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Review

What is the evidence for metabolic surgery for type 2 diabetes? A critical perspective

C. Amouyal, F. Andreelli *

AP–HP, Pierre and Marie Curie University (UPMC), Sorbonne University, Pitié-Salpêtrière–Charles Foix Hospital, Inserm UMRS 1166, Institute of Cardiometabolism and Nutrition (ICAN), Diabetology–Metabolism Department, 75013 Paris 6, France

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Abstract

Bariatric surgery has emerged as a highly effective treatment not only for obesity, but also for type 2 diabetes (T2D). A meta-analysis has reported the complete resolution of T2D in 78.1% of cases of morbidly obese patients after bariatric surgery. Such extraordinary results obtained in diabetic patients with body mass index (BMI) scores > 35 kg/m^2 have led investigators to question whether similar results might be achieved in patients with BMIs < 35 kg/m^2. Preliminary studies suggest that metabolic surgery is safe and effective in patients with T2D and a BMI < 35 kg/m^2, whereas other studies report that metabolic surgery is less effective for promoting T2D remission in these patients. Thus, the results are discordant. Long-term studies would be useful for determining the safety, efficacy and cost-effectiveness of metabolic surgery for this population with T2D. In 2015, it is probably premature to say that metabolic surgery is an accepted treatment option for T2D patients with BMIs < 35 kg/m^2.

Keywords: Bariatric surgery; Metabolic surgery; Obesity; Type 2 diabetes

1. Introduction

A large body of published work, as well as recommendations and clinical experience, demonstrate the metabolic benefits that can result from bariatric surgery. Many patients show indisputable postoperative improvement of their type 2 diabetes (T2D) [1]. Some authors consider bariatric surgery as having more powerful long-term benefits than therapeutic escalation of the hypoglycaemic treatments commonly used in diabetology [2]. Postoperative remission of T2D brings hope to patients who have this complex chronic disease, and demonstrates the potential reversibility of the disorder, formerly believed to inevitably worsen over time. Nevertheless, there are exceptions and, for some patients, in particular the most advanced, there is no major postsurgical recovery. Yet, the improvement of T2D for these patients, albeit less substantial, has more than negligible benefits for these patients by lowering HbA_{1c}, reducing the doses of treatments and the number of classes of hypoglycaemia treatments used, and restoring a degree of efficacy to treatments after all combinations have apparently become ineffective. Consequently, the notion of weight control is being replaced by the hope of possible surgical management of diabetes, including bariatric and metabolic surgery.

The present report has addressed a few simple questions about metabolic surgery by analysing the recent literature and focusing on the two most commonly used techniques, gastric bypass (Roux-en-Y gastric bypass [RYGBP]) and sleeve gastrectomy. Our study looked at who has been treated, when, how and with what results. Despite the widespread growing enthusiasm for surgical management of T2D, and even of prediabetes, some important questions remain.

2. Is metabolic surgery a logical extension of bariatric surgery?

The development of surgical techniques for obesity since the 1950s has had beneficial effects on its comorbidities, including

* Corresponding author. Pitié-Salpêtrière Hospital, Diabetology–Metabolism Department, 47–83, boulevard de l'Hôpital, 75651 Paris cedex 13, France. Tel.: +00 33 1 42 17 81 40; fax: +00 33 1 42 17 82 39.
E-mail address: fabrizio.andreelli@psl.aphp.fr (F. Andreelli).

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Table 1
Proposed definitions for remission and improvement of type 2 diabetes after bariatric surgery.

Authors, year [ref]	Fasting glucose (mg/dL)	HbA_{1c} (%)	Hypoglycaemic treatment
Remission			
Schauer et al., 2003 [8]	< 110	< 6.5	Absence
Buchwald et al., 2004 [9]	< 100	< 6.0	Absence
Dixon et al., 2008 [10]	< 126	< 6.2	Absence
Buse et al., 2009 [11]	< 100	< 5.7	Absence
Mingrone et al., 2012 [12]	< 100	< 6.5	Absence
Ikramuddin et al., 2013 [13]	–	< 7.0	Presence or absence
Schauer et al., 2014 [14]	–	< 6.0	Presence or absence
Improvement			
Schauer et al., 2003 [8]	Reduced by > 0.25 g/L	Reduced by > 1.0	Reduced treatment (stopping oral hypoglycaemic drugs, or 50% reduction of daily insulin dose)

T2D. It was clearly demonstrated in the 1970s that T2D could disappear after interventions such as jejunal–ileal bypass [3]. The first paper describing such cases was done in the 1990s by the team of Walter J. Pories, and clearly raised the issue in its title: "Who would have thought it? An operation proves to be the most effective treatment for adult-onset diabetes mellitus". This laid the foundation for innovative thinking on the possibility of T2D remission by bariatric surgery [4,5]. Since then, the revolution associated with laparoscopy, and improvements in anaesthesia and resuscitation of obese patients, has allowed bariatric surgery to become much more widely used. Also, the worldwide obesity and T2D epidemics have led to research interest in bariatric surgery as a treatment for both disorders.

