Timing of bariatric surgery in people with obesity and diabetes

Review Article

Timing of bariatric surgery in people with obesity and diabetes

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Abstract: The use of bariatric surgery in the clinical management of type 2 diabetes in severely obese subjects has been included in the clinical practice recommendations released by the most influential diabetologic associations. However, the timing during the diabetic course in which this use may have the better benefit/risk ratio remains debated. Is it better to use surgery very early in the course of the disease in order to anticipate clinical deterioration, or we should favour a delayed approach in which we reserve the more risky surgery only to patients not adequately controlled with the maximal pharmacologic strategy? In this paper, past and recent evidences about the role of bariatric surgery in the different stages of the clinical course of type 2 diabetes have been revised, starting from pre-diabetes and ending to long-standing diabetic state with established or end-stage macro- and micro-vascular complications. Available evidences strongly advocate in favor of the application of bariatric surgery in the early phase of this course, possibly in the pre-diabetic or in very early diabetic stages. To reserve surgery to more advanced and complicated stages of the disease seems to confer less benefits for the clinical course of diabetes and exposes these more frail patients to the possible side effects of a rapid weight loss.

Keywords: Bariatric surgery; metabolic surgery; type 2 diabetes

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The prevalence of type 2 diabetes is rapidly increasing worldwide, fuelled by the obesity epidemic, and type 2 diabetes constitutes now a major health and economic burden for many countries and health systems. Weight loss, achieved through reduction of energy intake and increased physical activity via lifestyle modification, is the cornerstone in the treatment of type 2 diabetes and in its prevention in high-risk populations (1). However, particularly in patients with severe obesity, weight loss is difficult to obtain and sustain with lifestyle changes alone (2). At the moment, bariatric surgery is the most effective weight loss strategy in patients with severe obesity and its use is recommended in adults with BMI >35 kg/m^2 and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy (1,3).

Type 2 diabetes is a chronic disease with a very long medical history (*Figure 1*). Diagnosis of type 2 diabetes usually follows a long asymptomatic pre-diabetic phase characterized by impaired fasting glucose or impaired glucose tolerance. As overt hyperglycaemia occurs, the pathologic processes leading to macro- and micro-vascular complications starts to accumulate, mainly driven by the level of glycaemic control and by the coexistence of other cardiovascular risk factors. Ultimately, macro- or micro-vascular major events will occur, causing patient death or disability. Weight loss produced by bariatric surgery may help to halt or to slow this clinical course, but may also cause additional arms and complications (1). As mentioned above, current guidelines endorse the application of bariatric procedures to the severe obese diabetic patients (1), but the timing during the diabetic course in which this application may have the better benefit/risk ratio remains debated. Is it better to use surgery very early in the course of the disease in order to anticipate clinical deterioration, or we should favour a delayed approach in which we reserve the more risky surgery only patients not adequately controlled with the maximal pharmacologic strategy? The International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention of Diabetes first attempted to answer this relevant clinical question in 2011 (4). According to IDF experts, while the indications for bariatric surgery typically classify those who are eligible for surgery,

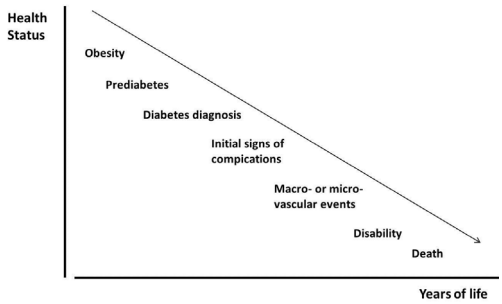

Figure 1 Clinical course of type 2 diabetes. Diagnosis of type 2 diabetes usually follows a long asymptomatic pre-diabetic phase. Overt time, macro- and micro-vascular complications starts to accumulate until major macro- or micro-vascular events will occur, causing disability and/or death.

