Bariatric Surgery: The Indications in Metabolic Disease

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Introduction

The primary focus of bariatric surgery since its introduction has been the reduction of body mass index (BMI) in obese individuals [1–3]. However, it is being increasingly recognized that this surgery can help several medical conditions associated with obesity. The beneficial effects of bariatric surgery on mortality and morbidity are well described in cardiovascular disease, cancer and airways disease [1, 2, 4]. In recent years, equally exciting developments have occurred when using it for the treatment of metabolic disorders.

It is now clear that bariatric surgery can be a more effective treatment for obesity-associated type 2 diabetes mellitus (T2DM) than best medical care [5, 6]. It improves glycemic control in the short to medium term, but also reduces mortality and maintains the remission of diabetes in the long term in many patients [1, 2]. In light of this, we will outline the data for using bariatric surgery as metabolic surgery, including those with a BMI <35 kg/m².

Key Words
Bariatric surgery · Diabetes mellitus · Metabolic disease

Abstract
As well as the pronounced effect on body mass index (BMI), bariatric surgery is increasingly recognized as being associated with improvements in morbidity and mortality in a range of conditions, from airways disease to cancer. In metabolic disease, the impact of bariatric surgery is particularly obvious with marked improvements in glycemic control in patients with type 2 diabetes mellitus, to the point of effecting diabetes remission in some. Hypertension and dyslipidemia, key components of the metabolic syndrome, also respond to bariatric surgery. Despite the increasing evidence of benefit in metabolic disease, the major national guidelines for selecting candidates for bariatric surgery retain their emphasis on body weight. In these guidelines, a BMI ≥35 kg/m² is needed to indicate surgery, even in those with profound metabolic disturbance. The recent International Diabetes Federation guidelines have identified the need to reorientate our focus from BMI to metabolic disease. In this review, we examine the developing indications for the use of bariatric surgery in metabolic disease. We will focus on type 2 diabetes mellitus and the metabolic syndrome.
of these developments, we must reexamine our indications for the use of bariatric surgery in metabolic disease. The remit of surgery is now beyond that of weight control or reduction, and we could consider this useful therapy in more of our patients. This is especially true of those with metabolic disease or dysfunction and, in particular, diabetes. This article will outline the current indications for bariatric surgery, and will briefly examine the data for expanding these indications in those with diabetes.

**Current Approaches and Indications**

The most commonly performed laparoscopic bariatric procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and vertical sleeve gastrectomy (VSG) [7]. Biliopancreatic diversion (BPD) with or without duodenal switch is less commonly performed [8]. Minimally invasive techniques including the endoscopically placed synthetic duodenojejunal bypass liners, such as the EndoBarrier®, are also used as they improve glycemic control within the first year of use [9].

Current patient selection criteria for bariatric surgery concentrate on BMI, while comorbidities, including metabolic disorders such as diabetes, are considered to be indications for surgery in those with a BMI >35 kg/m² [10, 11]. Bariatric surgery for individuals with a BMI <35 kg/m² with obesity-related comorbidities is under investigation but is not generally recommended [12]. However, the International Diabetes Federation has recognized that this may need to be addressed, given the continuing increase in the incidence and prevalence of obesity-associated T2DM and the increased complication rates associated with the difficulty in achieving adequate glycemic control in some of these patients [13].

The International Diabetes Federation statement is reflective of the clinical recognition, supported by emerging data comparing surgery to medical therapy, that obesity-associated T2DM may be best treated by bariatric surgery [5, 6, 13]; in its recommendations, a BMI of 30 kg/m² may be considered for bariatric surgery in the presence of T2DM that is not adequately responding to optimal medical treatment [13]. This is a continuation of the metabolic surgery concept, and means that bariatric procedures are now being considered in people with a wider range of BMIs. As well as the effect on glucose homeostasis, bariatric surgery may improve the outcomes of diabetic complications such as diabetic kidney disease [14, 15].

Therefore, the indications for bariatric surgery are changing, although current national guidelines often still lag behind. We expect that in the light of the emerging evidence, this surgery will be considered as an add-on therapy for diabetes in order to improve glycemic control and, potentially, to manage microvascular complications.