3. Metabolic surgery: what is it and who is it for?

Is it important to define metabolic surgery? There is increasing discussion of metabolic surgery, but its definition differs according to how the term "metabolic" and the targeted population are viewed. Bariatric surgery can be defined as the set of surgical techniques that promotes the loss of excess weight and its consequences in terms of comorbidities [6]. The population concerned is the one that national and international recommendations have determined as having a favourable benefit/risk balance for bariatric surgery – either a body mass index (BMI) > 35 kg/m^2 with one or more comorbidities, or a BMI > 40 kg/m^2. These patients are mostly managed in specialized multidisciplinary centres for the treatment of obesity.

All the currently available techniques have more or less favourable metabolic effects on glycaemic equilibrium, including dietary restriction, weight loss and additional specific effects with certain techniques (including incretin effects, changes in intestinal flora, reduction of low-grade inflammation, reducing fatty liver and stimulation of intestinal gluconeogenesis) [7].

Metabolic surgery is more strictly defined as a set of surgical techniques promoting improvement of glycaemic equilibrium with the least possible or no effect on weight. With this technique, the aim is to manage diabetes that is uncontrolled, despite hypoglycaemic treatment at its maximum dose, in slightly obese or simply overweight patients. These are the typical diabetic patients with metabolic problems.

The first definition (of bariatric surgery) refers to a super-obese population of patients with one or more comorbidities, of which one is T2D. The second definition (of metabolic surgery) refers to a population of patients with chronic uncontrolled diabetes exposed to complications and for whom recommended diabetes management strategies have failed, but who are not excessively overweight. These patients are principally treated by diabetologists. These are two very different populations, and their health challenges are equally different.

It is also important to consider how the postoperative evolution of T2D is defined, given the possible outcomes: cure (or remission); improvement; or failure (or worsening). Yet, the only criterion extensively used in the literature is the cure or remission of T2D. In the surgical literature, the postoperative evolution of T2D has the same importance as the loss of excess weight. Also, authors all over the world have not used the same definition for the cure of T2D (Table 1) [8–14], although the definition from Schauer et al. [8], published in 2003, has long been considered consensual (fasting glucose < 1.10 g/L or HbA_{1c} < 6.5% without treatment).

As for the diabetologist's point of view, a group of experts from the American Diabetes Association (ADA) proposed, in 2009, very strict definitions for the postoperative outcome of T2D after 1 year [11]: remission of T2D is defined as HbA_{1c} < 5.7% associated with fasting glucose < 5.6 mmol/L, without hypoglycaemic treatment; and partial remission (or improvement) is defined as HbA_{1c} < 6.4% associated with fasting glucose < 6.0 mmol/L, without hypoglycaemic treatment. While this is the strictest definition in terms of the chosen metabolic criteria, it is the one least used in studies.

Despite repeated attempts to define the postoperative metabolic status of patients, publications purportedly in the "metabolic surgery" domain continue to report fasting glucose, but not HbA_{1c}, or only report on the population in postoperative remission for T2D (but no other categories). The multiplicity of definitions makes any meta-analysis of the literature difficult. Also, these publications fail to describe either the treatment for diabetes or changes to treatment, which is important in any consideration of cohort follow-up. Better use of the more rigorous definitions is required to facilitate meta-analyses and comparisons of cohorts. This is particularly

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important given the likely increasing use of metabolic surgery for T2D.

4. What are the precautions to take when reading studies of metabolic surgery?

Most studies of different bariatric surgery techniques for glycaemic equilibrium involve populations of super-obese patients, of which some may have well-controlled diabetes or preoperative HbA_{1c} levels < 8.5%, with T2D patients as a subgroup of the population being studied. There have been many such publications and they have progressively led to the concept of metabolic surgery for T2D, including the idea that the excellent results obtained – at least 1 or 2 years after surgery – in a population of bariatric surgery patients might also be achieved in less-obese diabetic patients (for whom bariatric surgery is currently not recommended).

