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FIELD OF VISION

Bariatric surgery as a treatment option in patients with type 2 diabetes mellitus

Marianna Spanou, Konstantinos Tziomalos

Marianna Spanou, Konstantinos Tziomalos, First Propedeutic Department of Internal Medicine, Medical School, AHEPA Hospital, Aristotle University of Thessaloniki, 54636 Thessaloniki, Greece
Author contributions: Spanou M drafted the paper; Tziomalos K revised the draft critically for important intellectual content.
Correspondence to: Konstantinos Tziomalos, MD, PhD, First Propedeutic Department of Internal Medicine, Medical School, AHEPA Hospital, Aristotle University of Thessaloniki, 1 Stilponos Kyriakidi street, 54636 Thessaloniki, Greece. ktziomalos@yahoo.com
Telephone: +30-2310-994621 Fax: +30-2310-994773
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Abstract

Type 2 diabetes mellitus (T2DM) is a leading cause of blindness, non-traumatic amputation and end-stage renal disease as well as a major cardiovascular risk factor. Tight glycemic control reduces the incidence of microvascular complications of T2DM whereas its effects on macrovascular complication are more controversial. However, glycemic targets are achieved by a minority of diabetic patients despite the availability of several antidiabetic agents. In the present commentary, we discuss the findings of two recent randomized studies that compared bariatric surgery with medical treatment in patients with uncontrolled T2DM. Both studies showed that bariatric surgery results in remission of T2DM in the majority of patients. However, both studies were limited to relatively young patients without comorbidities, had relatively short follow-up and did not assess the effects of surgery on T2DM complications. Moreover, the perioperative complications of bariatric surgery and its limited availability in some areas are additional barriers to the wider implementation of this therapeutic approach. On the other hand, the elucidation of the mechanisms underpinning the resolution of T2DM following bariatric surgery might result in the development of novel, more effective pharmacotherapies for this common disease.

Key words: Type 2 diabetes mellitu; Bariatric surgery; Roux-en-Y gastric bypass; Biliopancreatic diversion; Sleeve gastrectomy; Adjustable gastric banding

Core tip: In the present commentary, we discuss the findings of two recent randomized studies that compared bariatric surgery with medical treatment in patients with uncontrolled type 2 diabetes mellitus (T2DM). Both studies showed that bariatric surgery results in remission of T2DM in the majority of patients. However, both studies were limited to relatively young patients without comorbidities, had relatively short follow-up and did not assess the effects of surgery on T2DM complications.

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COMMENTARY ON HOT TOPICS

Type 2 diabetes mellitus (T2DM) has become a global epidemic in the recent decades[1]. Diabetes mellitus affects 346 million people worldwide and T2DM accounts for 90% of the cases[1]. Moreover, T2DM is a leading cause of blindness, non-traumatic amputation and end-stage renal disease as well as a major risk factor for cardiovascular disease[1].

Tight glycemic control reduces the risk for the microvascular complications of T2DM whereas its effects on macrovascular complications are more controversial[2-8].

Methods to achieve glycemic control include lifestyle changes (diet and exercise) and pharmacotherapy with either oral or injectable agents, the latter primarily including insulin[9]. However, glycemic control progressively deteriorates during treatment with oral agents in the majority of patients as a result of the progressive decline in insulin secretion from pancreatic beta cells[10]. In addition, glycemic targets are achieved by a small minority of patients even in specialist centers[11,12]. Moreover, tight glycemic control is associated with increased risk for hypoglycemia and weight gain, resulting in decreased adherence to treatment, which in turn further worsens glycemic control[5-8]. In turn, suboptimal glycemic control is associated with increased risk for complications, particularly nephropathy and retinopathy[2,4,5].