**Diabetes Remission**

Diabetes remission (often termed ‘cure’ in the lay media) is an attractive target for bariatric surgery. However, despite the ‘cure’ tag given to this phenomenon, the remission of diabetes following bariatric surgery can be transient [1, 2]. In the most reliable long-term prospective data, the Swedish Obese Study, remission rates at 2 years halved at 10 years [1]. The majority of participants underwent vertical banded gastroplasty, with the remainder undergoing RYGB or AGB [1]. In the Swedish Obese Study, rates of diabetes remission per subgroup, and for RYGB specifically, are not yet available.

In prospective data of up to 6 years mean duration, RYGB was associated with 62% of patients with a glycosylated hemoglobin (HbA1c) of <6.5% (48 mmol/mol), a fasting glucose <7 mmol/l and independence from glycemic therapy [16]. The current American Diabetes Association (ADA) definition for diabetes remission is: a HbA1c of <6% (42 mmol/mol) and a fasting glucose <5.6 mmol/l off glycemic therapy [17]. Retrospective data at 9 years report that over 65% of patients with T2DM did not require glycemic therapy after RYGB [18]. This study also reported a 70% reduction in mortality, primarily due to a decrease in the number of cardiovascular deaths observed [18].

Patient selection impacts significantly on remission of T2DM after surgery. In the studies above, the candidates were not enrolled or specifically selected to induce remission of diabetes with bariatric surgery [16–18]. Therefore, the candidates had a wide range of ‘metabolic phenotypes’ [16–18]. The duration of diabetes and the level of preoperative glycemic control are important considerations. A longer duration of diabetes, higher preoperative HbA1c levels, preoperative insulin dependence and less weight loss after surgery are associated with a lower postoperative remission rate in RYGB and VSG [19].

Therefore, the heterogeneous clinical characteristics of the cohorts with diabetes in the available studies make interpretation of the data more difficult. This is especially true when changes in the definition of diabetes remission have been ongoing during the period of these studies.
When comparing studies, it is now possible to apply the standard ADA criteria. We do know that bariatric surgery can induce remission of diabetes using the current ADA criteria in at least 34% of all recipients at a mean follow-up of just under 2 years [17]. RYGB has greater efficacy in this regard, with a remission rate of over 40%, but selection bias may heavily influence these data, as may greater weight loss when compared to AGB in this cohort [17]. Future studies on diabetes remission should apply the ADA criteria to allow a fair comparison between results.

In current bariatric care, surgery should be considered as a therapy for diabetes. Given the available data, it may be offered with the potential for short-term remission of diabetes. However, even if remission is transient and is not effective in all candidates, bariatric surgery can achieve significantly lower HbA1c levels than medical therapy alone. Many authors have suggested that treating those with diabetes of a shorter duration may offer more impressive cure rates, although this may be unhelpful as these are the patients that diabetologists do not consider for bariatric surgery. In contrast, those with a longer history of diabetes, and more advanced metabolic dysfunction as demonstrated by uncontrolled hyperglycemia, are less likely to remit, but may also be more likely to benefit as they are at a much higher risk of developing vascular complications.

Therefore, if remission is the goal of treatment, the candidates should be selected on the basis of the duration of their diabetes, and on the range of their hyperglycemia. Additional analysis of the C-peptide levels before surgery may be of help, although the levels at which we can reliably predict remission have still to be determined [20]. This may, however, be a counterproductive approach if we try to increase the penetrance of a very effective treatment like bariatric surgery. The target treatment group, at least initially, should be patients with T2DM that is not controlled on optimal medical care.

**Glycemic Control in Diabetes**

With these reservations about inducing remission of diabetes, it would seem to be more useful to focus on the definitively proven greater glycemic control offered by bariatric surgery as compared to best medical therapy [5, 6]. Several randomized controlled trials have been completed, and have found that RYGB, BPD, VSG and AGB are all more effective at improving glycemic control than medical therapy alone [5, 6, 21]. AGB can result in over 70% of T2DM patients achieving a HbA1c of 6.2% (44 mmol/mol) or less compared to <15% among those attending a diabetes multidisciplinary team for medical and dietetic review every 6 weeks [21]. This was over a 2-year study period in adults with BMIs of 30–40 kg/m² and a duration of T2DM of under 2 years [21]. The improved glycemic control was in the context of a 10-fold greater weight loss in the AGB group compared to the medical group [21].

