



# Metabolic Surgery for Type 2 Diabetes: Changing the Landscape of Diabetes Care

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The accelerating pandemic of diabetes is recognized as one of the greatest global public health threats of our time (1). When one reviews the latest estimates for diabetes prevalence and projections worldwide, it is easy to appreciate the magnitude of the problem facing us not only today but also for generations to come. Given the microvascular and macrovascular complications associated with this disease, as well as the resulting morbidity and mortality, the personal, medical, and societal costs are enormous (2,3). In addition, despite continuing advances in diabetes pharmacotherapy, fewer than half of adults with type 2 diabetes mellitus (T2D) attain therapeutic goals designed to reduce long-term risks of complications, especially for glycemic control (4–6), and lifestyle interventions are disappointing in the long term (7). In facing these challenges, it is imperative that interventions that may interdict the disease process and complement existing therapies be expeditiously advanced into clinical practice while also balancing the costs attributed to each intervention.

This month's issue of *Diabetes Care* includes 11 articles that report the latest data supporting bariatric/metabolic surgery as a new treatment option in the management of T2D. In the centerpiece of this collection, Rubino et al. (8) report new evidence-based guidelines for surgical treatment of T2D, writing on behalf of 48 voting delegates (75% are nonsurgeons) of the 2nd Diabetes Surgery Summit (DSS-II), an international consensus conference organized in collaboration with major diabetes organizations. These recommendations, endorsed thus far by 45 international professional societies [see Table 1, Rubino et al. (8)], reflect a large body of evidence demonstrating that several gastrointestinal (GI) operations initially designed to promote weight loss (bariatric surgery) can improve glucose homeostasis more effectively than any known pharmaceutical or behavioral approach (9–24), causing durable remission in many patients with T2D (25,26). Formally ratified by an unprecedented array of societies representing diverse medical and surgical specialties from around the world, these new guidelines can serve as a global reference for the use and study of GI surgery as an intentional treatment option for T2D ("metabolic surgery") (8).

Interest in the use of metabolic surgery has been growing over the past decade, fueled by experimental evidence showing that rearrangements of GI anatomy similar to those in bariatric operations can directly affect glucose homeostasis, and not only through weight loss (27,28). Attempts to elucidate the exact mechanisms by which GI surgery ameliorates T2D have implicated changes in gut hormones, bile acid metabolism, intestinal nutrient sensing and metabolism, gut microbiota, and other factors (27–37). On the basis of such biological and clinical evidence, the first Diabetes Surgery Summit (DSS-I), held in Rome, Italy, in 2007, recognized the legitimacy of studying surgery as a treatment for T2D, encouraging randomized clinical trials (RCTs) to compare surgery versus various medical/lifestyle interventions head to head (28,38). Since DSS-I, RCTs have consistently demonstrated that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors in obese patients with T2D compared with various medical/lifestyle interventions (9–24).

However, despite recent obesity recommendations to expand the use of bariatric surgery in people with T2D (39), until now, surgery has not been considered as a common option. Consequently, most diabetes care providers and patients with the disease are inadequately informed about the indications, benefits, and limitations of metabolic surgery.

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The new guidelines provide much needed guidance for general practitioners, endocrinologists, and diabetes specialists about the use of metabolic surgery in the treatment of obese patients with T2D (8). Compared with previous guidelines for bariatric surgery (40), which used only BMI thresholds to select surgical candidates, the DSS-II recommendations introduce the use of diabetes-related parameters to help identify clinical scenarios where surgical treatment of T2D should be prioritized. In addition to helping clinicians select surgical candidates, the recommendations from DSS-II also inform the preoperative workup and postoperative follow-up of patients undergoing metabolic surgery for T2D.

The report from DSS-II in this issue of *Diabetes Care* reflects the most comprehensive and rigorous assessment of the available evidence on the subject to date, provides a thorough analysis of current knowledge gaps in the field, and identifies priorities for research designed to further refine the role of surgery in the diabetes management algorithm.

