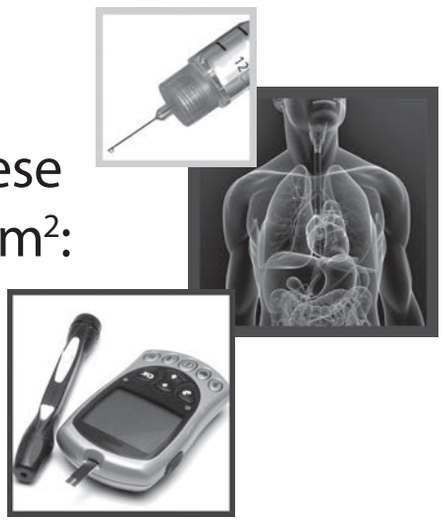

# Bariatric/metabolic surgery for the obese with Type 2 diabetes with BMI <35 kg/m$^2$: why caution is required

Luca Busetto*

**Practice Points**

- Strong evidence supporting the long-term efficacy and safety of bariatric/metabolic surgery in obese patients with Type 2 diabetes and BMI <35 kg/m$^2$ is still lacking.
- Bariatric/metabolic surgery is able to induce diabetes remission in approximately two-thirds of diabetics patients with BMI <35 kg/m$^2$, and the application of bariatric/metabolic surgery should be limited to obese class I diabetic patients with a higher probability of diabetes remission after the procedure.
- The benefit of weight loss on total and cardiovascular mortality is unknown in obese class I diabetic patients, and weight loss may be associated with increased mortality in high-risk/frailty patients.
- Any eventual benefit derived from intentional weight loss may be outweighed by unexpected/unknown long-term side effects of surgery.
- Surgical decision in a patient with Type 2 diabetes and BMI <35 kg/m$^2$ should be based on an individualized comprehensive evaluation of the patient's global health and on a reliable prediction of its future disease risk.

**SUMMARY** Bariatric/metabolic surgery is now widely accepted as a powerful tool for the management of Type 2 diabetes in patients with morbid obesity (BMI >35 kg/m$^2$). Some position statements recently suggested the possibility that bariatric/metabolic surgery may also have a role in the management of obese class I (BMI 30–35 kg/m$^2$) patients with Type 2 diabetes. Efficacy of bariatric/metabolic surgery in this particular group of patients was, however, supported largely by uncontrolled observational short-term studies, and we do not yet have any study analyzing its effects in the prevention of both macro- and micro-vascular hard end points. On the other hand, recent data suggest that the reduction in cardiovascular events and mortality that may be expected from weight loss in patients with Type 2 diabetes and moderate obesity may be smaller than that observed in patients with more severe obesity. Intentional weight loss seems to result in more harm than benefit in some particular subgroups. Bariatric/metabolic surgery has been associated with long-term adverse effects. Most of these adverse events are rare, but in patients with low BMI, their relative importance may be weighed against a possible minor beneficial effect carried by intentional weight loss. In conclusion, an individualized prudent approach appears to be reasonable, with the surgical decision based on a comprehensive evaluation of the patient's global health and on a reliable prediction of its future disease risk.

*Department of Medicine, University of Padova, Via Giustiniani 2, 35128, Padova, Italy
Tel.: +39 049 821 2149; Fax: +39 049 821 2149; luca.busetto@unipd.it

Future Medicine part of fsg

Bariatric or metabolic surgery has, in the last 20 years, emerged as a first-line option in the management of Type 2 diabetes in patients with morbid obesity (BMI >35 kg/m$^2$). Several observational clinical studies showed the benefits of bariatric surgery on diabetes in this subgroup of patients. A systematic review and meta-analysis including 621 studies with 888 treatment arms and 135,246 patients demonstrated an overall 78.1% complete resolution of Type 2 diabetes after surgery, with 86.6% of patients having diabetes improved or resolved [1]. The robustness of these estimations may be reduced by the acknowledgment that the large majority of the studies included in this review are observational retrospective not randomized studies without appropriate control groups [2]. However, the results of four randomized controlled trials [3–6], in which several bariatric procedures have been tested against best medical treatment, seem now to confirm the superiority of bariatric surgery in respect to conventional therapy for the induction of metabolic control and Type 2 diabetes resolution in patients with severe obesity. Dixon *et al.* firstly randomized 60 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 [3]. Schauer *et al.* randomized 150 obese patients (BMI range 27–43 kg/m$^2$) with uncontrolled Type 2 diabetes to intensive medical therapy alone versus 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 hemoglobin level ≤6.0% 12 months after treatment. The proportion of patients achieving the primary end point was 12% in the medical therapy group versus 42% in the gastric-bypass group ($p = 0.002$) and 37% (18 of 49 patients) in the sleeve-gastrectomy group ($p = 0.008$). Surgical arms were both superior to medical therapy in terms of the glycemic control and weight loss [4]. Mingrone *et al.* randomly assigned 60 patients with a BMI >35 kg/m$^2$, a history of at least 5 years of diabetes, and a glycosylated hemoglobin 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 versus 75% in the gastric bypass group and 95% in the bilio-pancreatic diversion group ($p < 0.001$ for both comparisons) [5]. Finally, Ikramuddin *et al.* randomized 120 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 hemoglobin 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 points [6].