Mingrone et al. [6] compared RYGB and BPD to intensive medical therapy in patients with a BMI ≥35 kg/m². This population had had T2DM for at least 5 years. In this study, 95% of BPD recipients achieved a HbA1c ≤6.5% (48 mmol/mol) compared to 75% of the RYGB group and 0% of the medical group after a 2-year follow-up. Unfortunately, the diabetes remission data using the ADA criteria were not reported. The participants in the intensive medical arm attended a diabetes multidisciplinary team every 12 weeks for optimization of their diet, lifestyle and medical therapy [6]. Over the 2-year study period, they lost nearly 5% of their baseline weight, which was less than the weight loss of over 30% reported in both surgical groups [6].

Schauer et al. [5] tested intensive medical therapy against RYGB and VSG. The medical therapy was intensive glycemic therapy administered along ADA guidelines. The cohort was obese with a mean BMI >35 kg/m². The study participants had had T2DM for a mean duration of 8 years and were not meeting their current glycemic targets [5]. A treatment target of HbA1c of 6% (42 mmol/mol) was set and was met by 42% of the RYGB group, 37% of the VSG group and 12% of the medical group on conclusion of the study [5].

Although these studies were relatively small with between 60 and 150 participants each, the findings were consistently significant [5, 6, 21]. Importantly, these were the first studies to use bariatric surgery as an ‘add-on therapy’ to best medical care, as the administration of metformin, lipid pharmacotherapy and renin-aldosterone-angiotensin system antagonists was continued after surgery where possible. Therefore, it is clear that in selected obese cohorts, bariatric surgery in combination with best medical therapy is more effective than intensified medical therapy at achieving glycemic control over a 2-year postoperative period.

These are exciting data, but must be understood in the context of longer-term studies, which suggest that glucose homeostasis worsens at 2 years after surgery [1, 13]. Long-term follow-up of these cohorts is necessary to ensure that the effects endure. However, these data do support the use of bariatric surgery in patients with obesity-asso-
associated T2DM who do not meet their treatment targets on medical therapy alone. This new indication is recognized in the most recent recommendations of the International Diabetes Federation, but is not part of the major national guidelines [13]. This should be more broadly considered, and obese patients with T2DM who are not meeting their glycemic targets may be candidates for bariatric surgery to improve their glycemic control. Further studies on cost and risk benefits should be completed to ensure that the complications and cost inherent to bariatric surgery do not outweigh the benefits in this group.

Bariatric Surgery and Microvascular Complications

An important consideration is the effect of the improved glycemic control that is associated with bariatric surgery on vascular disease and its complications. There are no randomized controlled trials examining the effect of bariatric surgery on microvascular outcomes as compared to intensive medical therapy. Emerging evidence would suggest that this is a field that may provide an even greater role for bariatric surgery in treating diabetes and its associated vascular complications.

Diabetic kidney disease is a common complication of T2DM [22]. Bariatric surgery can improve renal damage over a 5-year follow-up as measured by albumin:creatinine ratios [23]. At a 1-year follow-up in a retrospective analysis of 25 recipients of RYGB, estimated glomerular filtration rate (eGFR) changed from 48 to 60 ml/min/1.73 m² as measured with the Modified Diet in Renal Disease equation [24]. The risk with this type of data is that they may be falsely reassuring as any weight loss will reduce serum creatinine and thus the improved eGFR may reflect the reduction in lean body mass rather than improvements in renal function. Studies using creatinine-independent methods of assessing renal function are therefore required.

However, there is a dearth of long-term prospective human data on renal outcomes following bariatric surgery. In a study including participants with and without diabetes, RYGB improved renal function as measured by eGFR using creatinine clearance, with additional analysis using a urinary cystatin C:creatinine ratio [25]. When proteinuria is used as a marker of diabetic kidney disease, improvement can be demonstrated for up to 2 years after bariatric surgery in patients with T2DM [26]. This improvement continues for the duration of the 2-year follow-up  [26].

