Endocrinol Nutr. 2014;61(1):35–46

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo

REVIEW ARTICLE

Metabolic surgery: Quo Vadis?

Ana M. Ramos-Leví*, Miguel A. Rubio Herrera

Servicio de Endocrinología y Nutrición, Hospital Clínico San Carlos, IdISSC, Madrid, Spain

Received 26 February 2013; accepted 24 April 2013

KEYWORDS
Metabolic surgery;
Bariatric surgery;
Review;
Type 2 diabetes mellitus;
Type 2 diabetes mellitus remission;
Obesity;
Morbid obesity

Abstract The impact of bariatric surgery beyond its effect on weight loss has entailed a change in the way of regarding it. The term *metabolic surgery* has become more popular to designate those interventions that aim at resolving diseases that have been traditionally considered as of exclusive medical management, such as type 2 diabetes mellitus (T2D). Recommendations for metabolic surgery have been largely addressed and discussed in worldwide meetings, but no definitive consensus has been reached yet. Rates of diabetes remission after metabolic surgery have been one of the most debated hot topics, with heterogeneity being a current concern. This review aims to identify and clarify controversies regarding metabolic surgery, by focusing on a critical analysis of T2D remission rates achieved with different bariatric procedures, and using different criteria for its definition. Indications for metabolic surgery for patients with T2D who are not morbidly obese are also discussed.

PALABRAS CLAVE
Cirugía metabólica;
Cirugía bariátrica;
Revisión;
Diabetes mellitus tipo 2;
Remisión de la diabetes mellitus tipo 2;
Obesidad;
Obesidad mórbida

Cirugía metabólica: ¿Quo Vadis?

Resumen El impacto de la cirugía bariátrica más allá de su efecto sobre la pérdida de peso ha supuesto un cambio en la visión que se tiene de ella. Así, se ha hecho más popular la denominación «cirugía metabólica» para referirse a las intervenciones encaminadas a resolver enfermedades que tradicionalmente se han considerado de tratamiento exclusivamente médico, como la diabetes mellitus tipo 2 (DM2). En numerosos foros internacionales se han abordado y debatido las indicaciones recomendadas de la cirugía metabólica, pero no se ha logrado aún un consenso definitivo. Las tasas de remisión de la diabetes tras la intervención han sido uno de los temas más candentes, y sus valores heterogéneos siguen siendo objeto de preocupación. El objetivo de esta revisión es identificar y aclarar las controversias en torno a la cirugía metabólica, centrándose en el análisis crítico de las tasas de remisión de la DM2 obtenidas con distintas técnicas bariátricas, y utilizando criterios diferentes para su definición. Se comentan también las indicaciones de la cirugía metabólica en los pacientes con DM2 sin obesidad mórbida.

* Corresponding author.
E-mail addresses: ana.ramoslevi@gmail.com, ana_ramoslevi@hotmail.com (A.M. Ramos-Leví).

2173-5093/$ - see front matter
http://dx.doi.org/10.1016/j.endoen.2014.01.012

Why call it metabolic surgery?

Metabolic surgery has become the pathway for acceptance of surgical procedures for dealing with diseases traditionally considered as exclusively medically managed. If we look back in history, the classical example of metabolic surgery has been the *Program on the Surgical Control of the Hyperlipidemias* (POSCH),[1,2] where it was observed that partial ileal bypass was an intervention capable of producing a marked reduction of low-density lipoprotein cholesterol (LDL-c), and was consequently associated with a statistically significant decline in cardiovascular events and increase in life expectancy. In this way, the idea that surgery could be regarded as a valid option for the treatment of metabolic diseases turned out to be true. Buchwald and Varco, in 1978, specified the conception of metabolic surgery by defining it as ''the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain''.[3,4]

Another example of metabolic surgery with current clinical relevance is bariatric surgery. This was initially conceived with the aim of achieving sustained and significant weight loss by using restrictive, malabsortive and mixed techniques. The rise in the number of interventions performed for people with morbid obesity during the 1990s, revealed that not only was this goal achieved, but, in fact, other associated comorbidities, including type 2 diabetes (T2D) were also improved.[5] In 1995, the provocative title of Pories et al., ''*Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus*'',[6] showed that, indeed, bariatric surgery was able to resolve T2D of the adult, and emphasized that there were mechanisms beyond those merely anatomical inherent to the surgical technique responsible for this effect.

Buchwald et al. published in 2004 a systematic review and metaanalysis[7] of more than 22,000 patients who underwent bariatric surgery, and described improvement of diabetes in 86.6% of patients and complete resolution in 78.1%. Moreover, hyperlipemia was improved in 70% of cases, hypertension was resolved or improved in 78.5%, and obstructive sleep apnea was resolved in 85.7% of patients. Definitions of resolution and improvement differed across the studies included in this metaanalysis, but, given the results observed, it became evident that metabolic surgery was not used solely to designate procedures for the treatment of T2D, but also to refer to those interventions that aimed at reducing the impact of other cardio-metabolic aspects.