Recognizing the need to inform diabetes care providers about the rationale, mechanisms, outcomes, and cost-effectiveness of surgical treatment for T2D, this month's issue of *Diabetes Care* features the latest data on metabolic surgery. The topics range from an overview of the global burden of the disease to mechanisms by which surgery might improve glucose control, effects on micro- and macrovascular complications, and ethnic considerations in evaluating response. In addition, special populations for metabolic surgery (individuals with BMI <35 kg/m<sup>2</sup>, type 1 diabetes [T1D], and adolescents) are considered. This collection derives from a selection of themes presented at the joint 3rd World Congress on Interventional Therapies for Type 2 Diabetes and the DSS-II, held in September 2015 (8,41–50).

To put perspective on the global epidemic, Zimmet and Alberti (41) provide an eloquent narrative on the burden of diabetes. Specifically, they suggest that extant epidemiological data predict “an inexorable and unsustainable increase in global health expenditure attributable to diabetes” and stress the need for prevention. In addition, they make the case that future research must be aimed at important emerging factors,

such as the maternal environment and other early-life contributors, and changing trends in global demography to help design prevention programs. They also emphasize that, at this time, we all need a better understanding of the role of metabolic surgery in not only helping to optimize the management of patients with T2D but also addressing individuals at higher risk, particularly in developing nations. Unfortunately, these areas of the world suffer enormous disease burden but currently lack the resources to even consider surgery as a treatment option for T2D.

One of the many issues that remains unanswered for metabolic surgery pertains to the exact mechanisms of action. Specifically, we now recognize that postoperative improvements in metabolic control occur rapidly and out of proportion to weight loss, yet the physiological and molecular mechanisms underlying these beneficial glycemic effects remain incompletely elucidated. To address this dilemma, we feature two narratives in this issue of *Diabetes Care* that provide further mechanistic insights into metabolic surgery. Holst et al. (42) provide a very focused overview of the underlying mechanisms by which the GI tract helps regulate postprandial glucose profiles. Specifically, they discuss the intrinsic factors along with the metabolic, endocrine, and neural signals generated by the gut or associated with vagal activity to influence secretion of gut hormones that modulate postprandial glucose excursions (i.e., incretins). In the second article featuring mechanisms, Batterham and Cummings (43) review existing concepts regarding how metabolic surgery exerts its effects on T2D. They provide evidence to demonstrate that metabolic surgical procedures such as Roux-en-Y gastric bypass and vertical sleeve gastrectomy increase circulating levels of glucagon-like peptide 1, bile acids, and fibroblast growth factor 19, while also altering intestinal nutrient sensing, absorption, and metabolism, and the gut microbiome. The authors opine that these changes contribute to the anti-diabetes effects of surgery, along with well-known secondary consequences of weight loss (43).

Before we can fully appreciate the role of metabolic surgery in becoming a readily available, viable option in our treatment algorithm and expand the appropriate

candidate pool, we need to fully understand the efficacy, complications, long-term clinical outcomes, and costs. In particular, it will be important to clarify the financial implications to patients, providers, and insurers (both private and government sectors) and to appreciate that these barriers may be too hard to overcome in resource-poor areas of the world. Although we have excellent short- to medium-term level 1 evidence (up to 5 years) regarding the impact of metabolic surgery compared with medical/lifestyle interventions for glycemic control and weight loss, there is a paucity of long-term outcomes data from RCTs relating to microvascular and macrovascular complications. Published reports on such outcomes are currently limited to observational studies and non-randomized clinical trials. In this issue, we present two articles related to the assessment of outcomes. Schauer et al. (44) review the evidence to date regarding glycemic control, weight loss, and complications resulting from metabolic surgery. Adams et al. (45) follow this review and provide relevant background information regarding the overall management of diabetes and related complications. They also discuss research focusing on long-term vascular outcomes associated with bariatric/metabolic surgery. Both articles provide the latest data required to fully understand the clinical effects and modulation of disease processes resulting from metabolic surgery.