Table 1 Effects of bariatric surgery at the different stages of the clinical course of type 2 diabetes

Stage of type 2 diabetes	Effects of bariatric surgery
Prediabetes	Well documented, highly significant reduction of new cases of type 2 diabetes (5,6)
Recently onset type 2 diabetes	Well documented high potential for diabetes remission (7-10); documented reduction in the incidence of macro- and micro-vascular complications (11,12)
Type 2 diabetes with initial macro- and micro-vascular complications	Possible regression of macro- and micro-vascular complication suggested in some study (13,14)
Type 2 diabetes with established end-stage macro- or micro-vascular complications	No regression and in some cases progression of micro-vascular complications (diabetic nephropathy and retinopathy) (14,15); no gain in survival (16)

recommendations for surgical referral as best practice or prioritization has not been widely considered. Working on this framework, the IDF suggested the consideration for bariatric treatment for severely obese patients (BMI >40 kg/m^2) with type 2 diabetes not adequately controlled by lifestyle measures and metformin. Less severe obese diabetic patients (BMI 35-40 kg/m^2) should be eligible for surgery, and may be prioritized if they have poorly controlled diabetes despite fully optimized conventional therapy, especially if their weight is increasing or other weight responsive comorbidities (blood pressure, dyslipidemia and obstructive sleep apnoea) are not achieving targets on conventional therapy (4). This position may be reasonable, but it did not incorporate some recent relevant publication.

In this paper, new evidences about the effectiveness of bariatric surgery in the prevention and management of type 2 diabetes in obese patients will be briefly reviewed (*Table 1*) and some consideration on the more appropriate timing for bariatric surgery in the diabetic course will be developed.

The role of weight loss in type 2 diabetes: lessons from lifestyle studies

Two large seminal randomized control trials tested the efficacy of lifestyle modification programs for the prevention of type 2 diabetes in high-risk populations (17,18). In both the Finnish Diabetes Prevention Study (17) and the Diabetes Prevention Program (DPP) (18), overweight or obese patients with impaired glucose tolerance were assigned to standard care or to an intensive lifestyle intervention with specific dietary and physical activity goals, including the achievement and maintenance of a 5-7% weight loss. Despite the fact that only 40-50% of the patients achieved predefined weight loss levels and that weight regain was observed, a significant 58% reduction in the 4-year incidence of type 2 diabetes was achieved in both studies (5,6). Moreover, a prolonged protective effect of lifestyle modifications on diabetes was observed years after the termination of the trials, when most of the effects of the intervention program on body weight were no longer evident (19,20).

The Look AHEAD study was a very large RCT that examined the effects of an intensive lifestyle intervention on the incidence of major cardiovascular disease (CVD) events in overweight or obese individuals with type 2 diabetes (21). Patients were assigned to conventional diabetes support and education or to an intensive lifestyle intervention program with a 10% weight loss goal. Participants in the intensive lifestyle intervention lost an average of 8.6% of initial body weight in the first year of the study and maintained a mean weight loss of 4.7% after 4 years (2). This moderate but sustained weight loss was associated to improvements in fitness, glycemic control, and CVD risk factors (2) and to very small rates of complete diabetes remission (22). However, the National Institutes of Health decided to halt prematurely the Look AHEAD trial because of a failure to achieve a significant reduction in the occurrence of

cardiovascular events in the intervention group (23).

Even if we accept that a moderate weight loss is beneficial in overweight and obese patients with pre-diabetes (17,18) and overt diabetes (2), recent evidences seem to suggest that this may not be the case in selected diabetic groups. The relationship between weight change and mortality was investigated in a post-hoc analysis of data from the PRO active study, a randomized, double-blind, placebo-controlled trial investigating the effect of pioglitazone on mortality and cardiovascular events in patients with type 2 diabetes and pre-existing cardiovascular co-morbidity. Surprisingly, weight loss during the study was associated with increased, and not reduced, total and cardiovascular mortality (24). Results from a post-hoc analysis should be interpreted cautiously, but we cannot exclude the possibility that weight loss may confer more harm than benefits in patients with advanced diabetic course and established complications, as suggested in other advanced chronic disease, like heart failure (25) or end-stage renal disease (26).