The impact of bariatric surgery beyond its effect on weight loss entailed a change in the way of thinking of scientific societies. In 2007, the executive boards of the so-called *American Society for Bariatric Surgery* (*ASBS*) and *International Federation for the Surgery of Obesity* agreed to include the term *metabolic* in their designations, advocating the idea that metabolic surgery truly *operated on perfectly normal organs or organ systems to achieve a biological result for a potential health gain*: the treatment of metabolic illnesses, and not just excess weight. Thus, these societies have become to be known as the *American Society for Metabolic and Bariatric Surgery (ASMBS)* and the *International Federation for the Surgery of Obesity and Metabolic Disorders*. This renovation has also been adopted by the homologous Spanish society, which is now named *Sociedad Española de Cirugía de la Obesidad Mórbida y Enfermedades Metabólicas*.[8]

Intensive lifestyle intervention, as reported in the LOOK-AHEAD study,[9] achieves only modest T2D remission rates of 11.5% and 7.4% after one and four years of follow-up, respectively. These rates prove that an intensive lifestyle intervention is associated with a greater likelihood of partial remission of T2D in comparison with conventional support and educational management. However, intensive management still achieves results way lower than outcomes described after a surgical approach, where even the lowest rates reported were higher than with medical protocols.[10] The opinion that surgical interventions may be an alternative option for chronic and progressive medical issues such as obesity and T2D has gained acceptance and popularity, and superiority has been subsequently described in several studies.[10,11] Bariatric surgery has become, in this way, the prototype of metabolic surgery, to such extent, that both terms have often been considered synonymous.

But a recent study by Rubino et al.,[12] which aimed at investigating the practical clinical consequences of offering two different surgery programs, identified differences in patients' profiles depending on the denomination used: bariatric or metabolic. This may lead to considering distinctions between both denominations, based on what the foremost target is, i.e., weight reduction or treatment of metabolic illnesses. Nevertheless, once again, the debate may revive: can both problems be regarded on an individual basis, or should they be viewed as a whole?

This review aims to identify and clarify controversies regarding metabolic surgery for T2D and tries to guide the reader to an unbiased interpretation of published data.

Metabolic surgery: for whom?

There are several national and international guidelines and consensus statements that address the indications for bariatric surgery in patients with T2D.[13–17] They all share basic terms and conditions, such as failure of previous weight-loss attempts, no specific contraindications to surgery and the patient's commitment to long-term follow-up and after care. These guidelines used to be based on specific body mass index (BMI) cut-off levels. However, this requisite has been questioned over the last recent years. Table 1 shows current guidelines established by the International Diabetes Federation (IDF),[13,14] the American Diabetes Association (ADA),[15] the National Institute for Health and Clinical Excellence (NICE)[16] and the International Federation for the Surgery of Obesity and Metabolic Disorders – Asian Pacific Chapter (IFSO-APC).[17] Only the IDF and the Obesity Work Group from the *Sociedad Española de Endocrinología y Nutrición* (SEEN)[18] contemplate the possibility of bariatric surgery in cases with BMI < 35 kg/m^2. Nevertheless, in spite of these general guidelines, consensus and position statements regarding the management of hyperglycemia in T2D have not included surgical intervention in their step-by-step algorithms.

Table 1 Guidelines for eligibility for bariatric surgery in adults with T2D.

	International Diabetes Federation (IDF), 2011[13,14]	American Diabetes Association (ADA), 2013[15]	National Institute for Health and Clinical Excellence (NICE), 2006[16]	IFSO-Asian Pacific Chapter (IFSO-APC), 2011 (Asia) [17]
Recommended priority for surgery	BMI > 40 kg/m^2. BMI > 35 kg/m^2 when T2D and other comorbidities not controlled by optimum medical treatment.	No priority for any group.	BMI >50 kg/m^2	BMI > 35 kg/m^2 with or without comorbidities
Eligible BMI with T2D	BMI > 35 kg/m^2. BMI > 30 kg/m^2 when T2D and other comorbidities not controlled by optimum medical treatment.	BMI > 35 kg/m^2 if T2D or other comorbidities not controlled by lifestyle and pharmacological treatment.	BMI >35 kg/m^2 with one weight-loss responsive comorbidity.	BMI > 30 kg/m^2 when T2D and other comorbidities not controlled by optimum medical treatment.
Comments	Adjust BMI if Asian ethnic origin.	BMI < 35 kg/m^2 only in research protocols.		Consider non-primary alternative in BMI > 27.5 kg/m^2 if inadequately controlled T2D or metabolic syndrome

How is diabetes remission after metabolic surgery defined?

Distinction between successful treatment and cure may be difficult when talking about T2D, since diabetes is defined by hyperglycemia, which exists on a continuum, unlike other acute diseases. Cure is defined as restoration to good health, while remission is defined as reduction or disappearance of signs and symptoms of a disease.[19] Due to the chronicity of T2D, it seems reasonable and more accurate to use the term *remission*, which will be the one used throughout this review.

The Cochrane Database System Review[20] and Buchwald et al.'s review,[21] both published in 2009, demonstrated the effectiveness of bariatric surgery for improvement and resolution of T2D. However, remission rates described across different studies have varied widely. In general, T2D remission has been defined as ''the return to normal values of fasting glucose (FG) and glycosylated hemoglobin (HbA1c), in the absence of active pharmacologic treatment''. But cut-off levels used for these parameters have not always been homogeneous, and variations in the time of follow-up considered for evaluation have also occurred. Moreover, disparities amongst patients' baseline characteristics have contributed to this heterogeneity.

In an attempt to overcome this controversy and establish standardized remission criteria, a consensus group comprised of experts in endocrinology, diabetes education, transplantation, metabolism, bariatric/metabolic surgery and hematology-oncology, proposed specific definitions for diabetes remission (Table 2).[19] These new definitions rely on more stringent criteria for establishing glycemic control, and, consequently, remission rates have been communicated to be lower than previously reported in the literature.