Other areas addressed in this special collection involve expanding the use of metabolic surgery to populations that have traditionally not been considered candidates according to older recommendations. For example, as stated by Cummings and Cohen (46), consideration of bariatric surgery has been essentially dictated for the past 25 years by National Institutes of Health recommendations that suggested these operations be restricted to individuals with BMI  $\geq$ 35 kg/m<sup>2</sup> (40). However, arguments are now being made that because baseline BMI does not predict surgical benefits on glycemia or hard outcomes (51) and because bariatric procedures markedly improve T2D and promote remission in part through weight-independent mechanisms (29,43) appropriate candidates for metabolic surgery might indeed include individuals with T2D and BMI <35 kg/m<sup>2</sup>. Thus, given the review

of data in their article, the authors suggest that the existing evidence supports “new guidelines from the 2nd Diabetes Surgery Summit that advocate for the consideration of bariatric/metabolic surgery as one option, along with lifestyle and medical therapy, to treat T2D among patients with a BMI <35 kg/m<sup>2</sup>” (46). Other populations for whom bariatric/metabolic surgery has been proposed also include adolescents with T2D and patients with T1D. For example, Shah et al. (47) provide comment that increasing interest in consideration of bariatric/metabolic surgery for adolescents with T2D has occurred in large part due to evidence for the efficacy and benefits demonstrated in adult subjects with T2D. In their article, they provide a nice overview of the concerns regarding T2D in youth and discuss the outcomes and complications of bariatric/metabolic surgery in adolescents. In addition, Kirwan et al. (48) reviewed 17 publications—10 case series and 7 case reports—where bariatric surgery was performed in individuals with T1D and severe obesity. They report that surgery provided many benefits (substantial weight loss and significant improvements in insulin requirements and glycemic status) in these studies and suggest that “short-term results of bariatric surgery in patients with T1D are encouraging, but larger and longer-term studies are needed” (48).

Other considerations for bariatric/metabolic surgery presented in this collection include a discussion of the efficacy of metabolic surgery based on ethnicity. In this regard, Morton (49) comments that because the burden of obesity and diabetes vary depending on ethnicity, there may be differences regarding indications and outcomes for different ethnic groups following metabolic surgery. He suggests that “while there appears to be evidence for variation in weight loss and complications for different ethnic groups, comorbidity remission, particularly for diabetes, appears to be free of ethnic disparity following metabolic surgery” (49).

The last issue considered in this special collection is one that involves a discussion of conceptual and practical barriers to the appropriate use of bariatric/metabolic surgery. Thus, Rubin et al. (50) provide the summary report of a Policy Lab hosted at the 3rd World

Congress on Interventional Therapies for Type 2 Diabetes on 29 September 2015. Despite increasing recognition of the efficacy, safety, and cost-effectiveness of metabolic surgery, significant barriers to appropriate use of surgical procedures still prevent access to surgery for those who need it. They identify four “building blocks” to facilitate policy changes, as follows: “1) communicating the scale of the costs and harms associated with rising prevalence of type 2 diabetes, 2) properly articulating the role of bariatric/metabolic surgery for certain population groups, 3) identifying new funding sources for bariatric/metabolic surgery, and 4) incorporating surgery into the appropriate clinical pathways” (50). Even from the perspectives of the U.K. and the U.S., where studies have concluded that metabolic surgery has a very high likelihood of being cost-effective for people with T2D, the “up-front” costs of metabolic surgery were recognized as representing a challenge to limited health care budgets. These costs must, however, be carefully weighed against the current and future costs of T2D.

As can be appreciated, the present issue of *Diabetes Care* provides the most comprehensive and up-to-date collection of articles dealing with metabolic surgery. The area has grown tremendously in recent times, and the evidence for the benefits of metabolic surgery has outpaced guidelines regarding appropriate candidates. As in the past, *Diabetes Care* remains extremely honored to be the journal to host these articles and to disseminate the latest research that may improve care for our patients. These publications go a long way to providing guidance on current clinical care and informing the next steps for research in this area. The global diabetes burden is enormous, and as a medical community, we do not have the answers at this time to fully address the issue on a worldwide basis. However, it is an exciting time for those of us in diabetes research, and the ability to be part of a paradigm change in the understanding, approach, and management of the disease will keep us focused on the next steps to address the larger issue of prevention. Until then, it will continue to be the charge of *Diabetes Care* to provide the latest and most up-to-date information.

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