Publications on surgery for T2D patients with a BMI < 35 kg/m^2 are rare, with only short follow-ups and, often, little metabolic exploration. Also, many of the studies include only Asia–Pacific populations, for which BMI categories (> 23 kg/m^2 is overweight and > 25/m^2 is obese) are not the same as for Western populations [15]. The difference in BMI cutoffs between Asia–Pacific populations and Western populations is six points, so a BMI around 35 kg/m^2 in Asian populations corresponds to a BMI of 40–41 kg/m^2 in Western populations. Thus, any interpretation of descriptions of Asia–Pacific T2D patients with a BMI < 35 kg/m^2 needs to include the understanding that some of these patients are, in fact, severely or even morbidly obese.

5. Metabolic results of metabolic surgery

Data for bariatric surgery in general serve as the reference for the results of metabolic surgery. Certain effects of RYGBP on T2D are immediate and independent of weight loss, and the techniques that lead to the greatest weight loss in the medium- and long-term also result in the greatest improvement of glycaemic equilibrium. In the meta-analysis by Buchwald et al. [9], published in 2004, the overall rate of postoperative cure of T2D following bariatric surgery was 76.8% for all techniques combined. The T2D-specific remission rates were: gastric ring, 48%; RYGBP, 72%; biliary pancreatic diversion, 84%; and duodenal switch, 99%. The long-term T2D cure rate was, in part, dependent on weight loss. This meta-analysis used a definition for cure of T2D as the capacity to maintain glucose within normal limits without hypoglycaemic treatment.

Other recent meta-analyses with sufficient sample sizes and follow-ups of at least 3 years include those by Ganguly et al. [6] and Panunzi et al. [16]. The former authors reported that, for super-obese T2D patients, bariatric surgery using sleeve gastrectomy results in a diabetes remission rate of around 30% whereas, for those treated by RYGBP, the rate is between 38% and 75% [6].

Panunzi et al. [16] only considered randomised trials comparing different bariatric techniques and cohort studies with a follow-up of at least 1 year, with data extraction for two categories of T2D patients (preoperative BMIs < or > 35 kg/m^2). Articles published between 1980 and 2013 were identified, but only 94 were retained, encompassing a total of 94,579 patients, of which 4944 had T2D. Regardless of the preoperative BMI, the rate of T2D remission was 72% for all surgical procedures combined. Biliary pancreatic diversion resulted in remission of diabetes in 89% of cases, RYGBP in 77%, sleeve gastrectomy in 60% and gastric ring in 62%. This meta-analysis showed that:

- preoperative BMI does not predict the postoperative outcome of T2D;
- purely restrictive techniques, considered less effective for T2D (gastric ring, gastric sleeve), have almost the same efficacy as RYGBP for T2D remission.

These three meta-analyses agree on the effects of RYGBP (around 75% T2D remission rate), but are somewhat discordant regarding restrictive techniques: Buchwald et al. [9] and Ganguly et al. [6] found them less effective, whereas Panunzi et al. [16] found them more effective.

Despite these differences, it is clear that the results of most surgical techniques for super-obese T2D patients are good.

6. Are these impressive metabolic results, in particular for RYGBP, misleading?

Analyses of the metabolic effects of surgery depend on the definitions used for remission and improvement of T2D. Mas-Lorenzo et al. [17] compared rates of T2D remission based on two different definitions in prospective studies of T2D patients after RYGBP. Buchwald et al. [9] defined remission as fasting glucose < 1 g/L or HbA_{1c} < 6%, without treatment, and found a T2D remission rate of 93%, while Buse et al. [11] defined it as fasting glucose < 1 g/L and HbA_{1c} < 5.7%, without treatment (the ADA definition) and found a remission rate of 43.6%. The definition of remission thus appears to make a two-fold difference in reported rates.

Ribaric et al. [18] performed a meta-analysis comparing randomised trials for surgical vs medical treatment in T2D patients; the definition for diabetic remission used for the statistical analysis was an HbA_{1c} < 7% (without mentioning whether there was treatment or not). This definition is based on the general objectives of the ADA published in 2009 for the non-surgically treated T2D population, making its use in a meta-analysis of surgery questionable [19].

Very good results with malabsorptive bariatric surgery techniques are often observed after only 1 year of follow-up, whereas the results are significantly worse after 3 years. Furthermore, T2D patients are, in many studies, a subgroup of patients within the cohort, which poses methodological problems of specificity.

7. Metabolic results for super-obese T2D patients

One way to obtain a clearer picture is to analyse reports specifically dedicated to T2D with a sufficiently large cohort of patients and a postoperative follow-up of at least 2 years.

