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PERSPECTIVES

Type 2 diabetes and metabolic surgery guidelines and recommendations should urgently be unified

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Abstract
Metabolic surgery has been studied in the last decades as an effective and safe treatment for type 2 diabetes (T2D), and randomized controlled trials generally found surgery superior when compared with medical treatment. In 2016, the DSS-II Joint Statement recognized the importance of metabolic surgery in the treatment of T2D and urged clinicians to discuss, recommend, or at least consider this procedure for their patients. Diabetes societies also cogitate metabolic surgery as an option for T2D patients in their guidelines. However, there are some differences in recommendations that could lead a careful reader to some confusion. This was potentialized in a recent document published by the same DSS-II group concerning prioritization for surgery after the COVID-19 pandemic, in which the criteria suggested for an expedited recommendation that is not exactly evidence-based, and collided substantially with several clinical guidelines worldwide, especially with regard to secondary prevention of cardiovascular disease. A more harmonious discussion and unified guidelines between clinicians and surgeons are needed in order to provide the same message for those who read different articles.

Keywords Bariatric surgery · Metabolic surgery · Type 2 diabetes · Obesity · Cardiovascular disease · Guidelines · Diabetes treatment

Introduction

Bariatric surgery is a widely studied treatment for obesity, with clear benefits in terms of weight loss, improvement in comorbidities, and several observational evidences of reduced hard outcomes and mortality [1–4]. Any guideline for the treatment of obesity must include it, as it is the most effective therapy for this disease [3, 4].

The benefits of bariatric surgery for patients who also have type 2 diabetes led to the establishment of the expression "metabolic surgery," to shift the focus of weight loss to improvement in glycemia and other metabolic components [5, 6]. Here, we will use the terms metabolic and bariatric surgery interchangeably. Several observational studies and randomized controlled trials have evaluated metabolic surgery versus conventional treatment in different scenarios in patients with T2D, generally demonstrating superior glycemic control and higher remission rates in those patients submitted to surgery, as well as benefits in renal markers and reduced micro- and macrovascular events in observational data [7–12]. In this context, there is no doubt that metabolic surgery should be in the treatment algorithm of T2D and must be placed into context in guidelines. Its evidence should be analyzed, however, in the same way as for pharmacological treatments (although we acknowledge the difficulties of randomized controlled trials for surgical procedures) [13, 14]. On the one hand, many physicians who treat patients with diabetes have very little knowledge about bariatric surgery, the different procedures, long-term outcomes, and complications, and do not discuss seriously and profoundly this option with their patients [15]. On the other hand, many surgeons have little knowledge of the pathophysiology of T2D and clinical trials with pharmacotherapy, and this could lead to an indication of surgery for patients whose benefits would be limited [16, 17].

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This gap between endocrinologists and surgeons is easily perceivable in guidelines and other joint statements [13, 14, 18, 19]. Different articles, written by authors with different backgrounds, lead to very different recommendations.

Although this gap existed for a long-time, the recent COVID-19 pandemic helped to amplify it and to make it more discernible, as we can observe in the recent DSS recommendations for management of surgical candidates (both for obesity and T2D, but we will focus solely on the latter) and the prioritization of access to surgery in the COVID-19 era [18]. There is no doubt that, as elective surgeries were postponed amidst the crisis, an orderly restart with prioritizing criteria is imperative and there is much debate on whether bariatric surgery should be assigned merely as an elective procedure. As both diseases are associated with worse COVID-19 outcomes [20–22], restraining surgeries until the pandemics resolution can be counterproductive [23].

Nonetheless, the expert group defined the criteria for expedited surgery in individuals with T2D that was not based on the best evidence, and a regular patient suggested for prioritization would probably receive very different treatments, if evaluated by someone who generally reads diabetes guidelines, in which the evidences are much more balanced [14, 18].

A hypothetical case

Mr SPS is a 59-year-old male, with T2D diagnosed 10 years ago and a myocardial infarction 5 years ago (with a left coronary stent). His prescription includes: insulin degludec 20 IU once a day, metformin 2000 mg/day, and sitagliptin 100 mg/day. His HbA1c is 8.4%, eGFR of 55 ml/min/1.73 m^2, with microalbuminuria. His current BMI is 33.4 kg/m^2. He is well treated with regard to blood lipids, hypertension, and is in use of platelet antiaggregants. He was referred to two different endocrinologists. The first one, based on current ADA-EASD guidelines, recommended an SGLT2 inhibitor and considered the use of a GLP-1 agonist, if a good response is not achieved [14]. The second one, having read the recent DSS-II recommendation, recommended an expedited metabolic surgery [18]. How could a patient receive such different managements?