Prevention of type 2 diabetes by bariatric surgery

The potential of bariatric surgery in preventing the occurrence of type 2 diabetes in severely obese patients has been investigated in the seminal Swedish Obese Subjects (SOS) study, the first long-term, prospective, controlled long-term trial providing information about the effects of surgically induced weight loss on the incidence of diabetes, CVD events, cancer and overall mortality (5). The SOS study involved 2,010 obese subjects who underwent various bariatric procedures and 2,037 contemporaneously matched obese control subjects receiving usual care. In a recent update, bariatric surgery (as compared with usual care) reduced the risk of developing type 2 diabetes by 96%, 84% and 78% after 2, 10 and 15 years respectively (6). Interestingly, baseline BMI did not predict the diabetes preventive effect of bariatric surgery and the preventive effect is demonstrable also in the fraction of SOS patients having a baseline BMI below the current cut-offs of surgical eligibility (BMI <35 kg/m^2) (5). By contrast, as compared with normal fasting glucose, impaired fasting glucose at baseline was associated with a more pronounced diabetes preventive effect of bariatric surgery (5). NNT (Number Needed to Treat) to prevent one diabetes case over 10 years was only 1.3 in patients with pre-diabetes as compared to 7.0 in patients with normal fasting glucose (5). These results strongly claim in favor of the use of bariatric surgery in the prevention of type 2 diabetes in obese subjects, particularly in patients with a high diabetic risk and largely irrespective from BMI values.

Predictors of diabetes remission after bariatric/metabolic surgery

Since the pioneering reports of the last decade of 20th century (27,28), the efficacy of bariatric procedures in improving and even normalizing glucose levels in obese patients with type 2 diabetes has been confirmed by a large number of observational studies (29). More recently, four randomized controlled trials (7-10) confirm the superiority of bariatric surgery in respect to conventional therapy for the induction of type 2 diabetes remission. Dixon *et al.* firstly randomized patients with BMI ranging from 30 to 40 kg/m^2 and recent type 2 diabetes (less than 2 years from diagnosis) to laparoscopic adjustable gastric banding or to a program of conventional therapy with a specific focus on weight loss. After a 2-year follow-up, remission of type 2 diabetes was achieved by 73% of the patients in the surgical group and 13% in the conventional-therapy group (7). Schauer *et al.* randomized obese patients (BMI range 27-43 kg/m^2) with uncontrolled type 2 diabetes to intensive medical therapy alone *vs.* medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary end point of the study was the proportion of patients with a glycosylated haemoglobin level ≤6.0% 12 months after treatment. The proportion of patients achieving the primary end point was 12% in the medical therapy group *vs.* 42% in the gastric-bypass group and 37% in the sleeve-gastrectomy group. Surgical arms were both superior to medical therapy in terms of glycaemic control and weight loss (8). Mingrone *et al.* randomly assigned patients with a BMI >35 kg/m^2, a history of at least 5 years of diabetes, and a glycosylated haemoglobin level ≥7.0% to receive conventional medical therapy or undergo either gastric bypass or bilio-pancreatic diversion. At 2 years, diabetes remission occurred in no patients in the medical-therapy group *vs.* 75% in the gastric bypass group and 95% in the bilio-pancreatic diversion group (9). Finally, Ikramuddin *et al.* randomized patients with type 2 diabetes and BMI ranging from 30 to 40 kg/m^2 to intensive lifestyle-medical management and Roux-en-Y gastric bypass or intensive lifestyle-medical management alone. Main outcome of the study was a composite goal of glycosylated haemoglobin less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mmHg. After 12 months, 49% of the patients in the gastric bypass group

and 19% in the lifestyle-medical management group achieved the primary end point (10). Comparisons between these four studies are made difficult by the differences in inclusion criteria, applied procedures and outcomes definitions, but the general message is that bariatric/metabolic surgery in diabetic patients with BMI >30 kg/m^2 is always superior to the best lifestyle and pharmacologic approaches in improving metabolic control or inducing type 2 remission.