However, in studies fulfilling these criteria, there was a wide range of preoperative BMI scores, ranging from 30 kg/m^2 to > 40 kg/m^2.

Schauer et al. [14] compared surgical treatment (RYGBP or sleeve gastrectomy) with medical treatment in 150 randomised patients with uncontrolled T2D – an HbA$_{1c}$ of 9.3 ± 1.5% at inclusion and a preoperative BMI of 36.0 ± 3.5 kg/m^2. There were benefits for 24% of the sleeve patients and 38% of the RYGBP patients, with T2D remission defined as HbA$_{1c}$ < 6.5% without treatment after 3 years of postoperative follow-up. This was a less favourable result than the spectacular remission figures usually given, but which mostly refer to only 1 year of follow-up.

Halperin et al. [20] reported on 38 patients with uncontrolled T2D, and BMI scores of 30–42 kg/m^2, randomised into an RYGBP group and a medical-treatment group. After 1 year of follow-up, 56% and 16%, respectively, had fasting glucose < 1.26 g/L and HbA$_{1c}$ < 6.5% without hypoglycaemic treatment.

In the study by Ikramuddin et al. [13], 120 T2D patients, with levels of HbA$_{1c}$ > 8% at inclusion and preoperative BMIs of 30–39.9 kg/m^2, were randomised into an RYGBP group and a medical-treatment group. After 1 year of follow-up, 49% of the RYGBP group had an HbA$_{1c}$ < 7% without treatment vs 19% for the medical-treatment group.

These recent randomised trials included populations of T2D patients with preoperative BMIs closer to 35 kg/m^2 than seen in studies of the super-obese, and had a sufficient number of subjects; they had highly variable results for T2D remission after RYGBP, ranging from 49% after 1 year to 38% after 3 years of follow-up.

Mingrone et al. [12] reported much more striking results in 60 patients randomised for medical treatment, RYGBP or biliary pancreatic diversion, and followed for 2 years. Efficacy (T2D remission) was 75% with RYGBP and 95% with biliary pancreatic diversion. These rates of T2D remission are higher than for other studies cited, which may have been because the average preoperative BMI across the three groups of patients was close to 45 kg/m2: higher preoperative BMIs may be associated with higher rates of T2D remission, as suggested by numerous reports of metabolic success with bariatric surgery in the super-obese population.

The same team recently published a randomized single-centre study with a longer follow-up of 5 years [21]. In this study, 60 patients with T2D and a mean baseline BMI of 45 kg/m^2 were randomly assigned to receive either medical treatment (n = 20), RYGBP (n = 20) or biliary pancreatic diversion (n = 20). At baseline, 18 (47%) surgery patients required insulin, either alone or in combination with other drugs. The ADA definition was used to define total or partial remission of diabetes [11]. At the end of follow-up, up to 50% of patients who saw remission of their T2D at 2 years after the surgery had a relapse of mild hyperglycaemia. However, 82% of all surgically treated patients were able to maintain an HbA$_{1c}$ level < 7% with either diet or metformin therapy only, suggesting that surgery strongly improved T2D compared with baseline. In contrast, insulin use increased during the follow-up in the medical group.

The authors concluded that bariatric surgery helped morbidly obese patients with T2D to not only improve glucose homoeostasis, but also to maintain diabetes control with little or no need for antidiabetic drugs over the long-term.

8. Healthcare cost considerations

Beyond the clinical evidence that bariatric surgery may be added to the treatment algorithm for T2D, an interesting question is to estimate the healthcare costs of bariatric surgery according to glucose status at baseline. Can a reduction in total healthcare costs be expected when a population with T2D is surgically treated compared with conventional treatment? As long-term follow-up is needed to provide a response, there are few reports available in the literature. However, one interesting paper by Keating et al. [22] assessed the healthcare costs over a 15-year follow-up in the Swedish Obese Subjects (SOS) study, a prospective study comparing bariatric surgery and conventional treatment of adults (age 37–60 years; BMI ≥ 34 kg/m^2 in men and ≥ 38 kg/m^2 in women) recruited from 25 Swedish surgical departments and 480 primary healthcare centres. Conventional treatment ranged from no treatment to lifestyle interventions and behavioural modifications. During the follow-up, costs for inpatient and outpatient visits and prescription drugs were retrieved through questionnaires and the nationwide Swedish Prescribed Drug Register. Patients were recruited between 1 September 1987 and 31 January 2001.