The benefits of bariatric surgery on Type 2 diabetes in morbidly obese patients observed in these short-term uncontrolled and controlled randomized studies have also been confirmed in long-term observations. In the Swedish Obese Subjects (SOS) study, the long-term outcome of a large group of morbidly obese patients treated by bariatric procedures was compared with the outcome of a well-matched group of highly comparable morbidly obese patients participating in a national obese registry and not willing to undergo surgery. The proportion of patients with Type 2 diabetes at baseline being normoglycemic without pharmacologic treatment 10 years after enrolment (long-term remission) was higher in the surgically treated group (36%) than in the control group (13%), with a probability of being free from diabetes 10 years after surgery 3.45 (95% CI: 1.64–7.28) times higher in the surgical group [7]. These effects on diabetes remission, along with other metabolic benefits and weight loss, were associated in the surgical arm of the SOS study with a significant reduction in total mortality [8], with a reduced number of cardiovascular deaths [9], and with a lower incidence of cardiovascular events [9]. The reduction in total mortality observed in the prospective SOS study has been confirmed in several retrospective cohort studies [10–12]. Both Sjöström *et al.* [8] and Adams *et al.* [11] found the decreased mortality was primarily secondary to a decreased rate of cardiovascular deaths. Furthermore, a markedly decreased mortality for diabetes was reported in the Adams *et al.* study [11].

The availability of this substantial evidence in favor of the use of bariatric surgery in the clinical management of Type 2 diabetes in patients with

morbid obesity (BMI >35 kg/m²) ultimately convinced the most influential scientific associations in the field to consider bariatric surgery for patients with BMI >35 kg/m² and Type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy [13]. Some accumulating evidence, and the inclusion in three of the four randomized trials quoted above of patients with less severe degrees of obesity, recently suggest the possibility that bariatric or metabolic surgery may have a role also in the management of obese class I (BMI 30–35 kg/m²) patients with Type 2 diabetes. The first significant attempt to consider offering bariatric surgery to patients whose BMI was under 35 kg/m² was by the International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention of Diabetes in 2011 [14]. After reviewing the accumulating studies on the role of bariatric and metabolic surgery on diabetes, a consensus multidisciplinary panel concluded that there was clear evidence that bariatric surgery is a very effective therapy for obese patients with Type 2 diabetes, and suggested that diabetic patients with class I obesity (BMI 30–35 kg/m²) may be eligible, but not prioritized, for surgery if they have poorly controlled diabetes (glycosylated hemoglobin >53 mmol/mol or 7.5%) despite fully optimized conventional therapy, especially if their weight is increasing or other weight-responsive comorbidities (blood pressure, dyslipidemia and obstructive sleep apnea) are not achieving targets on conventional therapy [14]. This prudent position appears to be reasonable, taking into account that the evidence in favor of the efficacy of metabolic surgery for diabetic patients with BMI <35 kg/m² is less strong than for morbid obesity, particularly in the long-term, and that the risk:benefit ratio of surgery and weight loss in this group of patients is less clearly established.

## Efficacy of bariatric/metabolic surgery for obese diabetic patients with BMI <35 kg/m²

As mentioned before, three of the four randomized trials evaluating the effects of bariatric/metabolic surgery in obese patients with Type 2 diabetes also included a fraction of patients with BMI <35 kg/m². More specifically, only 13 of 60 patients had a baseline BMI <35 kg/m² in the Dixon *et al.* trial [3], 51 of 150 in the Schauer *et al.* study [4], and 71 of 120 in the Ikrammuddin *et al.* study [6]. However, neither of these three studies separately and specifically reported the results obtained in patients with BMI <35 kg/m² from those obtained in patients with BMI >35 kg/m².