DSS-II statements and recommendations are only partially evidence-based and contradictory by themselves

The first coordinated document published regarding metabolic surgery in the treatment of T2D was the DSS-2 Joint Statement, which, undoubtedly, was a game changer, highlighting the importance for endocrinologists to recommend or at least consider metabolic surgery to their patients [13]. In this paper, metabolic surgery should be recommended for those with BMI of 40 kg/m^2 or more, or of 35 kg/m^2 or more, and poor glycemic control and should be considered for those with a BMI of 30–34.9 kg/m^2 with poor metabolic control.

The specific part of considering surgery for those with BMI less than 35 kg/m^2 and poor glycemic control was already the subject of our critique in another recent review [17]. Although we agree that there is no evidence that a clear BMI threshold exists and there are many other relevant factors (as diabetes duration, age, preoperative glycemic control, insulin use and beta-cell responsiveness, among others), it is clear from many studies that one of the main predictors of long-term glycemic response is postoperative weight loss, and individuals with lower BMIs tend to lose less weight [17, 24–27]. Surely, there is evidence on the literature about weight-independent effects of surgery on glycemic improvement, with increase in incretin hormones, biliary acids, and gut microbiota [6, 28, 29]. Nonetheless, there are studies that question the importance of those mechanisms to the overall glycemic response and point to a more direct effect of caloric restriction followed by weight loss and maintenance [17, 30–34]. In this context, the real contribution of weight-independent effects of surgery in diabetes remission and improvement is still an open question. DiRECT trial, for example, demonstrated that clinically induced caloric restriction in the first 6 years after diabetes diagnosis can lead to a high rate of diabetes remission, which is weight-dependent, and after 2 years, diabetes relapse after remission is predicted by the amount of weight gained [35, 36]. The great challenge of the DiRECT protocol is long-term weight maintenance, but the study serves as an excellent proof of concept of the dramatic effects of weight loss in glycemic control. The evidence is not as different as with surgery, in which shorter diabetes duration is associated with higher remission rates, the amount of weight loss predicts glycemic improvement and weight regain predicts relapse [7, 17, 24–27, 37]. Understanding that non-surgical weight loss programs can have a huge impact on glycemic outcomes is utterly important as we can offer those strategies for those in which surgery is not feasible, indicated, or desired [17, 33].

In this context, one of our concerns about recommending surgery for those with a BMI of less than 35 kg/m^2 is the low total number of individuals studied in RCTs and with longer follow-up. In 2016, after the release of the guideline, we pointed out in a letter that only about 70 patients with this lower BMI threshold performed RYGB in RCTs (the gold-standard metabolic procedure) with at least a 2-year follow-up [38]. Moreover, poor glycemic control (the criteria used by DSS-II to consider surgery for those with lower BMIs) as well as longer diabetes duration is associated with an impaired glycemic metabolic response after surgery [17, 26, 27]. In this context, an individual with a BMI lower than 35 kg/m^2 and poor glycemic control will probably be exactly the patients who would benefit less from the procedure [38].

One argument in favor of surgery even in those who would have a poorer glycemic response is the reduction in micro- and macrovascular complications, and even mortality, seen in many observational cohorts. However, the mean BMI on most of those studies was over 40 kg/m, ^{2} and there is evidence that lower BMI reduction after surgery is associated with reduced benefits [39–41].

In the DSS-II guideline, there is no mention of consideration or recommendation of surgery in individuals with established CVD, nor is there any mention of albuminuria or chronic kidney disease [13].

However, in the document recently published, concerning prioritization for bariatric surgery in the COVID-19 era, the criteria were changed [18]. If there was a group in the original DSS Joint Statement, in which MS should be “recommended” and another group that should be “considered,” the most obvious choice was to use these criteria to prioritize the first group. However, in the article, the characteristics that defined expedited access were very different: HbA1c > 8.0%, insulin use, history of CV disease, NASH, or two or more other metabolic conditions increasing CV risk, albuminuria or chronic kidney disease, and more than 5 years of diabetes. No BMI cutoff was provided.

Many of these criteria are associated with worse glycemic outcomes in the long term (higher HbA1c, longer diabetes duration, and insulin use, for example) [17]. Very limited data regarding long-term reduced micro- and macrovascular risk exist in those patients with a longer diabetes duration. In the SOS study, for example, only those with shorter diabetes duration—4 years—had reduced hard outcomes [40]. In the STAMPEDE trial, a less than 8-year duration of diabetes was associated with a fourfold increased odd of achieving the primary endpoint [7]. In that way, at least in those with hyperinsulinemia, or established T2D, it appears that “the earlier the better” and maybe there is a “window of opportunity”, in order to prevent beta-cell loss and probably atherosclerosis progression [33, 42, 43]. In this context, priority of those who are near the 8-year diabetes duration could be considered, but probably a maximal threshold should also be imposed. However, we acknowledge that there are still debate and open questions, as some recent meta-analyses and post hoc analysis paradoxically associated reduced mortality in bariatric surgery only in those with older mean age, and found increased mortality after surgery in those with diabetes younger than 43 years old [44, 45].