Given the limited efficacy of existing antidiabetic agents in achieving glycemic targets, bariatric surgery has been evaluated for the management of severely obese patients with T2DM and yielded promising results in uncontrolled studies[13]. Recently, two studies compared bariatric surgery with medical treatment in patients with uncontrolled T2DM[14,15]. In the first study, Mingrone *et al*[14] evaluated two types of bariatric surgery, laparoscopic Roux-en-Y gastric bypass and open biliopancreatic diversion, in patients 30-60 years-old with a body mass index (BMI) $\geqslant$ 35 kg/m^2, who had T2DM for $\geqslant$ 5 years and hemoglobin A1c (HbA1c) levels $\geqslant$ 7%. Patients with type 1 diabetes mellitus, severe diabetes complications, other severe medical conditions or previous bariatric surgery were excluded from the study[14]. Sixty patients were randomly assigned into three treatments: Roux-en-Y gastric bypass, biliopancreatic diversion and medical treatment (lifestyle modification, oral hypoglycemic agents and/or insulin)[14]. The primary endpoint was the rate of remission of T2DM at 2 years, defined as fasting plasma glucose levels < 100 mg/dL (5.6 mmol/L) and HbA1c levels < 6.5% for at least 1 year without pharmacologic treatment[14]. Diabetes remission was achieved at 2 years in 75 and 95% of patients who had undergone gastric bypass and biliopancreatic diversion, respectively. None of the patients assigned to medical treatment achieved T2DM remission ($P < 0.001$ *vs* both surgery groups)[14]. Age, sex, baseline BMI, diabetes duration and weight change did not predict T2DM remission[14]. Weight loss was similar in the two surgical groups (approximately 33%) and smaller in the medical treatment group (4.7%)[14]. Regarding other cardiovascular risk factors, serum low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels showed a similar reduction in the medical treatment and gastric bypass groups but decreased more in the biliopancreatic diversion group[14]. In contrast, serum high density lipoprotein cholesterol (HDL-C) levels showed a similar increase in the medical treatment and biliopancreatic diversion groups but increased more in the gastric bypass group[14]. Blood pressure (BP) decreased and the number of antihypertensive agents was reduced to a comparable extent in the three groups[14].

In the second study, Schauer *et al*[15] compared intensive medical treatment alone and intensive medical treatment combined with either laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy in 150 patients 20-60 years old with a BMI between 27 and 43 kg/m^2, and with HbA1c levels > 7%. Patients with uncontrolled medical or psychiatric disorders or previous bariatric or complex abdominal surgery were excluded from the study[15]. The primary endpoint, the rate of patients with HbA1c levels $\leqslant$ 6% at 12 mo with or without antidiabetic medications, was achieved in 42% of patients who underwent gastric bypass, in 37% of patients who underwent sleeve gastrectomy and in 12% of patients in the medical treatment group ($P = 0.002$ and $P = 0.008$ for the comparison between medical treatment with gastric bypass and sleeve gastrectomy, respectively)[15]. Age, baseline BMI, diabetes duration and use of insulin did not predict the primary outcome[15]. Percentage weight loss was greater with gastric bypass than with sleeve gastrectomy (27.5% and 24.7%, respectively; $P = 0.02$) whereas patients assigned to medical treatment lost less weight (5.2%; $P < 0.001$ *vs* both surgical groups)[15]. In both surgical groups, serum high sensitivity C-reactive protein levels decreased and HDL-C levels increased compared with the medical treatment group[15]. In contrast, serum TG levels decreased only in the gastric bypass group compared with the medical treatment group[15]. Serum LDL-C levels and BP did not differ among groups after 12 mo but the use of lipid-lowering and antihypertensive medications declined significantly only in the surgical groups[15].

Overall, both studies suggest that bariatric surgery is more effective in achieving glycemic control than medical treatment and results in T2DM remission (*i.e.,* no need for antidiabetic medications) in a sizeable proportion of patients[14,15]. The higher remission rates in the study by Pournaras *et al*[16] might be due to differences in operative technique and the less stringent criteria for defining remission, the longer follow-up or the shorter duration of T2DM; on the other hand, the smaller sample size suggests the possibility of a type 1 statistical error[14,15]. In both studies, other cardiovascular risk factors, including dyslipidemia and hypertension, also improved substantially after bariatric surgery[14,15]. Importantly, the benefits of bariatric surgery appeared to be independent of the preoperative BMI[14,15] and, in the study by Schauer *et al*[15], to apply not only to patients with BMI > 35 kg/m^2 but also to those with BMI 27-35 kg/m^2. This finding suggests that current recommendations that propose bariatric surgery only for patients with T2DM with BMI > 35 kg/m^2 might need to be modified[17]. The benefits of bariatric surgery were also independent of age (within the age range of 20-60 years-old)[14,15]. Diabetes remission rates were also independent of diabetes duration[14,15] whereas previous retrospective studies reported that patients with longer-lasting T2DM show lower rates of T2DM resolution after bariatric surgery[18]. Therefore, this finding should be interpreted with caution because both studies were rather small and probably underpowered to detect an association between T2DM remission rates and dia-