Table 2 Definitions of T2D remission according to Buse et al.[19]

Partial remission	Subdiabetic hyperglycemia: - HbA1c not diagnostic for diabetes (<6.5%). - Fasting glucose 100–125 mg/dL (5.6–6.9 mmol/L). No active pharmacologic treatment or ongoing procedures. At least one year's duration.
Complete remission	Normal glycemic measures: - HbA1c in the normal range (<6%). - FG <100 mg/dL (<5.6 mmol/L). No active pharmacologic treatment or ongoing procedures. At least one year's duration.
Prolonged remission	Complete remission of at least five year's duration.

For instance, in the review by Buchwald et al.,[21] T2D remission was reported in 78% of patients after gastric bypass, but its definition was largely based on clinical reports, rather than in specific biochemical parameters, there were few good quality studies with a high level of evidence, and patients' preoperative information and follow up of most cohorts was not described in detail. Nonetheless, these outstanding results reaffirmed surgeons' optimism for the treatment of T2D. A low level of quality and evidence has been a common attribute of well-known studies, whose reports have been mostly based on

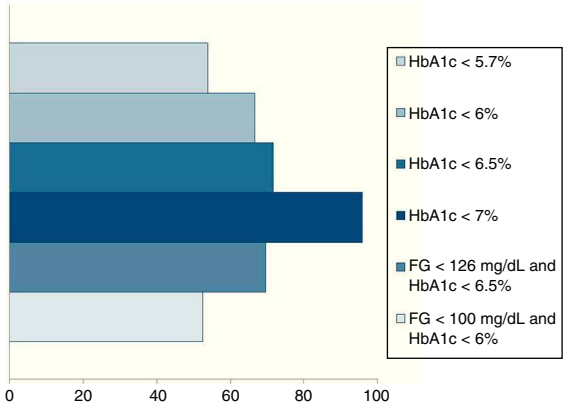

Figure 1 T2D remission rates according to different criteria (percentages estimated for the same population).

case-series, with no methodological control.[6,22–24] The studies by Sjostrom et al.,[25] Dixon et al.,[26] Schauer et al.[10] and Mingrone et al.,[11] on the other hand, have been considered of higher quality, given its controlled design. But remission rates still varied due to differences in criteria used and baseline patients' features. Overall, data from large, adequately powered, long-term randomized controlled trials in bariatric surgery are still lacking, although a trend for an increasing number has been observed in recent years.[27]

Pournaras et al.[28] and Blackstone et al.[29] compared remission rates using different models of remission criteria: those previously reported in literature, versus the ones proposed by Buse et al.,[19] and observed a significant reduction in remission rates to around 50%. This may be a more realistic approximation of what can be expected after metabolic surgery, taking also into account existing differences between population's features. Table 3 highlights the main characteristics of the most relevant publications over the last recent years regarding T2D remission after bariatric surgery. Fig. 1 represents an estimate of the range of remission rates that would be obtained by using different criteria for the same population. It can be observed that frequencies vary from around 50%, when using the more stringent criteria, to near 90%, if only an adequate metabolic control is considered, defined by HbA1c levels below 7%. It must be noted, however, that these results are generally referred to the period of maximum weight-loss, that is, the first two years after surgery, and long-term evaluation may reveal lower remission rates.

Given the difficulty of establishing remission of a disease whose definition is based on a continuous variable, we suggest that, for example, ADA's HbA1c cut-off levels for diagnosis of diabetes[53] could perhaps be helpful, more straightforward, and clinically practical for doing so (Table 4). A comparison of this model of criteria with the one proposed by the 2009 consensus group was recently published,[54] and no significant differences were found.

However, scientific societies have not yet formally accepted any specific criteria and there has been no definitive positioning regarding this matter, so heterogeneity across subsequent publications persists.

What factors may affect type 2 diabetes remission after metabolic surgery?

Published reports have described a set of predictors of T2D remission:

1. *Previous duration of diabetes*. Duration of diabetes has been taken as an estimate of disease severity. The longer this period, the lower remission rates. It is one of the most frequently identified predictors of remission across numerous reports.[35,42,52,54,55] Some have proposed different thresholds, ranging between 5 and 10 years, for which the probability of achieving diabetes remission decreases, and it has been proposed that T2D duration longer than 15 years would imply no remission.
2. *Previous insulin treatment*. The use of insulin therapy prior to surgery has been associated to lower rates of remission, in comparison to those patients who were treated with oral agents exclusively: 13.5% vs. 53.8% in Blackstone et al.'s report.[29] The explanation lies on the assumption that insulin treatment could also be regarded as an estimation of disease severity, duration of diabetes and worse control, presumably due to deterioration of pancreatic beta-cells.
3. *Weight loss*. The complex association between obesity and T2D justifies the fact that percentage of weight loss (%WL) and percentage of excess weight loss (%EWL) influence diabetes remission. Insufficient %WL seems to be one of the main reasons for inadequate T2D control, and this may sometimes be linked to a lack of patient's commitment to long-term follow-up, or even to failure of the surgical technique.[56] A %EWL of at least 50% (or 30% of %WL) is required to allow a significant improvement or even remission of T2D.[57] Nevertheless, improvement of glycemic control after surgery can be observed as early as in the immediate postoperative period, when a significant weight loss has not yet been achieved,[58,59] and, consequently, surgeons have promoted the use of metabolic surgery in patients with only mild obesity, or even with mere overweight.[39,44,60,61] Several weight-independent mechanisms are involved in the short and mid-term amelioration of glucose metabolism, but, there are no studies that evaluate their efficacy in the long-term, in the absence of an associated fat reduction. The association between T2D and excess adiposity is complex; in fact, it has been observed that up to 80% of individuals classified as overweight (BMI 25.0–29.9 kg/m^2) and up to 29% of lean subjects (BMI 20.0–24.9 kg/m^2) have a body fat percentage that could be judged as within the obesity range, when determined by air displacement plethysmography.[62] Excess body fat, especially abdominal visceral fat, may explain the development of metabolic disorders such as T2D and atherogenic dyslipemia in patients with BMI < 30 kg/m^2. This circumstance can be remarked in the particular case of Asian populations, in whom and elevated risk of T2D, hypertension and hyperlipemia has been observed at a relatively low level of BMI. As a result, surgical indications have been deliberated and BMI criteria have been adapted for this specific group of patients, as it was described earlier.[17] Revaluation of T2D in patients with

Table 3 Main characteristics of the most relevant reports concerning T2D remission after metabolic surgery.