Bad news from randomized studies are that, even in the best clinical conditions or by using the most metabolically effective procedures, still some diabetic patients remain who did not achieve diabetes remission or improvement after surgery. Several factors have been proposed as positive or negative predictors of diabetes remission, but the more consistent one was diabetes duration. A shorter history of diabetes has been found to be associated to a greater chance of diabetes remission after any type of bariatric procedure (30,31). This latter observation may be expected, given that progressive deterioration of beta-cell function driven the progression from glucose intolerance to overt hyperglycemia. If the bariatric procedure is performed before irreversible beta-cell failure has occurred, then a higher likelihood of long-term remission may be expected. This observation further supports the IDF proposal claiming for a consideration for bariatric treatment very early in the therapeutic algorithm, in obese patients with type 2 diabetes not adequately controlled by lifestyle measures and metformin (4).

The diabetic patients with advanced disease and complications

The SOS study was the first controlled intervention trial to demonstrate that weight loss in obese subjects was associated to a reduction of major cardiovascular events (11). Combining stroke and myocardial infarction, both fatal cardiovascular events and first total cardiovascular events were significantly less frequent in the surgical than in the control group (11). These results were observed in general severely obese population and not specifically in obese patients with type 2 diabetes. However, one of the more interesting aspects of the SOS study was that both in the surgical group and in the control group the rate of cardiovascular events were not related to the baseline BMI, but to the fasting insulin baseline levels. Most of the difference in the events rate between surgical and control group was observed in the most hyperinsulinemic patients (11). This seems to suggest that a particular preventive effectiveness on macro-vascular events should be expected in patients with type 2 diabetes.

The SOS study remains the only prospective controlled trial on major outcomes after bariatric surgery, but the rates of macro- and micro-vascular events observed in patients with type 2 diabetes having had a bariatric procedure (2,580 cases) or not having had bariatric surgery (13,371 cases) have been recently analyzed retrospectively, by using a large administrative health database (12). Major outcomes evaluated in this study were the first occurrence of any macro-vascular (myocardial infarction, stroke, or all-cause death) or microvascular event (new diagnosis of blindness, laser eye or retinal surgery, non- traumatic amputation, or creation of permanent arteriovenous access for haemodialysis), assessed in combination and separately, as well as other vascular events (carotid, coronary or lower extremity revascularization or new diagnosis of congestive heart failure or angina pectoris). Having had a bariatric procedure was associated with a lower risk of any vascular event (combined outcome), any macro-vascular event, any micro-vascular event or any other vascular event. Authors concluded that bariatric surgery was associated with a 65% reduction of major macro and micro-vascular events in obese patients with type 2 diabetes (12).

In summary, the possibility that we can prevent macro- and micro-vascular complications of type 2 diabetes by surgically induced weight loss, albeit not proved by randomized controlled trial, is suggested by good quality prospective and retrospective data. On the other hand, we have very few evidences that weight loss might have any regressive effect on established or end-stage complications. Heneghan *et al*. recently reported the fate of diabetic nephropathy, as measured by the presence of micro-albuminuria or macro-albuminuria, in a prospective uncontrolled study (13). In diabetic patients with pre-operative micro-albuminuria or macro-albuminuria, diabetic nephropathy resolved in 58.3% at a mean follow-up of 66 months (13). The potential for surgery to induce remission of albuminuria is also supported by a recent systematic review on the effects of bariatric surgery on microvascular complication of type 2 diabetes (14). However, the same review underlines that the impact of surgery on patients with more advanced diabetic kidney disease remains unclear and may be influenced by the potential for a critical threshold of renal function to be required to tolerate sequelae of bariatric surgery, such as acute post-surgical renal impairment and longer-term hyperoxaluria, given their potential to superimpose additional insults on already damaged kidneys (14). It is useful to remember here that, at