Among all those criteria, however, the most astonishing and non-evidence based is prior cardiovascular disease [18, 46]. Although there is a rationale to believing that surgery could be an option in this context, there are virtually no studies of secondary prevention of MS in T2D or even in non-T2D populations and concerns about increased perioperative risks exists [45–50]. Moreover, the perioperative risks of bariatric surgery are increasingly reducing, but are still higher in those with metabolic syndrome and T2D, and is expected that the risk would be greater in those with previous CVD [27, 51]. In the SOS study, only 1.5% of patients had a previous history of CV disease [47]. In some of the trials, such as the STAMPEDE, preceding CV disease was even an exclusion criterion [7, 52]. Early this year, in a retrospective study of nearly 7000 patients who performed BS for obesity, only 3.6% had previous CVD, and the rates of postoperative complications were significantly higher compared with those without CVD [48].

Nevertheless, this “standard patient,” who was considered to be prioritized, with previous CV events, HbA1c > 8%, and diabetes duration superior to 5 years is exactly the most widely studied, with regard to drug therapy and several options have emerged with cardiovascular protection, mainly GLP-1 agonists and SGLT2 inhibitors [51–55]. Many guidelines around the world have been changed in past years in order to incorporate all the new evidence of CVOTs [14, 19, 56, 57].

In the ADA/EASD guidelines and several guidelines from cardiology societies, the presence of CVD disease should lead to the prescription of a SGLT2 inhibitor and/or GLP-1 analog with proven cardiovascular benefits [14, 56, 57]. More than 30,000 and 40,000 patients with established CV disease were randomized in SGLT2 inhibitors and GLP-1 trials, respectively, in which a similar 14% reduction of the primary endpoint was observed [51–55]. Importantly, the main effect of those drugs seems to be independently related to glycemic control, and in many countries, they are labeled not only to reduce glycemia but also to reduce CV events. SGLT2 inhibitors also have a clinically relevant impact on hard renal outcomes [55].

In this context, someone who read the DSS recommendation could be puzzled: Should Mr. SPS, regardless of his baseline BMI, with CVD disease and high HbA1c, using insulin, be referred with priority for metabolic surgery or should he receive medications with proven CV benefits, as recommended by several different guidelines?

Unifying guidelines

Obesity guidelines written by clinicians and endocrinologists recognize bariatric surgery as the most effective and evidence-based treatment for class II and III obesity [3, 58, 59]. There is evidence of much superior weight loss compared with lifestyle changes or pharmacotherapy as well as reduced morbidity and mortality with different bariatric procedures [1, 2, 60, 61].

In the diabetes field, however, the acceptance of surgery in the treatment algorithm is still in early stages. Even the discussion of weight loss strategies has been neglected in guidelines for many years, despite the undisputable association of both diseases [33, 62, 63]. Fortunately, this has changed in the last years, but the discrepancies in recommendations by clinicians (mainly endocrinologists and cardiologists) and surgeons are still very clear [14, 18].

The last ADA-EASD guidelines highlighted the importance of weight loss in the management of T2D, which was a welcome inclusion compared with older guidelines [14, 64]. A small section was devoted to metabolic surgery, in which there was a recommendation of the procedure for those with a BMI higher than 40, or higher than 35 for those "who do not achieve durable weight loss and improvement in comorbidities with reasonable non-surgical methods" [14]. In the body of the text, there is a mention that surgery may be considered for those patients between 30 and 35 kg/m^2, in the same situation. In this guideline, differently from the DSS-II, the indication for class I obesity does not rely on glycemic control itself, but on weight loss and comorbidities, which seems more in line with the evidence [17]. Even so, diabetes duration, probably the most important factor regarding glycemic benefits, was omitted once again.

We believe that it is of particular importance for diabetes guidelines to have a longer section devoted to metabolic surgery and probably to invite some members of the original DSS-II to participate, in order to support the message. There is no doubt that MS is an excellent therapeutic approach, widely underused, with dramatic glycemic and non-glycemic benefits in those with T2D and probably reduced hard outcomes [5–7, 39]. However, the evidence should be evaluated in light of what exists, with regard to other potential clinical treatments.

In the same way, future guidelines focusing specifically on metabolic surgery should also include specialists in CVOTs with diabetes drugs, including endocrinologists, cardiologists, and nephrologists, in order to put all this information into context. Otherwise, the same patient, depending on whether seeing a doctor that has read a clinical or a surgical guideline, can receive very different therapies.

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Compliance with ethical standards

Conflict of interest BH received travel grants from Novo Nordisk and Aché Pharmaceuticals, received honoraria for lectures from Novo Nordisk, Eli Lilly, and Boehringer-Ingelheim, and is on the Advisory Board for Novo Nordisk and Eli Lilly. MCM received travel grants from Novo Nordisk, received honoraria for lectures from Novo Nordisk, EMS Pharmaceutical, and Eurofarma Pharmaceuticals, and is on the Advisory Board for Novo Nordisk.

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