Type of surgery	Author, year	Study population	Definition of T2D remission	T2D remission rate (%)
LAGB	Dolan et al., 2003[30]	BMI 45 kg/m^2	No hypoglycemic treatment	65.3
	Pontiroli et al., 2005[31]	BMI 48 kg/m^2	Not specified Assumed FG < 7 mmol/l	45
	Dixon et al., 2008[26]	BMI 30–40 kg/m^2 T2D < 2 years	HbA1c < 6.2%, FG < 7 mmol/l, no treatment	73
	Buchwald et al., 2009[21]	BMI 48 kg/m^2 No other details	HbA1c < 6%, FG < 100 mg/dl	57
	Dixon et al., 2012[32]	Heterogeneity	Improvement to normal HbA1c (differences across studies)	53–70
	Keogh et al., 2012[33]	BMI 41.5 kg/m^2 T2D duration 8 years	HbA1c < 6.5%, no treatment	16
RYGB	Schauer et al., 2003[22]	BMI > 40 kg/m^2 or BMI > 35 kg/m^2 +comorbidities	FG < 110 mg/dl and ''normal'' HbA1c (<6%)	
	Adams et al., 2010[34]	BMI > 35 kg/m^2	FG < 126 mg/dl, no treatment	79
	Hall et al., 2010[35]	BMI 47 kg/m^2 T2D duration 5.5 years Insulin in 26%	HbA1c < 6.5%, no treatment	68.4
	Hofso et al., 2010[36]	BMI 45.1 kg/m^2 HbA1c 7.1%	FG < 126 mg/dl, HbA1c < 6.5%, no treatment	70
	De Sa et al., 2011[37]	BMI 30–35 kg/m^2 T2D duration 8.8 years Insulin in 22%	FG < 100 mg/dl, HbA1c < 6%, no treatment	48
	Nora et al., 2011[38]	BMI 44.3 kg/m^2 T3D duration 6.2 years Insulin in 9.6%	No T2D criteria, without treatment (FG < 126 mg/dl and HbA1c < 6.5%)	92.7
	Blackstone et al., 2012[29]	BMI > 35 kg/m^2	5 models	43.2–59.4
	Cohen et al., 2012[39]	BMI 30–35 kg/m^2 T2D duration 12.5 years	HbA1c < 6.5% and no treatment	80–90
	Leslie et al., 2012[40]	BMI > 35 kg/m^2	HbA1c < 7%, LDL < 100 mg/dl and TAS < 130 mmHg	38.2
	Arterburn et al., 2013[41]	HbA1c > 6.5% (no treatment) or HbA1c < 6.5% (treatment) BMI 45 kg/m^2 T2D duration 4.5 years Insulin in 21.8% USA	Partial: FG < 126 mg/dl and/or HbA1c < 6.5% without treatment >90 days. Complete: FG < 100 mg/dl and/or HbA1c < 6% without treatment >90 days.	Partial: 47.2 (1 year) 76.9 (5 years) Complete: 37.1 (1 year) 68.2 (5 years)
	Dixon et al., 2013[42]	BMI 37.2 kg/m^2 T2D duration 2 years Insulin in 15% China	HbA1c < 6%, no treatment	69.5
BPD	Sánchez-Pernaute et al., 2010[43]	BMI 44.2 kg/m^2 Insulin in 52% HbA1c 7.6%	HbA1c < 6.5%	100
	Scopinaro et al., 2011[44]	BMI 25–30 kg/m^2 T2D duration 11.2 years HbA1c 9.3%	HbA1c < 7% and no treatment	80
	Sánchez-Pernaute et al., 2012[45]	BMI 44.6 kg/m^2 T2D duration 9.8 years HbA1c 7.9%	HbA1c < 6%	92

Table 3 (*Continued*)

Type of surgery	Author, year	Study population	Definition of T2D remission	T2D remission rate (%)
SG	Gill et al., 2010[46]	BMI 47.4 kg/m^2		66.2
	Abbatini et al., 2012[47]	BMI 52.1 kg/m^2 T2D duration 7 years Insulin in 3%	FG < 100 mg/dl, HbA1c < 6.5%, no treatment	87.9 (1 year) 76.9 (5 years)
	Benaiges et al., 2013[48]	BMI 45 kg/m^2 T2D duration 1.5 years HbA1c 6.9%	FG < 100 mg/dl, HbA1c < 6%, no treatment	60 (2 years)
MIX	Sjostrom et al., 2004[25]	BMI 41 kg/m^2 Sweden	FG < 7 mmol/l, no treatment	72 (2 years) 36 (10 years)
	Vidal et al., 2008[50]	Spain	FG < 126 mg/dl, HbA1c < 6%	85
	Buchwald et al., 2009[21] Pournaras et al., 2012[28]	BMI ≈ 45 kg/m^2	FG < 100 mg/dl, HbA1c < 6%, no treatment	40–60
	Lee et al., 2011[51]	BMI 25–35 kg/m^2	FG < 126 mg/dl, HbA1c < 6.5%, no treatment	50–90
	Hamza et al., 2011[52] Miingrone et al., 2012[11]		FG < 100 mg/dl, HbA1c < 6.%, no treatment	40–80
	Schauer et al., 2012[10]	BMI 27–43 kg/m^2	HbA1c < 6.5%, no treatment	35–40
	Ramos-Leví et al., 2013[54]	BMI 43.6 kg/m^2 T2D duration 7.6 years Insulin in 44.5%	2 models (2009 consensus statement and HbA1c criteria)	50

LAGB = laparoscopic adjustable gastric band; RYGB = Roux-en Y gastric bypass; BPD = biliopancreatic diversion; SG = Sleeve gastrectomy; MIX = mixed techniques.