The number of observational uncontrolled studies evaluating the effects of bariatric/metabolic surgery specifically in patients with Type 2 diabetes and a BMI <35 kg/m² is rapidly growing, and several meta-analysis/systematic reviews have been recently published. Li *et al.* systematically evaluated a total of 13 studies including 357 patients with Type 2 diabetes and BMI <35 kg/m² [15]. Both traditional (gastric bypass and bilio-pancreatic diversion) and experimental (duodenal-jejunal bypass and ileal interposition with sleeve gastrectomy) bariatric/metabolic procedures were included. Nine studies were prospective and four studies were retrospective. Follow-up length ranged from 6 to 48 months for 11 studies, with only two studies lasting more than 5 years. Resolution of Type 2 diabetes was defined and reported in a variety of ways. When defined as a normal fasting plasma glucose (<100 mg/dl), a normal HbA1c (<6%) and no need for diabetic medications, 66.3% of the patients approached resolution. Glycemic control was achieved if the HbA1c was <7% and the patient was off all diabetes medications, and 80.0% of the patients obtained these results. Shimizu *et al.* identified 18 studies including 477 patients with Type 2 diabetes and BMI <35 kg/m² [16]. Surgical procedures included Roux-en-Y gastric bypass, duodenal-jejunal bypass, bilio-pancreatic diversion, mini-gastric bypass, ileal interposition with sleeve or diverted sleeve gastrectomy, sleeve gastrectomy and stomach and pylorus-preserving bilio-pancreatic diversion. Sixteen studies were prospective and two studies retrospective. The follow-up period ranged from 6 months to 18 years, with the same two studies reporting the results of a longer than 5-year follow-up. The definition of resolution or remission of Type 2 diabetes again varied, but when it is defined as fasting plasma glucose <126 mg/dl and/or glycosylated hemoglobin <6.5% without the use of antidiabetic medication, 64.7% of the patients met the criteria. Remission rates varied according to duration of Type 2 diabetes, being 66.0% in patients with a short diabetes history (≤8 years) and 52.9% in patients with a long diabetes history (>8 years). Finally, Reis *et al.* analyzed a total of 29 studies, with 1209 patients with Type 2 diabetes and BMI <35 kg/m² [17]. Effects of ileal interposition, duodenal-jejunal

bypass, gastric bypass. bilio-pancreatic diversion, adjustable gastric banding, mini gastric bypass and sleeve gastrectomy were evaluated. Type 2 diabetes remission was considered when the subjects presented fasting plasma glucose <100 mg/dl or glycosylated hemoglobin <6% without the use of any antidiabetes medication at the end of the study. Diabetes control was identified when fasting plasma glucose was between 100 and 125 mg/dl or glycosylated hemoglobin varied from 6.0 to 7.0% without antidiabetes medication, and diabetes improvement occurred when there was improved fasting plasma glucose, improved glycosylated hemoglobin and/or reduced use of antidiabetes medications. Under these definitions, Type 2 diabetes remission, control and improvement were observed in 55.4%, 28.6% and 14.4%, respectively.

In summary, efficacy of bariatric/metabolic surgery for the patients with Type 2 diabetes and BMI <35 kg/m$^2$ was at present supported largely by uncontrolled observational short-term studies including a maximum of 1000 patients in total. No randomized control studies with the inclusion of a control group treated with the best medical therapy, including the most recent classes of antidiabetic drugs, has been performed specifically in this subgroup of patients. In the studies we have to date, bariatric/metabolic surgery seems to be fully effective (Type 2 diabetes remission) in approximately two-thirds of the patients and partially effective (better metabolic control achieved with a reduced need for antidiabetic medications) in the majority of them. It is reasonable to suppose that the better control of refractory Type 2 diabetes with the surgical approach could lead to decreased long-term micro- and macro-vascular complications. However, we do not yet have any study specifically analyzing the effects of bariatric/metabolic surgery in the prevention of both macro- and micro-vascular hard end points in patients with Type 2 diabetes [2]. Some studies on this topic are now underway, but the results are still pending. This lack of knowledge may be particularly important in diabetic patients with class I obesity, where the beneficial effects of weight loss on long-term outcomes are less clearly established than in more severe obese patients.

