 35 kg/m^2 (89%complete remission inbiliopancreatic diversion, 77% in DGYR, 62% in adjustable gastric banding, and 60% after vertical gastrectomy). Surprisingly, among several baseline characteristics of the patients, the only significant predictor of the magnitude of postoperative decrease in HbA1c was lower preoperative abdominal circumference[31].

In September 2015, the Diabetes Surgery Summit IIwas held in London, that brought together several experts to design new guidelines for the indication of metabolic surgery independentlyof baseline BMI. A meta-analysis was performed specially for the event encompassing 11 published randomized clinical trials that directly compared surgical vs non-surgical approaches for treatment of T2DM, including patients with BMI<35 kg/m^2. All 11 studies reported superior results aftersurgery. This this is a unanimousLevel 1A ofevidence, showing that surgery leads to improvement more significantly than the best medical treatment, includinglifestyle changes[18].

The good outcomes reported regarding T2DM remission, as glycemic control, and reduction ofHbA1c levels when compared to clinical interventions are similar between studies where patients have BMIs either greater or below 35 kg/m^2. This conclusion is clearly visible in the STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) study, arguably the best randomized trial published to date. At all times over three years, surgical patients exhibited greater reduction in HbA1c when compared to the medical arm. This findings were similar among participants where the average baseline BMI was below or above 35 kg/m^2 [28,40].

Metabolic surgery safety in patients with BMI<35 kg/m^2

The safety in this group was examined in large systematic review published by the Agency for Healthcare Research and Quality in the USA. Surgery caused greater BMI, HbA1c, blood pressure, LDL and triglyceridesreductions than clinical interventions. Surgical adverse events were relatively low; surgical mortality varied from 0.0 to 0.3%, similar to historical data for patients with BMI≥35 kg/m^2. Most surgical complications were not serious, not requiring major interventions. It was also seen that there was no excessive weight loss in those patients when standard surgical techniques were used[39].

Long-term effects of surgery in patients with initial BMI of <35 kg/m2

The efficacy and safety of RYGB were studied prospectively in 66 patients with T2DM and BMI 30-35 kg/m^2, followed up for over six years. This cohort had a mean duration of diabetes of 13 years, mean HbA1c of 9.7%, with 40% using insulin. However, there was a rapid decrease in the mean HbA1c in the first months to non-diabetic levels, with subsequent maintenance of this degree of improvement inglycemia over six years. At the end of the study, 88% of participants with T2DM remained in remission (defined as HbA1c<6.5% without medication), 11% improved(HbA1c<6.5% with medication) while only 1% remained unchanged. There was no relationship at any point of follow-up (from one month to six years) between the magnitude of weight loss and the degree of improvement of glycemic control. Blood pressure decreased during the study, and the total cholesterol, LDL cholesterol and triglycerides, while HDL cholesterol increased progressively for six years. These changes have led to significant improvement in eventualcardiovascular risk measured by a surrogate cardiovascular risk engine[11].

A recent study by Hsu et al.[20] showed similar results among patients from the Asia-Pacific region with T2DM and BMI<35 kg/m^2. With a postoperative follow-up greater than five years, they examined the antidiabetic effects of both RYGB and vertical sleeve gastrectomy compared to the clinical treatment in 351 patients. Despite efforts to get similar populations, the surgical group had a higher baseline HbA1c average (9.1% vs. 8.1%) and longer duration of T2DM, introducing conservative biases against the surgical superiority over fastingglycemia. However, HbA1c and BMI were both reduced to a much greater extent

in the surgical group, and these changes were largely stable since six months to five years after surgery.

The maintenance of HbA1c<6.5% without antidiabetic medication was achieved in 64% of the surgical patients compared with 3% of those fromthe medicalarm. At five years, the surgical group also exhibited greater reduction in abdominal circumference, central adiposity, LDL cholesterol, triglycerides and blood pressure. The mortality rate was statistically equivalent (1.9% after surgery, 3.0% after clinical treatment)[41]. These findings among this BMI range are comparable to long-term studies of metabolic surgery for individuals with T2DM and BMI≥35 kg/m^2 [8,4,23,41].

Proposal

Based on scientific evidences of potent antidiabetic mechanismsand showing similar results of those obtained in grades II and III obese patients , with low morbidity and mortality, and withlevel 1 and 1Aof evidence in short and long term follow up, the Societieshere represented propose surgical treatment indications for uncontrolled T2DM using the **Metabolic RiskScore** (Figure 1), a disease based recommendation.

CONCLUSIONS

1) T2DM is chronic and progressive illness and in some situations difficult to control with the best medical treatment and behavioral changes.

2) Metabolic surgery has well-defined mechanisms of action both in experimental and in humansstudies. Gastrointestinal interventions in diabetics with BMI≤35 kg/m^2 has similar safety and efficacy to groups with higher BMIs, leading to excel T2DM improvement when compared to the medical managementincluding lifestyle changes, in part through weight loss independent mechanisms. There is no correlation between baseline BMI and weight loss in the long term with the success rate after the surgical treatment.

3) Surgical treatment is an option for patients with T2DM without adequate clinical control, with BMI between 30 and 35, after a thorough evaluation following the described criteria of the Metabolic Risk Score .

4) RYGB is indicated for the eligible patients selected by the metabolic risk score. Eventually, a vertical sleeve gastrectomy may be suitable in the presence of absolute contraindication to RYGB.

5) The patient should be evaluated by a multidisciplinary team of surgeons, internists, nutritionists and mental health professionals, all of themactively involved in the indication, preoperative workup and postoperative follow-up with strict monitoring of eventual micro and macrovascular complications.

METABOLIC RISK SCORE	
Mandatory indicators	T2DM diagnosis
	Age between 30-65 years-old
	BMI ≥ 30 kg/m^2
	Baseline C peptide>1 ng/dL and anti-GAD negative
	Glycated hemoglobin 2 points above the reference value method, despite regular medical treatment.
	Surgical indication supported by the multidisciplinary team
Additional indicators	BMI: 30 to 30.9 kg/m^2: 0 points 31 to 31.9 kg/m^2: + 1 point 32 to 32.9 kg/m^2: +2 points 33 to 33.9 kg/m^2: + 3 points 34 to 34.9 kg/m^2: +4 points
	Albuminuria> 30 mg/g of creatinine in isolated sample: + 1 point
	C peptideafter mixed meal test higher than 50% from baseline: +1 point
	Hypertension: + 1 point
	Dyslipidemia: + 1 point
	Macrovasculardiseaseevidence: + 1 point
	Non-alcoholic fatty liver disease: + 1 point
	Provensleepapnea: + 1 point
	T2DMduration: 2-5 years: + 2 points 5-10 years: +1 point > 10 years: -1 point (negative) > 15 years - 2 points (negative)
	Use of insulin> 5 years: -1 point (negative)
It is understood that to have surgical indication, the patient must meet all mandatory criteria, with the total equal to or greater than 7 points of complementary indicators. Roux-en-Y Gastric Bypassisthe preferred technique. If there are absolute contraindications,vertical sleeve gastrectomy may be considered.	

FIGURE 1 - Metabolic risk score established byan Inter Societary guideline carried outby the Brazilian Society of Metabolic and Bariatric Surgery (SBCBM), Brazilian College of Surgeons (CBC) and Brazilian College of Digestive Surgery (CBCD)

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