betes duration[14,15] and also because the variability of T2DM duration was very small in the study by Mingrone *et al*[14] (mean duration, 6.0 ± 1.1 years). The findings of these trials are in agreement with previous uncontrolled studies that reported resolution of T2DM in 65%-83% of patients[13,18-22] and with a smaller study in 60 diabetic patients with BMI 30-40 kg/m^2 where laparoscopic adjustable gastric banding and medical treatment resulted in T2DM remission in 73% and 13% of patients, respectively[23]. In addition, these benefits add to the other positive effects of bariatric surgery including remission of other obesity-associated comorbidities such as hypertension, dyslipidemia, metabolic syndrome, chronic kidney disease, left ventricular hypertrophy, non-alcoholic fatty liver disease and obstructive sleep apnea[24,25]. Preliminary data from uncontrolled studies also suggest a reduction in cancer rates following bariatric surgery[26,27]. Bariatric surgery also appears to reduce the risk of T2DM in obese patients[28]. However, it should be noted that other studies did not show a beneficial effect of bariatric surgery on obesity-related comorbidities, including non-alcoholic fatty liver disease and obstructive sleep apnea[29,30].

Is therefore bariatric surgery an alternative option for patients with T2DM? Probably not yet, for both medical and logistic reasons. First, bariatric surgery is infrequently associated with both short- and long-term complications, including mortality, even in experienced centers[31]. In the two described studies, there were no perioperative deaths but 6 patients (4.3%) required reoperation[14,15]. However, these studies were small, had a relatively short-term follow-up and were performed in experienced centers[14,15]. Perioperative mortality rates of bariatric surgery range between 0.10% and 0.35%[31]. Non-fatal perioperative complications, including anastomotic and staple line leaks, wound infections, pulmonary embolism and hemorrhage occur at higher rates (1.7%-3.1%) even though they are progressively becoming less frequent, mainly as a result of higher hospital volumes[32,33]. Second, it is still unclear whether bariatric surgery reduces cardiovascular events, even though uncontrolled studies suggested a cardiovascular morbidity and mortality benefit[26,34,35]. Third, existing randomized studies excluded patients with comorbidities and those older than 60 years, who constitute the majority of patients with T2DM[14,15]. Finally, the lack of experienced surgeons in many areas and the cost of bariatric surgery are additional barriers to the wider implementation of this treatment, even though the cost of bariatric surgery might compare favorably with the costs of the lifelong management of diabetes and of its micro- and macrovascular complications[36-38].

In conclusion, bariatric surgery might be considered in relatively young patients with uncontrolled T2DM despite adequate pharmacological treatment, without comorbidities, and with BMI > 35 kg/m^2. Current guidelines state that bariatric surgery may be considered for adults with BMI ⩾ 35 kg/m^2 and T2DM, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy (level of evidence B)[17]. They also state that there is currently insufficient evidence to generally recommend surgery in patients with BMI < 35 kg/m^2 outside of a research protocol (level of evidence E)[17]. Even though existing guidelines do not mention specific contraindications for bariatric surgery, it is clear that the risk of peri- and postoperative complications should be balanced against the benefits of bariatric surgery[17]. However, given the high and rising prevalence of T2DM as well as the lack of long-term data on safety and efficacy of bariatric surgery, this treatment will probably have limited impact on the T2DM epidemic. On the other hand, weight loss cannot entirely explain the beneficial effects of bariatric surgery because these occur soon after the operation and before maximum weight loss is achieved[13-15]. Changes in the bioavailability of gut hormones, fat malabsorption and improvement of insulin resistance might also play a role[39-45]. In contrast, the exclusion of proximal small intestine does not appear to contribute to the improvement in glucose homeostasis[45]. On the other hand, accumulating data suggest that newer classes of antidiabetic agents, including thiazolidinediones and incretin-based agents, might delay the decline in beta cell function by alleviating glucolipotoxicity[46]. Recent data suggest that bariatric surgery also has a beneficial effect on beta cell function[44]. The extensive discussion of the mechanisms involved in the remission of T2DM after bariatric surgery is beyond the scope of this commentary; several comprehensive reviews on the topic have been published recently[47,48]. The elucidation of the pathophysiologic mechanisms underpinning the resolution of T2DM and other obesity-associated comorbidities after bariatric surgery might lead to the development of novel and more effective pharmacotherapies for these common diseases.

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