Table 4 Proposed simplified criteria for T2D remission, according to ADA's definition of diabetes.[53,54]

Remission	HbA1c < 5.7% No active hypoglycemic treatment
Improvement	HbA1c 5.7–6.4% No active hypoglycemic treatment
No remission	HbA1c > 6.5% Active hypoglycemic treatment
Optimal control	HbA1c < 7% With or without active hypoglycemic treatment

lower BMI with other alternative assessment tools deems, therefore, necessary to manage these individuals, for which well-designed randomized trials should be carried out.

4. *Preoperative baseline C-peptide*. Baseline C-peptide is a surrogate of pancreatic beta-cell mass and insulin secretion. High levels have been identified in obese patients, and significant reductions have been observed after bariatric procedures. Some reports have proposed high preoperative C-peptide levels (around >3 ng/mL) as predictors of remission,[42,55,63,64] although there is no established agreement on preoperative cut-off values and its clinical relevance has not been thoroughly analyzed, especially because levels may be influenced by hypoglycemic treatment. Stimulated C-peptide levels and evaluation of incretin effects require further investigation.
5. *Age*. Older age has been associated to no remission, presumably due to deterioration of pancreatic beta-cells and T2D progression.[55] However, not all studies have found differences in age between remitters and non-remitters. Furthermore, the majority of studies include patients under the age of 60, making the distinction between the effect of age itself and T2D duration confusing.
6. *Sex*. Some studies suggest male sex as a predictor of remission, although this has not been consistent across all reports.[29] However it is worth remarking the fact that, in general, men tend to lose more weight than women, but T2D remission rates adjusted for gender have not been found to be significantly different.
7. *Inadequate diagnosis of T2D*. Late autoimmune diabetes of the adult (LADA), type 1 diabetes and some forms of maturity-onset diabetes of the young (MODY) prove lower rates of resolution after bariatric surgery, apparently due to other concomitant pathogenic factors involved. Inclusion of these patients in bariatric series may, therefore, influence remission reports.

Bariatric surgery in patients with type 2 diabetes and BMI < 35 kg/m^2

Bariatric surgery offers an effective treatment option for glycemic control in patients with T2D and morbid

obesity, and numerous papers have reported profound weight loss and amelioration of all obesity-related comorbidities in patients with BMI > 35 kg/m^2.[7,21,25] These encouraging results, together with the identification of weight-independent mechanisms responsible for resolution of diabetes, have prompted consideration of bariatric surgery for less obese individuals.

Recent reports have described that bariatric surgery was also effective for diabetes resolution in cases with BMI < 35 kg/m^2,[39] a finding with important clinical relevance, since patients with a BMI between 30 and 35 kg/m^2 constitute the most numerous class of obese people. In this setting, metabolic surgery purely aims at resolving T2D, not so much obesity. However, as it was previously outlined, individuals with BMI 30–35 kg/m^2 still have an elevated body fat percentage, with visceral preponderance, making reduction of this adipose tissue a perdurable main priority for the amelioration of metabolic disorders. It is, therefore, important that patients with T2D and only ''mild'' obesity receive correct information regarding the main objectives and what to expect of the surgical procedure. Moreover, reduction of micro and macrovascular complications, as well as of long-term cardiovascular morbidity and mortality, should also be aimed, not only an improved BMI, but data in literature is still scarce.[65–67]

Additionally, several questions have been set to debate in this context. Firstly, the appropriate time to recommend surgery in these cases is not well established, and there are no agreements in consensus statements, since there is insufficient evidence-based data from large randomized controlled trials in this range of BMI. Also, deliberation regarding risks and benefits of surgery should be contemplated. Furthermore, previous diabetes status should be taken into account, since patients would obtain benefit from surgery mainly due to weight-independent mechanisms, and if pancreatic reserve is downgraded, effectiveness would be diminished.

Due to the above-mentioned issues, metabolic surgery for patients with T2D and BMI < 35 kg/m^2 is contemplated by the IDF[13,14] and the Obesity Work Group from the *Sociedad Española de Endocrinología y Nutrición* (SEEN),[18] for patients with poor glycemic control and associated cardio-metabolic risk factors, in whom other alternative treatment strategies have failed. Additionally, the American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery (AACE/TOS/ASMBS) in their recently updated guidelines,[81] consider that patients with BMI of 30–34.9 kg/m^2 with diabetes or metabolic syndrome may also be offered a bariatric procedure. Nevertheless, they acknowledge that current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit, and they also remark that there is insufficient evidence for recommending bariatric surgical procedures specifically for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone, independent of BMI criteria. The ADA,[15] on the other hand, considers that there is not enough safety and efficacy data to be able to recommend metabolic surgery in this group of patients outside clinical trials and research protocols. But the Food and Drug Administration (FDA) has recently approved the use of gastric banding and sleeve gastrectomy also for patients with BMI of 30–34.9 kg/m^2. Further high-quality long-term studies seem necessary.