## Benefits from weight loss in obese diabetic patients with BMI <35 kg/m$^2$

Intentional weight loss was considered beneficial in adults with overweight/obesity and Type 2 diabetes, and it was highly recommended by current clinical practice guidelines [13]. However, the extent to which the metabolic improvements associated with weight loss may translate to a reduction in the incidence of major macro- and micro-vascular complications of Type 2 diabetes remains less clear. The early cessation of the Look Ahead study for failing to demonstrate hard cardiovascular and mortality advantage in overweight and obese participants to an intensive lifestyle program including intentional weight loss, despite the observation of clear metabolic benefits, seems to suggest that any effect on major hard end points from intentional weight loss would be small in class I individuals with Type 2 diabetes [18]. Moreover, recent data seem to suggest that weight loss may not be beneficial and may be instead harmful at least in some diabetic patients. Carnethon *et al.* revised the association between weight status and mortality in a pooled analysis of five longitudinal studies with 2625 middle-aged patients with incident diabetes [19]. Patients were classified as normal weight or overweight/obese (BMI >25 kg/m$^2$). During a total follow-up of 27,125 person/years, the rates of total, cardiovascular and noncardiovascular mortality were higher in normal-weight participants than in overweight/obese participants. After adjustment for multiple confounding factors, hazard ratios comparing normal-weight participants with overweight/obese participants for total, cardiovascular and noncardiovascular mortality were 2.08 (95% CI: 1.52–2.85), 1.52 (95% CI: 0.89–2.58) and 2.32 (95% CI: 1.55–3.48), respectively. This may suggest a protective effect of overweight in patients with Type 2 diabetes. Epidemiologic observations may be affected by several biases, but even some controlled prospective clinical data seem to go on the same way. Doehner *et al.* assessed the relationships between body weight and weight change and mortality 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 5238 patients with Type 2 diabetes and pre-existing cardiovascular comorbidity [20]. In the placebo group, the lowest mortality was seen in patients with BMI 30–35 kg/m$^2$ at baseline. In comparison to this reference group, both patients in the placebo group with BMI <22 kg/m$^2$ and patients with BMI 22–25 kg/m$^2$ had a higher all-cause mortality. In the same setting, weight loss during

the study, and not weight gain, was also associated with increased total and cardiovascular mortality [20].

In conclusion, available clinical data suggest that the reduction in cardiovascular events and mortality that may be expected from weight loss in patients with Type 2 diabetes and BMI 30–35 kg/m² may be smaller than in patients with more severe obesity. Moreover, intentional weight loss seems to result in more harm than benefit, at least in patients with Type 2 diabetes and established cardiovascular diseases. This latter observation may be included in the so called 'obesity paradox' phenomenon. The term 'obesity paradox' refers to a body of epidemiological observations in which having a BMI level in the overweight or moderate obesity range seems to confer a survival advantage with respect to normal weight and underweight patients in selected clinical situations and/or in frailty patients. A survival advantage in people with overweight or moderate obesity, when compared with underweight or normal weight subjects, has been indeed described not only in diabetic patients with pre-existing cardiovascular comorbidity [20], but also in patients with chronic heart failure [21–23], in end-stage renal disease [24], after major vascular surgery for peripheral arterial disease [25], in patients who underwent a percutaneous coronary intervention for coronary artery disease [26], in patients who are medically treated for non-ST-segment elevation acute coronary syndrome [27], and in the first 30 days after general nonbariatric surgery [28]. Several explanations for the 'obesity paradox' have been advocated. One common suggestion is that the very concept of the obesity paradox may be driven by the deleterious effects of cachexia and not by salutary effects of obesity [29]. The protective effect of a relatively high BMI level in such stressful clinical situations may be therefore driven by having a good fat-free mass and a good nutritional status, instead of by a protective effect of adiposity alone. However, we cannot exclude that increased fatness may confer *per se* some mortality advantage in selected clinical situations, not excluding patients with Type 2 diabetes and established cardiovascular diseases.