In retinopathy and neuropathy, there is a greater paucity of data for outcomes following bariatric surgery. However, data from our group suggest that at a follow-up of 1 year after bariatric surgery, there was no change in retinopathy scores in a group with T2DM and retinopathy [15]. This is reassuring, given the dramatic improvements sometimes seen in glycemic control after bariatric surgery [5, 6, 21].

At present, the role of bariatric surgery in treating those with microvascular complications has not been proven. Early evidence suggests that it is beneficial in diabetic kidney disease and may improve renal function [22–25]. There are no data to support the use of bariatric surgery in treating diabetic retinopathy or neuropathy, but emerging evidence finds that it may not be detrimental in the case of established retinopathy. This is a field that requires much more focused research to determine its effect on microvascular complications.

Bariatric Surgery in Those with a BMI <35 kg/m²

At present, the general national and international recommendations are to avoid bariatric surgery in those with a BMI <35 kg/m² [10, 11, 13]. As previously mentioned, a BMI <35 kg/m² but >30 kg/m² can be considered in those with poorly controlled diabetes in accordance with the International Diabetes Federation guidelines [13]. Approximately 33% of the Schauer et al. study [5] had a BMI <35 kg/m². There were 3 participants in the Mingrone et al. study [6] with a BMI <30 kg/m². Given the small numbers, subgroup analysis was not completed, but there are data that provide interesting information on the potential benefits of bariatric surgery in this population. This is pertinent for those with a metabolic dysfunction such as diabetes who do not fall within the standard BMI treatment criteria.

The data from the major randomized controlled trials find that the subgroups with a BMI <35 kg/m² have a mean weight loss that brings them into the nonobese range [27]. This is in tandem with improved fasting glucose levels and improved lipid profiles [27]. In the diabetic subgroups with a BMI <35 kg/m², over 80% achieve a HbA1c of <7% (53 mmol/mol) [27]. This is in the context of a 3% major complication rate and no mortality [27]. A strategy targeting the metabolically unhealthy cohort with a BMI of 30–35 kg/m² may also be cost-effective and lasting, with prospective data reporting 88% of RYGB recipients with a BMI of 30–35 kg/m² maintaining a HbA1c of <6.5% (48 mmol/mol) 6 years after surgery  [20,
28]. The ADA criteria for diabetes remission were not used in these cohorts.

In patients with a BMI $< 30$ kg/m$^2$, bariatric surgery is not as well tested. One prospective study investigated the use of RYGB in 40 T2DM patients with a BMI of 25–35 kg/m$^2$ who were not at treatment target. RYGB improved the mean HbA1c in this cohort from $>9\%$ (75 mmol/mol) to $6\%$ (42 mmol/mol) [29]. There was no mortality and only two episodes of complications were reported; one had defecatory dysfunction and one experienced a gastrointestinal hemorrhage [29]. The mean BMI fell from 31 kg/m$^2$ to 23 kg/m$^2$, with none below 18 kg/m$^2$ [29].

Similar data have been produced elsewhere [30–32]. Experimental procedures such as ileal interposition with VSG, designed to test mechanisms of glucose homeostasis rather than weight loss, have been used in cohorts with nonobese and normal BMIs [31, 32]. Both these procedures and classic procedures like RYGB can induce significant changes in metabolic measurements, including glucose homeostasis, blood pressure and lipid profiles, without an increased complication rate [32]. Excessive weight loss is a concern in this group, but is seen in $<3\%$ of cases [32].

BPD has been tested with success in improving glucose homeostasis in those with a BMI $< 35$ kg/m$^2$ [33]. In this study, half of the participants had a BMI $< 30$ kg/m$^2$ and all had T2DM (with a mean duration of 11 years) and suboptimal glycemic control [with a mean HbA1c of $>9\%$ (75 mmol/mol)]. Over a 1-year follow-up period, over 80% of this cohort (n = 30) achieved glycemic targets with a HbA1c of $<7\%$ (53 mmol/mol) off glycemic pharmacotherapy [33]. The mean BMI stabilized to 25 kg/m$^2$ and there was no excessive weight loss [33].

These data show that bariatric surgery could be considered in those with a BMI $< 35$ kg/m$^2$ in the presence of diabetes. This is particularly relevant in patients that are not meeting their treatment targets despite intensive medical therapy. Based on the available data, surgery in such candidates would improve glycemic control from high-risk to near-normal ranges without a significant increase in complication rates and with a low rate of excessive weight loss.