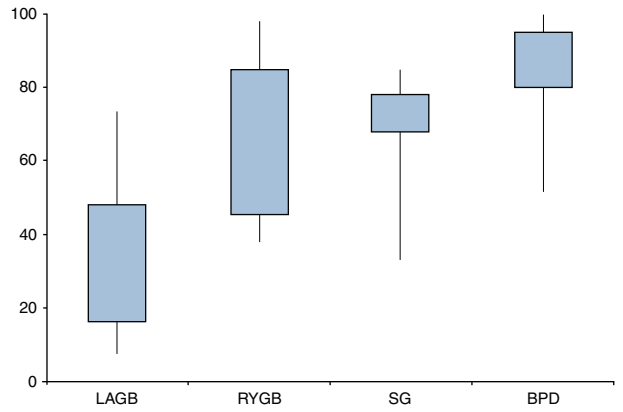

Figure 2 Type 2 diabetes remission rates according to different bariatric procedures: laparoscopic gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and biliopancreatic diversion (BPD). Percentages taken and adapted from results from different studies, which include different remission criteria.

Are all types of surgeries equally effective?

Resolution of diabetes following bariatric surgery occurs because of both weight-dependent and independent mechanisms.[58,59,68] Therefore, the type of surgical procedure will influence rates of remission. Several studies and reviews have addressed the different approaches and their overall results, reporting T2D remission rates ranging from 7–70% for laparoscopic adjustable gastric banding (LAGB), 38–98% for Roux-en-Y gastric bypass (RYGB), 33–85% for sleeve gastrectomy (SG), and 52–100% for biliopancreatic diversions (BPD) (Fig. 2).

Nevertheless, it is essential to bear in mind that there are few studies that directly compare two different techniques[10,11,48–51,69]; therefore, it is difficult to reach definitive conclusions about the relative effectiveness of various surgical techniques beyond mere and prudent speculations concerning each individual report. And moreover, once again, the use of arbitrary remission criteria and heterogeneous study populations, mainly regarding differences in BMI and previous insulin use, may bias results and confound our interpretations.

Laparoscopic adjustable gastric banding

Laparoscopic adjustable gastric banding (LAGB).[7,26,32,58,70] Overall, remission rates after LAGB have been described to be lower than with other types of interventions, presumably because the core mechanism involved is weight loss. Buchwald et al.[7] described remission rates below 50%. Conversely, in the unblinded randomized controlled trial by Dixon et al.,[26] which included patients with BMI between 30 and 40 kg/m^2 and a recently diagnosed T2D (<2 years) undergoing LAGB, 73% of patients achieved remission, defined as FG < 126 mg/dL and HbA1c < 6.2%, without diabetes medications. The systematic review by Dixon

et al.[32] included studies from 2000 to 2011 and reported that remission or improvement in diabetes ranged from 53% to 70%, with consistent results in patients with sustained weight loss, but there were few high-quality and long-term studies.

Roux-en-Y-Gastric Bypass

Roux-en-Y Gastric Bypass (RYGB), with different lengths of the alimentary and biliopancreatic limbs, has been one of the most reported interventions for the surgical resolution of T2D, and its safety and long-term efficacy has been well established. Two large case-series studies by Pories et al.[6] and Schauer et al.[22], described return to ''normal'' HbA1c levels without hypoglycemic medications, in 91% and 83% of patients, respectively, yet these series included patients with prediabetes. The multicenter Swedish Obese Subjects (SOS) study,[71] which compared three types of surgery versus medical treatment, reported the highest weight loss in patients with RYGB and a 2-year recovery rate from diabetes significantly higher (73%), although it decreased at 10-year follow-up to 36%.[25]

Variations in intestinal limb lengths have often made comparison and assessment of operation outcomes difficult. Two recent reviews[72,73] aimed to compare the effect of different limb lengths on weight loss: Orci et al.[72] observed a trend to support that a longer Roux-limb would be more efficient in superobese patients. Stefanidis et al.[73] described that a Roux-limb of at least 150 cm was associated with a modest weight loss advantage in the short-term in superobese patients, but no significant impact was seen in patients with BMI < 50 kg/m^2; they focused on the common channel as the way to achieve a significant weight loss due to malabsorption, promoting a length of at least 100 cm.

However, debate exists on whether or not the length of intestinal limbs may affect T2D remission rates, to such an extent, that some surgeons have empirically, and not evidence-based, attempted to use different measures and distinguish between bariatric and metabolic surgery.

Sleeve gastrectomy

Sleeve gastrectomy (SG) was initially conceived as a merely restrictive procedure, but has gained popularity over recent years. Ongoing observations have described its efficacy for T2D improvement, mainly because, apart from its effect on reduced food intake, several physiologic mechanisms develop, such as reduction of ghrelin secretion due to resection of the gastric fundus, and early incretin stimulation due to rapid gastric emptying.[46–48] Additionally, the easiness of its laparoscopic performance and its low rate of complications has prompted its use as a first-step intervention in extremely obese patients, whose surgical risk is high and T2D control is poor. Thus, data is becoming more available.