## Safety of bariatric/metabolic surgery for obese diabetic patients with BMI <35 kg/m²

An acceptable perioperative safety of bariatric/metabolic surgery in patients with Type 2 diabetes and BMI <35 kg/m² has been demonstrated in systematic reviews and meta-analyses [15,16]. However, we have very few data on the incidence of adverse effects of bariatric/metabolic surgery on the long-term. A short list of potential long-term adverse effects of bariatric/metabolic surgery is reported in **Box 1**. Most of these adverse events are rare and have been described primarily or exclusively in morbidly obese bariatric patients. Therefore, their incidence in patients with Type 2 diabetes and class I obesity remains to be determined.

An interference with calcium and vitamin D absorption may be observed after several bariatric procedures and a sizable reduction (8–10%) of bone mineral density both at the femoral neck and at the lumbar spine has been demonstrated in prospective studies in the first postoperative year following malabsorptive procedures [30]. Despite that we do not have conclusive evidence of an increased incidence of osteoporosis/osteomalacia or increased fracture risk after bariatric/surgery, this remains a possible caution in the long-term. Severe hyperinsulinemic hypoglycemia is considered a rare consequence of bariatric/metabolic surgery and occurs in both diabetic and nondiabetic individuals, mostly after gastric bypass, as a possible deleterious consequence of the same metabolic effects that exerts positive effects on Type 2 diabetes [31]. The incidence of post-bariatric hypoglycemia is unknown. Kellog *et al.* estimate a postoperative prevalence of at least 0.36% [32]. Less than 1% of patients treated with gastric bypass required hospitalization for hypoglycemia in the Swedish Bariatric Surgery registry [33]. The incidence of this complication in patients with Type 2 diabetes and BMI <35 kg/m² is completely undetermined. Moreover, a high glycemic variability, with unrecognized hyperglycemic peaks and a tendency to postprandial hypoglycemia, has been observed by continuous glucose monitoring after gastric bypass [34]. The prognostic significance of these higher glycemic excursions, undetected by standard glucose monitoring, on diabetic macro- and micro-vascular complications remains also to be determined. Internal hernia with bowel obstruction is a well-known long-term complication for some bariatric procedures [35]. A marginally higher suicidal rate [36] and a higher risk of alcohol abuse [37] have both been reported in morbidly obese patients after bariatric surgery. Both these events are rare, but should still be taken into account in

**Box 1. Potential long-term side effects of bariatric/metabolic surgery in the long-term.**

- Excessive weight loss
- Reduced bone mineral density
- Hypoglycemia and increased glycemic fluctuations
- Internal hernias
- Increased suicidal rate
- Increased risk of alcohol and drug abuse
- Increased risk of colon cancer in males

the calculation of the global risk:benefit ratio of surgery. Finally, whereas a reduced incidence of cancer has been demonstrated in morbidly obese women [38] and men [39] after bariatric surgery, a recent report suggests a slightly increased risk of colorectal cancer in men [40]. The clinical significance of this latter observation may, however, be reduced by the fact that the authors compared the incidence of cancer in men after having had bariatric surgery to the entire Swedish population and not to BMI-matched men for BMI [40].

A long-term side effect of bariatric/metabolic surgery that may require special attention in patients with BMI <35 kg/m$^2$ is excessive weight loss, with fat-free mass and muscle mass loss, leading to an increased risk of sarcopenia and disability in later life. This problem would probably be more important when applying traditional bariatric procedures, like the gastric bypass or sleeve gastrectomy, which have a substantial effect on body weight, to this subgroup of patients. The problem of excessive weight loss has been specifically analyzed by Shimizu *et al.* in their review of metabolic surgery for Type 2 diabetes in patients with a BMI <35 kg/m$^2$ [16]. Overall, the risk of excessive weight loss after metabolic surgery was estimated at 2.7% [16]. Within the studies included in the review, one study reported one of 15 patients in the mildly undernourished range (BMI: 17–18.5 kg/m$^2$) after RYGB [41]. Therefore, a small, but sizable proportion of patients having a very low BMI after surgery may be expected when applying traditional bariatric procedures to patients with