A total of 2010 adults treated with bariatric surgery and 2037 treated conventionally were enrolled in the SOS study. At baseline, 2836 patients were euglycaemic, 591 patients had prediabetes and 603 had T2D. Total healthcare costs were higher for those with euglycaemia (surgery: US$ 71,059 vs conventional treatment: $ 45,542; adjusted mean difference: $ 22,390, 95% confidence interval [CI]: $ 17,358–27,423; P < 0.0001) or prediabetes (surgery: US$ 78,151 vs conventional treatment $ 54,864; adjusted mean difference: $ 26,292, 95% CI: $ 16,738–35,845; P < 0.0001) in the surgery group than in the conventional-treatment group. In contrast, there was no difference in total healthcare costs in either the surgery or conventional-treatment groups for T2D patients.

Thus, contrary to expectations, no reduction in healthcare costs was observed after bariatric surgery in the population with T2D in the SOS study. While more studies are certainly needed, the report by Keating et al. [22] suggests that healthcare costs should also be considered when the development of metabolic surgery is discussed.

9. Metabolic surgery for T2D patients without major obesity

What are the lessons of the papers describing T2D patients with preoperative BMIs < 35 kg/m^2? Reis et al. [23] performed a meta-analysis of 29 articles following post-RYGBP outcomes for 675 T2D patients with preoperative BMIs < 35 kg/m^2. The average follow-up duration was 18 months. All were in agreement over the postoperative evolution of both BMI (an overall decline of 4 kg/m^2 from 29.95 ± 0.51 kg/m^2 to

Table 2
Publications reporting the effects of gastric bypass in type 2 diabetes patients with preoperative body mass index (BMI) scores < 35 kg/m^2.[a]

Authors, year [ref]	Patients (*n*)	BMI at inclusion (kg/m^2)	Follow-up (years)	Gender ratio (W/M)	Age at inclusion (years)	Known diabetes duration (years)
DeMaria et al., 2010 [25]	109	< 35	2	NS	52.8	NR
Huang et al., 2011 [26]	22	25.0–34.8	1	20/2	28–63	1–20
Lee et al., 2011 [27]	62	23.0–35.0	2	38/24	32–54	5.4 ± 5.1
Boza et al., 2011 [28]	30	30.4–35.0	3.5	17/13	28–65	4.0 ± 2.9
Serrot et al., 2011 [29]	17	< 35	1	13/4	56 ± 7	NR
de Sa et al., 2011 [30]	27	< 35	7	20/7	50.3 ± 8.3	8.8 ± 6.7
Zhu et al., 2012 [31]	30	19.3–32.6	1	8/22	29–66	5.98 ± 4.54
Navarrete Aulestia et al., 2012 [32]	15	30.0–34.7	1	14/1	15–52	1–9
Lanzarini et al., 2013 [33]	31	30.1–34.8	2.5	16/15	34–66	1–15

Results are presented as range of distribution or means ± SD; W: women; M: men; NR: not reported.
[a] Based on the meta-analysis by Rao et al. [24].

Table 3
Effects of gastric bypass on type 2 diabetes (T2D) remission and HbA_{1c} in T2D patients with preoperative body mass index (BMI) scores < 35 kg/m^2.[a]

Authors, year [ref]	Patients (*n*)	Total remission[b] (%)	Partial remission[c] (%)	No effect[d] (%)	Preop HbA_{1c} (%)	Postop HbA_{1c} (%)	Postop follow-up (years)
DeMaria et al., 2010 [25]	109	55	NR	NR	NR	NR	1
Huang et al., 2011 [26]	22	63.6	27.3	9.10	10.4 ± 2.0	6.0 ± 1.1	1
Lee et al., 2011 [27]	62	57.15	35.71	7.14	9.7 ± 1.9	5.8 ± 0.5	2
Boza et al., 2011 [28]	30	83.80	NR	NR	8.1 ± 1.8	5.9 ± 1.1	3.5
Serrot et al., 2011 [29]	17	23.5	41.2	35.3	8.2 ± 2.0	6.1 ± 2.7	1
de Sa et al., 2011 [30]	27	48.15	44.44	7.4	8.36 ± 2.05	5.97 ± 0.74	7
Zhu et al., 2012 [31]	30	30	NR	NR	8.02 ± 1.17	5.59 ± 1.02	1
Navarrete Aulestia et al., 2012 [32]	15	93	0	7	7.60 ± 0.73	5.53 ± 0.64	1
Lanzarini et al., 2013 [33]	31	93.6	6.4	0	7.7 ± 2.1	5.47 ± 0.70	2.5

Results are presented as means ± SD; Preop/Postop: pre-/postoperative; NR: not reported.
[a] Based on the meta-analysis by Rao et al. [24].
[b] HbA_{1c} < 6% without hypoglycaemic treatment.
[c] HbA_{1c} 6–7% without hypoglycaemic treatment.
[d] HbA_{1c} > 7% without hypoglycaemic treatment.