Vidal et al.[50] reported resolution of T2D (defined as fasting plasma glucose <126 mg/dl and HbA1c in the normal range, in the absence of hypoglycemic treatment) at 12 months in 85% of the 39 patients whose mean BMI and HbA1c was 52 kg/m^2 and 7.4%, respectively, without significant differences compared to gastric bypass. Benaiges et al.,[48] also found equivalent results between SG and RYGB, with T2D remission rates around 60%. On the other hand, in the randomized controlled trial by Lee et al.,[51] only 14 of 30 patients (47%) achieved remission after SG, yet their mean preoperative BMI was 30 kg/m^2 and their mean HbA1c level was 10%. Recently, Abbatini et al.[47] evaluated long-term remission of T2D after SG in 33 patients with mean BMI of 52 kg/m^2 and mean HbA1c 7.3%. They reported discontinuation of diabetes medications in 89% of patients at 3 months, 85% at 36 months, and 77% at 60 months, remarking the benefit of SG for the treatment of T2D. There is insufficient evidence to recommend SG over RYGB or BPD, and, again, patients' preoperative features, including their T2D conditions, will influence surgical outcome.

Biliopancreatic diversion

Biliopancreatic diversion and other variations, such as duodenal switch and single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S), have been reported to be the most effective procedures for resolution of T2D,[7,21,24,43–45] with rates reaching more than 90%. Buchwald et al., in their metaanalysis of 2004[7] and 2009,[21] reported remission rates in 98% and 95% of patients, respectively, and these rates have been observed to be maintained for several years.[24,74] However, attention must be drawn to the fact that these malabsorptive procedures may lead to undesirable adverse effects such as vitamin deficiency and risk of malnutrition.

Novel techniques

Novel techniques have been recently attempted, conceived as primarily antidiabetic, such as duodeno-jejunal bypass, ileal interposition and endoluminal duodeno-jejunal sleeve, with promising results in the short-term evaluation.[58]

What can we expect on the long-term follow-up?

The promising results for the short and mid-term follow up may be jeopardized when patients are evaluated in the long-term. In fact, different case series have reported a rate of T2D recurrence of 50–90% 5 years or more after metabolic surgery.[25,33,41,75–78] T2D relapse may be explained by unfavorable preoperative factors, inadequate weight loss and weight regain, lack of patient's commitment to treatment and follow-up, failure of the surgical technique, and inadequate incretin stimulation following surgery.[56] It is probable that a publication bias exists, with studies that obtain disappointing results not being reported.

Management of T2D relapse after metabolic surgery may be challenging and has not been thoroughly evaluated. Anatomic modifications determine pathophysiological changes that may alter the effects of oral hypoglycemic medications and increase insulin sensitivity.[79] The presence of weight regain may be helpful to rule out pancreatic beta-cell exhaustion, and may guide us into the best treatment alternatives. However, there are no evidence-based data to

make clinical recommendations. Increase in the number of metabolic procedures performed and long-term follow-up will provide additional data regarding the best approach in these cases.

What happens with those who do not achieve diabetes remission?

As it has been previously outlined, stringent criteria have lowered diabetes remission rates. Furthermore, observational studies with mid and long-term follow-up have shown an increased number of patients who do not strictly fulfill these criteria, or in whom T2D reappears after an initial amelioration. This was observed, for example, in the SOS study, where T2D remission rates went from around 70% at 2 years, to around 30% at 10 years, basically due to weight regain.

However, defining an individual as ''non-remitter'' of diabetes according to biochemical criteria should not underestimate the role that metabolic surgery plays in cases with poorly controlled and long-standing T2D. Indeed, these patients benefit from significant reductions in FG and HbA1c levels, as well as form decreasing insulin requirements and use of hypoglycemic medications. Likewise, the number of patients who reach an optimum combined metabolic control, as defined by ADA's target recommendations[15] (HbA1c < 7%, LDLc < 100 mg/dL, tryglicerides < 150 mg/dL and HDLc > 40 mg/dL in male or >50 mg/dL in female), significantly increases, with barely any difference between ''remitters'' and ''non-remitters''[82]. Furthermore, since hypertension is also improved or even resolved after metabolic surgery, ADA's target blood pressure levels[15] (<140/80 mmHg) may be more easily achieved, yet amelioration of hypertension is less obvious, due to other pathogenic mechanisms involved. And also, preliminary analysis point out that bariatric surgery appears to be cost-effective, although long-term data are still needed.[80]

For these reasons, even though a patient could be initially considered as a poor candidate for T2D resolution after bariatric surgery owing to, for example, his long diabetes duration, high insulin requirements and previous deficient control, this possibility should not be disregarded. In fact, quite the opposite: indication for surgical procedures should be taken into account, since overall metabolic improvement, which is the foremost goal of bariatric surgery, may be attained, with little surgical risk.[21,25,34]

Final considerations

The impact of bariatric surgery for the treatment of diabetes and other obesity-associated comorbidities has led to widespread of the term *metabolic surgery* to describe interventions that aim at improving these diseases. T2D remission rates have varied over a wide range across published studies, mainly due to heterogeneity in criteria used for definition, patients' baseline characteristics, and the type of procedure performed. A valid estimate would be to establish remission of diabetes in around 50% of patients, yet these observations can only apply in the short-term evaluation (up to 2 years of follow-up).

Even in ''non-remitters'', surgery allows and overall benefit regarding combined metabolic control. Thus, T2D remission should not be aimed as the foremost goal, to the extent of developing new types of interventions that would risk nutritional health status. Correct metabolic control using the least number of medications as possible should be thought of as enough, and therefore regarded as the overall core objective if patient's quality of life improves.

In this way, metabolic surgery should not be applied only to those with established T2D diagnosis or a specific BMI cut-off level, but also to patients with further signs of metabolic syndrome, such as insulin resistance, arterial hypertension, hyperlipemia, hyperuricemia, liver steatosis, polycystic ovarian syndrome and endothelial disease, amongst others. These patients benefit as well from the impact of surgery on cardio-metabolic comorbidities.