It can be argued that in patients who are less obese, their adiposity contributes less to their T2DM. Thus, even if they reduce their body weight, the relative benefit obtained may be less than patients with a higher BMI who lose the same percentage of weight [33]. However, the less obese population may still obtain an advantage by deferring the onset of diabetic complications [33]. This is a controversial topic, and firm data supporting this suggestion are still in development. This issue does emphasize the importance of considering weight-loss-independent benefits of surgery when deciding which operation should be selected. This should indeed be a prime focus in future research in metabolic surgery.

**Bariatric Surgery and the Metabolic Syndrome**

As well as the effects on diabetes, bariatric surgery has an effect on the other components of the metabolic syndrome, namely waist circumference, dyslipidemia and hypertension [1, 28, 34]. Ten years after surgery, bariatric surgery results in lower rates of hypertension and hypertriglyceridemia and elevated high-density lipoprotein concentrations, when compared to a matched control group [1]. This may contribute to the lower cardiovascular mortality over 15 years [2].

Despite these data, bariatric surgery is not currently indicated to treat cardiovascular risk per se. The available guidelines can be interpreted as operating on candidates with a BMI $\geq 35$ kg/m$^2$ in the presence of the metabolic syndrome, although this is not explicitly stated [10, 11, 13]. However, patients with a BMI $< 35$ kg/m$^2$ may also benefit in terms reduction of cardiovascular risk [30, 35].

In this group, bariatric surgery, including RYGB, can improve blood pressure and lipid profiles in tandem with improvements in glucose homeostasis [30, 35]. Experimental procedures such as ileal transposition with VSG achieved improvements in hypertension and correction of the metabolic syndrome lipid profile in over 90% of recipients with a BMI $< 30$ kg/m$^2$ [31]. In prospective data over a median follow-up of 5 years, the reduction in blood pressure and improvements in lipid profiles associated with RYGB reduced cardiovascular risk by over 80% [20].

However, the data do not all agree. It may be that the persistent use of lipid or antihypertensive pharmacotherapy was responsible for the reduced blood pressure and improved lipid profiles in this group [12]. The lipid data are particularly contentious. In meta-analyses of the data on bariatric surgery within cohorts of patients with a BMI $< 35$ kg/m$^2$, there was a reduction in total cholesterol and triglyceride concentrations, but HDL levels were unaffected [27].

Therefore, the use of metabolic surgery to treat cardiovascular risk in those with a BMI $> 35$ kg/m$^2$ is not explicitly proven, but seems reasonable given the long-term data from now almost 20 years [2]. Further prospective study in this area is needed with a specific emphasis on the lower-range BMIs and cardiovascular and metabolic out-
comes. In those, there are less data on patients with a BMI <30 kg/m², and what is available is less convincing. While a strong argument cannot be made for treating cardiovascular risk with bariatric surgery in the lowest BMI ranges at present, it should continue to be evaluated and may be worth considering in those with an extremely high cardiovascular risk that is refractory to medical therapy.

**Conclusion**

According to the current guidelines, bariatric surgery should be considered in candidates with a BMI ≥35 kg/m² in the presence of metabolic disease including T2DM and the metabolic syndrome. We would agree with the International Diabetes Federation recommendations to reduce the lower BMI limit to 30 kg/m² in those patients with diabetes that is not at treatment targets despite intensive medical therapy. However, we would also suggest that the use of BMI as a primary marker for considering bariatric surgery may not be the most useful means of determining who will benefit most from the intervention.

For those with T2DM, metabolic syndrome or a high cardiovascular risk refractory to medical therapy, BMI may be irrelevant. This is a controversial statement, and still has to be proved. However, the finding of available studies is that even those in the normal or near-normal BMI ranges can benefit from bariatric/metabolic surgery in terms of glucose homeostasis and cardiovascular risk, particularly if best medical therapy is not adequate to prevent micro- and macrovascular complications. More studies are needed to determine the role of surgery as an adjunct to optimal medical therapy in this group of patients with ‘difficult to control’ T2DM.

**References**