24.83 ± 0.44 kg/m^2) and HbA_{1c} (a drop of 8.89 ± 0.15% to 6.35 ± 0.18%). As for glycaemic equilibrium, the rate of remission was 55.47%, the rate of T2D control was 28.59% and improvement was 14.37%. Only 1.63% of the patients ($n = 11$) showed no improvement or had postoperative worsening of their diabetes.

Rao et al. [24] performed a meta-analysis of articles published between 1980 and 2013 on the effects of RYGBP in T2D in populations with BMIs < 35 kg/m^2. The applied criteria were > 15 T2D patients with a preoperative BMI < 35 kg/m^2 and a minimum follow-up duration of 12 months. Nine articles were included (Table 2) [25–33]. The postoperative follow-up lasted from 1 to 7 years. In these studies as a whole, the HbA_{1c} (mean ± standard deviation [SD]) dropped from a preoperative value of 8.34 ± 1.80% to 5.79 ± 0.80% at the end of follow-up (Table 3), and the mean BMI fell from 31.0 ± 2.1 kg/m^2 to 25.3 ± 3.4 kg/m^2 (Table 4). Using a definition of T2D remission based on an HbA_{1c} level < 6% without hypoglycaemic treatment, the overall T2D remission rate was 57% (range: 23–93%; Table 3). The complication rate during the entire follow-up varied from 6.7% to 25.9%, depending on the study, with no mortality.

These two meta-analyses show favourable T2D outcomes after RYGBP in a population of patients with BMIs < 35 kg/m^2. However, the rate of T2D remission was close to 50% and lower than in super-obese populations.

A review of the literature for bariatric surgery of T2D patients with preoperative BMIs < 35 kg/m^2 and postoperative follow-ups of between 6 and 216 months by Fried et al. [34] is consistent with this observation. They found that metabolic improvement was greater in patients with high (30–35 kg/m^2) vs lower (25–29.9 kg/m^2) preoperative BMIs. This suggests that the more-obese patients are better candidates for metabolic surgery. This review also noted that the malabsorptive techniques were the most effective for resolution of T2D and did not result in inappropriate weight loss (average BMI went from 29.4 kg/m^2 to 24.2 kg/m^2), indicating they are safe even for patients without major obesity.

However, the metabolic effects of bariatric surgery appear to be less pronounced for less-obese patients than for super-obese patients. This suggests that the pathophysiology of diabetes differs between the super-obese and less-obese/overweight patients, and that weight loss is a major feature of the long-term effects of the surgery.

Table 4
Effects of gastric bypass on body mass index (BMI) in type 2 diabetes patients with preoperative BMIs < 35 kg/m^2.[a]

Authors, year [ref]	Patients (n)	Preoperative BMI (kg/m^2)	Postoperative BMI (kg/m^2)	Postoperative follow-up (years)
DeMaria et al., 2010 [25]	109	33.7 ± 1.1	27.1 ± 4.5	2
Huang et al., 2011 [26]	22	30.8 ± 2.9	23.7 ± 1.6	1
Lee et al., 2011 [27]	62	30.1 ± 3.3	22.6 ± 2.3	2
Boza et al., 2011 [28]	30	33.5 ± 1.2	24.4 ± 2.3	3.5
Serrot et al., 2011 [29]	17	34.6 ± 0.8	25.8 ± 2.5	1
de Sa et al., 2011 [30]	27	33.5 ± 1.5	25.7 ± 2.9	7
Zhu et al., 2012 [31]	30	32.2 ± 1.5	28.5 ± 2.0	1
Navarrete Aulestia et al., 2012 [32]	15	32.8 ± 1.4	24.2 (−26.7%)	1
Lanzarini et al., 2013 [33]	31	33.1 ± 2.0	24.3 ± 3.1	2.5

Data are presented as means ± SD unless otherwise specified.
[a] Based on the meta-analysis by Rao et al. [24].

10. To what extent do the beneficial effects of bariatric surgery depend on weight loss?

The acute and immediate effects of RYGBP are independent of weight loss, and its long-term metabolic results are also relatively independent of weight change, perhaps because RYGBP has different effects on insulin sensitivity and secretion [7]. The question remains: is the relative independence from weight loss equally observed in T2D patients with preoperative BMIs < 35 kg/m^2?