the epidemiological level, weight loss in patients with end-stage kidney disease has been associated to increased, and to reduced, total mortality (25). A similar scenario may be depicted for diabetic retinopathy (14). A preventive effect of bariatric surgery on the incidence of new cases of diabetic retinopathy has been demonstrated in some retrospective studies (12,15,32). However, in patient with established retinopathy, a few cases of regression, but also a few cases of progression have been observed after surgery (15,32). This mixed picture in relation to evolution of established diabetic retinopathy after surgery suggest that the complication may be progressively intractable as a function of disease severity at the time of surgery (14).

The effects of bariatric surgery in diabetic patients with established macro-vascular complications are difficult to evaluate at present, given the paucity of data specifically collected in these particular patients. Only a very few subjects with pre-existing ischemic heart disease, irrespective from the diabetic status, were included in the SOS study (21 in the surgical and 14 in the control group). Weight loss in the surgical group was satisfactory and clinical conditions, defined as the presence of chest pain or shortness of breath, were improved. However, the number of new cardiovascular adverse events, including myocardial infarction, coronary revascularization, and cardiovascular deaths, was not different in the two groups (33). Similarly, in a small prospective controlled study performed in obese patients with severe systolic heart failure, surgical weight loss was associated with a significant improvement in functional status, but with mixed results for the ejection fraction, with some patients gaining function and other patients not having any change (34). In summary, even if some clinical improvements can be observed, we have not convincing data demonstrating that weight loss induced by bariatric surgery may change the fate of cardiovascular diseases: no prevention of further cardiovascular events in patients with pre-existing ischemic disease and no consistent improvements of heart function and structure in patients with heart failure. Moreover, weight loss has been found to be associated to higher mortality rates in patients with heart failure (25) in epidemiologic studies.

The SOS study firstly demonstrated a reduction of fatal and total cardiovascular events (11) and total mortality (35) in severely obese patients treated by bariatric surgery as compared to conventional treatment. Lower total mortality rates in severely obese patients treated with surgery have been found in several other restrospective studies (36). Most of these studies, including the SOS, enrolled mostly young severely obese female subjects with a relatively low risk of death. Maciejewski *et al*. more recently evaluated survival after bariatric surgery in a cohort of older male patients with a high comorbidities burden, and they found no reduction in total mortality after surgery (16). Reasons because bariatric surgery was not associated with better survival in this study might be the higher perioperative mortality observed in older cohorts and the lower health benefits observed with weight loss in older patients with advanced comorbidities (16). Delaying surgery to late stage of life and chronic diseases might therefore reduce the potential benefits of bariatric surgery on survival observed in younger and relatively healthy patients.

Conclusions

The effects that bariatric surgery may have on the course of type 2 diabetes at its various stages of progression are summarized in *Table 1*. As reported above, we have very convincing evidences supporting the efficacy of surgery in preventing diabetes in high-risk patients and in remitting diabetes when the duration of the disease is short. Moreover, surgically induced weight loss seems to have the potential for preventing or delaying the occurrence of macro- and micro-vascular complications. On the contrary, the effects of bariatric surgery on established complications are far less good and patients with advanced or complicated disease may do not benefit in term of total mortality.

Taking together, these results strongly claim in favor of an early application of bariatric surgery in obese patients with type 2 diabetes. IDF statement suggested the consideration for bariatric treatment very early in the diabetic therapeutic algorithm (type 2 diabetes not adequately controlled by lifestyle measures and metformin) only for severely obese patients (BMI >40 kg/m^2) (4). Considering the new more recent findings presented in this review, this recommendation should be extended also to diabetic patients with a lower BMI level. Moreover, robust evidences on the preventive effect of bariatric surgery on diabetes prevention strong claim in favor of the extension of the use of bariatric surgery in obese patients with pre-diabetes or high diabetic risk.

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