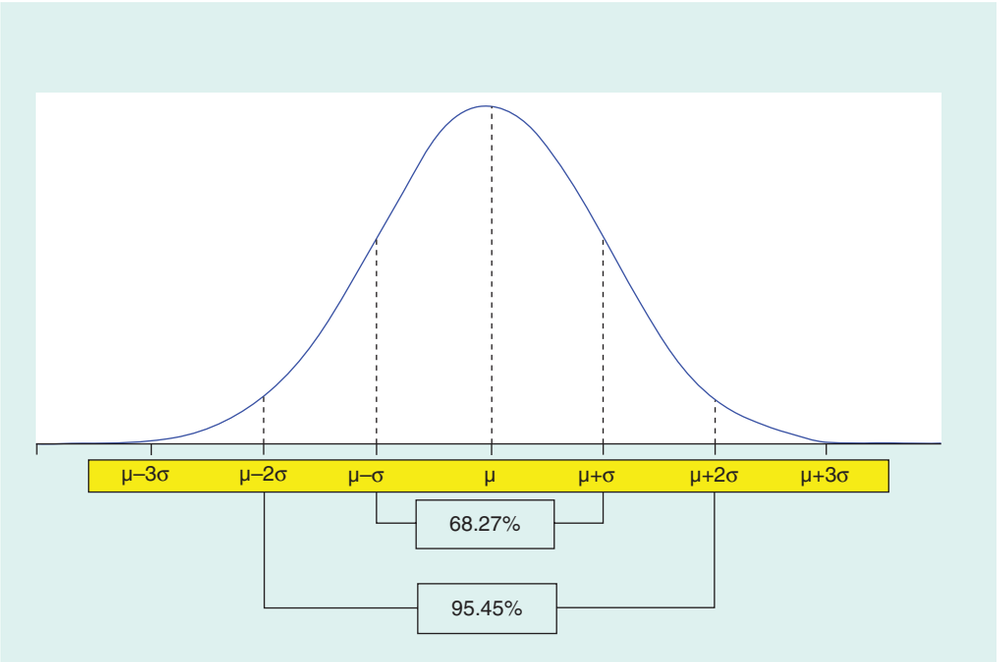


**Figure 1. A small, but sizable proportion of patients having low BMI after surgery may be expected when applying traditional bariatric procedures to patients with BMI <35 kg/m$^2$.** The values in the figure have been calculated by using the data reported by Boza *et al.* [43], who treated 30 patients with Type 2 diabetes and BMI 30–35 kg/m$^2$ (mean baseline BMI: 33.7 ± 1.2 kg/m$^2$) with a Roux-en-Y gastric bypass. Mean BMI 2 years after surgery was reported to be 23.9 ± 2.4 kg/m$^2$. Assuming a normal distribution for BMI after surgery, 16% of patients having a BMI <21.5 kg/m$^2$ and 2.5% of patients having BMI <19.1 kg/m$^2$ may be expected. These low BMI levels cannot be achieved without a substantial loss of fat-free mass and skeletal muscle mass.

Type 2 diabetes and a BMI <35 kg/m$^2$ **(Figure 1)**. These low BMI levels cannot be achieved without a substantial loss of fat-free mass. Considering the 'obesity paradox' and the postulated protective effect of good fat-free mass and good nutritional status in stressful clinical situations, excessive weight loss may be particularly dangerous in middle-aged Type 2 diabetic patients with established macro- or micro-vascular complications.

## Conclusion & future perspective

In conclusion, strong evidence supporting the long-term efficacy and safety of bariatric/metabolic surgery in obese patients with Type 2 diabetes and BMI <35 kg/m$^2$ is still poor. Moreover, the benefit of weight loss on total and cardiovascular mortality is less clear in obese class I diabetic patients than in patients with more severe obesity, and weight loss may be associated with increased mortality in high-risk/frailty patients. Therefore, the risk:benefit ratio of surgery in this group of patients remains less clearly established.

To deny the possible benefits arising from bariatric/metabolic surgery to an obese patient with Type 2 diabetes simply for having a BMI slightly below the accepted 35 kg/m$^2$ BMI threshold may appear unreasonable and unpleasant, particularly taking into account the known limits of BMI as an index of adiposity and disease risk [42]. On the other hands, an unrestricted and indiscriminate opening to the use of bariatric/metabolic surgery in this group of patients may open the way to unexpected negative outcomes, particularly in the long-term. Given the present paucity of specific long-term data, an individualized prudent approach appears to be more reasonable, with the surgical decision based on a comprehensive evaluation of the patient's global health and on a reliable prediction of its future disease risk.

## Financial & competing interests disclosure

*L Busetto declares to have received support for travel to meetings and payment for lectures from Allergan Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

## References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Buchwald H, Estok R, Fahrbach K *et al.* Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am. J. Med.* 122(3), 248–256 (2009).