To our knowledge, only a single study clearly addressed this question. Kaska et al. [35] reported on the post-RYGBP metabolic evolution of T2D patients with preoperative BMIs < or > 35 kg/m^2. T2D patients who underwent RYGBP between 2007 and 2010 were prospectively followed for 36 months: 30 had a (mean ± SD) BMI at inclusion of 29.10 ± 2.15 kg/m^2; and 82 had a baseline BMI of 44.20 ± 5.49 kg/m^2. These patients were, on average, 46 years old, and their known duration of diabetes was (mean ± SD) 7.90 ± 3.91 years for those with BMIs < 35 kg/m^2 and 6.80 ± 3.63 years for those with BMIs > 35 kg/m^2. Approximately 40% of patients in the two groups were treated with insulin therapy.

HbA_{1c} levels at inclusion were also similar (8.9%) between the two groups. Excess weight loss was faster and greater in the most overweight group (BMIs > 35 kg/m^2): those with preoperative BMIs of 44.2 kg/m^2 dropped to 31.2 kg/m^2 6 months after the procedure and stabilized at 29.4 kg/m^2 after 36 months. For the other group, those with preoperative BMIs of 29.1 kg/m^2 fell to 24.4 kg/m^2 6 months after the procedure, then stabilized at 25.0 kg/m^2 after 36 months.

In addition, the evolution of HbA_{1c} and fasting venous glucose levels was exactly the same in the two groups, despite the large difference in weight loss. HbA_{1c} dropped from a preoperative value of 8.9% to 6.0% at 6 months after the procedure, and remained stable for the rest of the study. The number of patients in T2D remission (fasting glucose < 1 g/L and HbA_{1c} < 6% without hypoglycaemic treatment) was similar in both groups: 80% at 6 months and 78% at 36 months after the procedure. The frequency of symptomatic postoperative hypoglycaemia that required resugaring was equally similar in the two groups (37%, with the disappearance of such episodes in all patients). Postoperative surgical complications, however, were more frequent in the group with BMIs > 35 kg/m^2 at inclusion.

Thus, RYGBP is a therapeutic approach with a favourable benefit/risk ratio for T2D patients with BMIs < 35 kg/m^2, and the relatively small loss of excess weight (−4 kg/m^2) in this group was not a limiting factor for the effectiveness of the operation against diabetes.

The maintenance of long-term positive metabolic effects of bariatric surgery in super-obese patients requires weight control. Indeed, the SOS study reported that 72% of patients were in remission from diabetes after 2 years, although this fell to 36% after 10 years. This shows that 50% of the patients with rapid remission of their diabetes (after a 2-year follow-up) relapsed afterwards [36]. Long-term weight control is essential for avoiding a relapse of T2D. Unfortunately, the lack of long-term data for patients with BMIs < 35 kg/m^2 makes it impossible to report on any postoperative weight changes in this population.

Many studies of Asia-Pacific populations report that the short-term cure rate for T2D is less in populations with BMIs < 35 kg/m^2 than in those with higher BMIs or those in Western super-obese populations (Table 5). Dixon et al. [37] studied the effects of RYGBP in 103 Chinese and Korean T2D patients with BMIs < 30 kg/m^2 (range: 18.9–30 kg/m^2); the remission rate (HbA_{1c} < 6%) after 1 year was only 30%. Malapan et al. [38] analysed the post-RYGBP evolution in 29 Chinese T2D patients with preoperative BMIs of 20.9–26.9 kg/m^2 and reported a 1-year T2D remission rate of 38%. These results contradict those published by Lee et al. [39], who reported a 1-year T2D remission rate (but using less-strict criteria: fasting glucose < 1.26 g and HbA_{1c} < 6.5% without hypoglycaemic treatment) of 93% in 30 Chinese T2D patients with initial BMIs of 25–35 kg/m^2. However, there was no information on the distribution of patients according to their initial BMI, so it is not possible to know whether the beneficial results were for the most obese patients in this study. However, Yin et al. [40] addressed this issue in 68 Chinese patients with uncontrolled T2D who underwent RYGBP. The T2D remission rate was 80.9% for the entire cohort 1 year after the procedure, whereas the T2D remission rate was only 32.1% for the 28 patients with preoperative BMIs < 27.5 kg/m^2. Thus, RYGBP has a lower metabolic effect

Table 5
Effects of gastric bypass on remission of type 2 diabetes (T2D) in severely obese Caucasian and Asian patients with preoperative body mass index scores < 35 kg/m^2.