2 Busetto L, Sbraccia P, Frittitta L, Pontiroli AE. The growing role of bariatric surgery in the management of type 2 diabetes: evidences and open questions. *Obes. Surg.* 21(9), 1451–1457 (2011).

3 Dixon JB, O'Brien PE, Playfair J *et al.* Adjustable gastric banding and conventional therapy for type 2 diabetes. A randomized controlled trial. *JAMA* 299(3), 316–323 (2008).

4 Schauer PR, Kashyap SR, Wolski K *et al.* Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N. Engl. J. Med.* 366(17), 1567–1576 (2012).

5 Mingrone G, Panunzi S, De Gaetano A *et al.* Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N. Engl. J. Med.* 366(17), 1577–1585 (2012).

6 Ikramuddin S, Korner J, Lee WJ *et al.* Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia. The diabetes surgery study randomized clinical trial. *JAMA* 309(21), 2240–2249 (2013).

7 Sjöström L, Lindroos AK, Peltonen M *et al.* Lifestyle, diabetes and cardiovascular risk factors 10 years after bariatric surgery. *N. Engl. J. Med.* 351(26), 2683–2693 (2004).

8 Sjöström L, Narbro K, Sjostrom CD *et al.* Effects of bariatric surgery on mortality in Swedish obese subjects. *N. Engl. J. Med.* 357(8), 741–752 (2007).

9 Sjöström L, Peltonen M, Jacobson P *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 307(1), 56–65 (2012).

10 Christou NV, Sampalis JS, Liberman M *et al.* Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese. *Ann. Surg.* 240(3), 416–424 (2004).

11 Adams TD, Gress RE, Smith SC *et al.* Long-term mortality after gastric bypass surgery. *N. Engl. J. Med.* 357(8), 753–761 (2007).

12 Busetto L, Mirabelli D, Petroni ML *et al.* Comparative long-term mortality after laparoscopic adjustable gastric banding versus nonsurgical controls. *Surg. Obes. Relat. Dis.* 3(5), 496–502 (2007).

13 American Diabetes Association. Executive summary: standards of medical care in diabetes–2011. *Diabetes Care* 34(Suppl. 1), S4–S10 (2011).

14 Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet. Med.* 28(6), 628–642 (2011).

▪▪ **The International Diabetes Federation for the first time considered the use of bariatric/metabolic surgery in patients with Type 2 diabetes and class I obesity (BMI 30–35 kg/m$^2$).**

15 Li Q, Chen L, Yang Z *et al.* Metabolic effects of bariatric surgery in type 2 diabetic patients with body mass index of 35 kg/m$^2$. *Diabetes Obes. Metab.* 14(3), 262–270 (2012).

16 Shimizu H, Timratana P, Schauer PR, Rogula T. Review of metabolic surgery for type 2 diabetes in patients with a BMI <35 kg m$^2$. *J. Obes.* doi:10.1155/2012/147256 (2012) (Epub ahead of print).

- **Recent and updated review on the efficacy and safety of bariatric/metabolic surgery in patients with Type 2 diabetes and BMI <35 kg/m$^2$, with special attention on the problem of excessive weight loss.**

17 Reis CEG, Alvarez-Leite JI, Bressan J, Alfenas RC. Role of bariatric-metabolic surgery in the treatment of obese type 2 diabetes with body mass index <35 kg/m$^2$: a literature review. *Diabetes Technol. Ther.* 14(4), 365–372 (2012).

18 Arterburn DE, O'Connor PJ. A look ahead at the future of diabetes prevention and treatment. *JAMA* 308(23), 2517–2518 (2012).

19 Carnethon MR, De Chavez PJD, Biggs ML *et al.* Association of weight status with mortality in adults with incident diabetes. *JAMA* 308(20), 581–590 (2012).

20 Doehner W, Erdmann E, Cairns R *et al.* Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the proactive study population. *Int. J. Cardiol.* 162(1), 20–26 (2012).

21 Habbu A, Lakkis NM, Dokainish H. The obesity paradox: fact or fiction? *Am. J. Cardiol.* 98(7), 944–948 (2005).

22 Fonarow GC, Srikanthan P, Costanzo MR *et al.* An obesity paradox in acute heart failure: analysis of body mass index and in hospital mortality for 109, 927 patients in the acute decompensated heart failure national registry. *Am. Heart J.* 153(1), 74–81 (2007).

23 Oreopoulos A, Padwal R, Kalantar-Zadeh K *et al.* Body mass index and mortality in heart failure: a meta-analysis. *Am. Heart J.* 156(1), 13–22 (2008).

24 Kalantar-Zadeh K, Kopple JD, Kilpatrick RD *et al.* Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am. J. Kidney Dis.* 46(3), 489–500 (2005).

25 Galal W, Van Gestel YR, Hoeks SE *et al.* The obesity paradox in patients with peripheral arterial disease. *Chest* 134(5), 925–930 (2008).

26 Hastie CE, Padmanabhan S, Slack R *et al.* Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. *Eur. Heart J.* 31(2), 222–226 (2010).

27 Diercks D, Roe MT, Mulgund J *et al.* The obesity paradox in non-ST-segment elevation acute coronary syndromes: results from the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American college of cardiology/American heart association guidelines quality improvement initiative. *Am. Heart J.* 152(1), 140–148 (2006).

28 Mullen JT, Moorman DW, Davenport DL. The obesity paradox. *Ann. Surg.* 250(1), 166–172 (2009).

29 Morse SA, Gulati R, Reisin E. The obesity paradox and cardiovascular disease. *Curr. Hypertens. Rep.* 12(2), 120–126 (2010).

- ■ **An extensive review on the problem of the 'obesity paradox', with an emphasis on the possible pathophysiological pathways.**

30 Scibora LM, Ikramuddin S, Buchwald H *et al.* Examining the link between bariatric surgery, bone loss, and osteoporosis: a review of bone density studies. *Obes. Surg.* 22(4), 654–667 (2012).

31 Cui Y, Elahi D, Andersen DK. Advances in the etiology and management of hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass. *J. Gastrointest. Surg.* 15(10), 1879–1888 (2011).

32 Kellogg TA, Bantle JP, Leslie DB *et al.* Post gastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. *Surg. Obes. Relat. Dis.* 4(4), 492–499 (2008).

33 Marsk R, Jonas E, Rasmussen F, Naslund E. Nationwide cohort study of post-gastric bypass hypoglycemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia* 53(11), 2307–2311 (2010).

34 Hanaire H, Bertrand M, Guerci B, Anduze Y, Guillaume E, Ritz P. High glycemic variability assessed by continuous glucose monitoring after surgical treatment of obesity by gastric bypass. *Diabetes Technol. Ther.* 13(6), 625–630 (2011).

35 Iannelli A, Facchiano E, Gugenheim J. Internal hernia after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Obes. Surg.* 16(10), 1265–1271 (2006).

36 Peterhänsel C, Petroff D, Klinitzke G, Kersting A, Wagner B. Risk of completed suicide after bariatric surgery: a systematic review. *Obes. Rev.* 14(5), 369–382 (2013).

37 Svensson PA, Anveden A, Romeo S *et al.* Alcohol consumption and alcohol problems after bariatric surgery in the Swedish obese subjects study. *Obesity (Silver Spring)* 21(12), 2444–2451 doi:10.1002/oby.20397 (2013) (Epub ahead of print).

38 Sjöström L, Gummesson A, Sjöström D *et al.* Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish obese subjects study): a prospective, controlled intervention trial. *Lancet Oncol.* 10(7), 653–662 (2009).

39 Adams TD, Stroup AM, Gress RE *et al.* Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)* 17(4), 796–802 (2009).

40 Derogar M, Hull MA, Kant P, Ostlund M, Lu Y, Lagergren J. Increased risk of colorectal cancer after obesity surgery. *Ann. Surg.* 258(6), 983–988 (2013).

41 Shah SS, Todkar JS, Shah PS, Cummings DE. Diabetes remission and reduced cardiovascular risk after gastric bypass in Asian Indians with body mass index <35 kg/m$^2$. *Surg. Obes. Relat. Dis.* 6(4), 332–338 (2010).

42 Pories WJ, Dohm LG, Mansfield CJ. Beyond the BMI: the search for better guidelines for bariatric surgery. *Obesity (Silver Spring)* 18(5), 865–871 (2010).

- ■ **A stimulating editorial on the limitation of BMI for the phenotypization and selection of obese patients for surgery.**

43 Boza C, Munoz R, Salinas J *et al.* Safety and efficacy of Roux-en-Y gastric bypass to treat Type 2 diabetes mellitus in non-severely obese patients. *Obes. Surg.* 21(9), 1330–1336 (2011).