Authors, year [ref]	T2D patients (*n*)	Geographical origin of patients	Preoperative BMI range (kg/m^2)	T2D remission 1 year after gastric bypass (%)
Meta-analyses or studies of super-obese patients				
Buchwald et al., 2004 [9]	1846		32.3–68.8	83.7
Panunzi et al., 2015 [16]	1138		28–33	77
	3380		45–49	77
Mas-Lorenzo et al., 2014 [17]	55		41–49	93.0[a] 43.6[b]
Studies or meta-analyses of Caucasian patients with BMI < 35 kg/m^2				
Mingrone et al., 2012 [12]	60		31–51	75
Ikramuddin et al., 2013 [13]	120		30–39.9	49
Schauer et al., 2014 [14]	150		33–39.5	38
Halperin et al., 2014 [20]	38		30–42	56
Reis et al., 2012 [23]	675		29–30	55.4
Rao et al., 2015 [24]	343		30–34	61
Fried et al., 2010 [34]	343		25–35	85.3
Kaska et al., 2014 [35]	30		27–31	78
	82		39–49	78
Studies of only Asian patients				
Dixon et al., 2013 [37]	103	China, South Korea	18.9–30	30
Malapan et al., 2014 [38]	29	China	20.9–26.9	38
Lee et al., 2011 [39]	30	China	25–35	93
Yin et al., 2014 [40]	68	China	≤ 27.5 (*n* = 28) > 27.5 (*n* = 40)	32 68

Definition of diabetes remission: for all studies excepted [17]: HbA_{1c} < 6% without hypoglycemic treatment.
[a] For study [17]: fasting glucose < 1 g/L or HbA_{1c} < 6% without treatment.
[b] For study [17]: fasting glucose < 1 g/L and HbA_{1c} < 5.7% without treatment.

in patients with lower BMIs. The authors suggested that weight loss made a large contribution to the postoperative metabolic benefits of RYGBP.

11. Metabolic surgery: should we go ahead? What are the recommendations for 2016?

The increasing demand for metabolic surgery in T2D patients who are not extremely obese is due to its potential to manage the disorder after pharmaceutical failure. The surgical management of T2D is increasingly recommended, but still primarily for patients with BMIs > 35–40 kg/m^2:

The ADA proposes that bariatric surgery must remain in the sphere of medical research for T2D patients with BMIs < 35 kg/m^2 [41].

The International Diabetes Federation (IDF) recommends bariatric surgery for patients if their HbA_{1c} is > 7% with metformin treatment as monotherapy – in other words, very early in the evolution of the disorder [2].

The European recommendations for metabolic and bariatric surgery, published in 2014, indicate that T2D patients with BMIs of 30–35 kg/m^2 can be considered for bariatric surgery on a case-by-case basis [42]. Nevertheless, they state that complementary studies are necessary to better identify which of these T2D patients might benefit the most from surgical treatment.

In summary, international recommendations are cautious and recommend further studies, except for the proposal by the IDF (which is not widely followed).

12. Conclusion

The results of the available studies on metabolic surgery are mixed. The literature is centred on remission of T2D, even though the more limited improvement in metabolic equilibrium would constitute a major advance in T2D patients facing therapeutic failure. Reducing the level of HbA_{1c} from 12% to 8% and, thus, lowering the category of metabolic severity would be a substantial step forward even if hypoglycaemic treatment continues to be necessary. In such a population, it makes no sense to research predictive factors in the postoperative evolution of T2D; they need a rescue strategy. Thus, for a diabetologist, the recommendation of metabolic surgery after the failure of pharmacological management of T2D is contrary to that of surgical reports, which continue to recommend the use of surgery early in the evolution of T2D.

Studies of patients with uncontrolled T2D (therapeutic failures) but who are not severely obese are clearly needed. It is still not known whether there is genuine benefit from surgery or what the benefit/risk ratio is for serious micro-/macroangiopathic complications. The question remains whether it is not already too late to consider bariatric surgery for T2D patients in therapeutic failure. It may be of benefit to operate earlier, but there are no data to indicate the most opportune moment. Potential times for surgical intervention could be: when going from bi- to tritherapy; at the metabolic syndrome stage; when a target HbA_{1c} is surpassed even with monotherapy; or some other point. The best-suited operative technique also remains to be determined. Future studies focused on these issues and done with both diabetologists and surgeons in collaboration would be highly valuable.

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The authors declare that they have no competing interest.

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