It would be desirable that scientific societies dealing with T2D and metabolic surgery elaborated a consensus document in which guidelines for eligibility for surgical procedures were addressed for patients with T2D and different BMI categories, and universal criteria for evaluation, both in the short and long-term, were also established.

Conflict of interest disclosure statement

The authors declare no conflict of interest.

Acknowledgment

We acknowledge grant support from the Fundación Mutua Madrileña de Investigación Biomédica AP 89592011.

References

1. Buchwald H, Varco RL, Matts JP, Long JM, Fitch LL, Campbell GS, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). N Engl J Med. 1990;323:946–55.
2. Buchwald H, Campos CT, Boen JR, Nguyen PA, Williams SE. Disease-free intervals after partial ileal bypass in patients with coronary heart disease and hypercholesterolemia: report from the Program on the Surgical Control of the Hyperlipidemias (POSCH). J Am Coll Cardiol. 1995;26:351–7.
3. Buchwald H, Varco RL, editors. Metabolic surgery. New York: Grune and Stratton; 1978.
4. Buchwald H. Metabolic surgery: a brief history and perspective. Surg Obes Relat Dis. 2010;6:221–2.
5. Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. Lancet. 2012;16:2300–11.
6. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222:339–52.
7. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and metaanalysis. JAMA. 2004;292:1724–37.
8. Sánchez-Pernaute A, Torres-García AJ. Cirugía metabólica. Cir Esp. 2008;84:1–2.

9. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al., Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA. 2012;308:2489–96.
10. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Eng J Med. 2012;366:1567–76.
11. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366: 1577–85.
12. Rubino F, Shukla A, Pomp A, Moreira M, Ahn SM, Dakin G. Bariatric, metabolic and diabetes surgery. What's in a name? Ann Surg. 2013.
13. Rubino F, Kaplan LM, Schauer PR, Cummings DE. The Diabetes Surgery Summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. Ann Surg. 2010;251:399–405.
14. Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese type 2 diabetes. Diabet Med. 2011;28:628–42.
15. American Diabetes Association. Standards of medical care in diabetes 2013 (position statement). Diabetes Care. 2013;36 Suppl. 1:S11–66.
16. NICE. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: National Institute for Health and Clinical Excellence; 2006.
17. Kasama K, Mui W, Lee WJ, Lakdawala M, Naitoh T, Seki Y, et al. IFSO-APC consensus statements 2011. Obes Surg. 2012;22:677–84.
18. Lecube A, Burguera B, Rubio MA, Grupo de Trabajo de Obesidad de la Sociedad Española de Endocrinología y Nutrición (GOSEEN). Breaking therapeutic inertia: should metabolic surgery be considered one more option for the treatment of type 2 diabetes mellitus? Endocrinol Nutr. 2012;59:281–3.
19. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care. 2009;32:2133–5.
20. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database Syst Rev. 2009;2:CD003641.
21. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and metaanalysis. Am J Med. 2009;122:248–56.
22. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238:467–84.
23. Sugerman HJ, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. Ann Surg. 2003;237:751–6.
24. Scopinaro N, Marinari GM, Camerini GB, Papadia FS, Adami GF. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. Diabetes Care. 2005;28:2406–11.
25. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351:2683–93.
26. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299:316–23.
27. Chan CP, Wang BY, Cheng CY, Lin CH, Hsieh MC, Tsou JJ, et al. Randomized controlled trials in bariatric surgery. Obes Surg. 2013;23:118–30.
28. Pournaras DJ, Aasheim ET, Søvik TT, Andrews R, Mahon D, Welbourn R, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg. 2012;99:100–3.
29. Blackstone R, Bunt JC, Cortés MC, Sugerman HJ. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose, and medication status. Surg Obes Relat Dis. 2012;8:548–55.
30. Dolan K, Bryant R, Fielding G. Treating diabetes in the morbidly obese by laparoscopic gastric banding. Obes Surg. 2003;13:439–43.
31. Pontiroli AE, Folli F, Paganelli M, et al. Laparoscopic gastric banding prevents type 2 diabetes and arterial hypertension and induces their remission in morbid obesity. A 4-year case-controlled study. Diabetes Care. 2005;28:2703–9.
32. Dixon JB, Murphy DK, Segel JE, Finkelstein EA. Impact of laparoscopic adjustable gastric banding on type 2 diabetes. Obes Rev. 2012;13:57–67.
33. Keogh JB, Turner KM, McDonald F, Toouli J, Clifton PM. Remission of diabetes in patients with long-standing type 2 diabetes following placement of adjustable gastric band: a retrospective case control study. Diabetes Obes Metab. 2013;15:383–5.
34. Adams TD, Pendleton RC, Strong MB, et al. Health outcomes of gastric bypass patients compared to nonsurgical, nonintervened severely obese. Obesity (Silver Spring). 2010;18: 121–30.
35. Hall TC, Pellen MG, Sedman PC, Jain PK. Preoperative factors predicting remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery for obesity. Obes Surg. 2010;20:1245–50.
36. Hofsø D, Nordstrand N, Johnson LK, et al. Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur J Endocrinol. 2010;163:735–45.
37. de Sa VC, Ferraz AA, Campos JM, et al. Gastric bypass in the treatment of type 2 diabetes in patients with a BMI of 30 to 35 kg/m^2. Obes Surg. 2011;21:283–7.
38. Nora M, Guimarães M, Almeida R, et al. Metabolic laparoscopic gastric bypass for obese patients with type 2 diabetes. Obes Surg. 2011;21:1643–9.
39. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL, Cummings DE. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012;35:1420–8.
40. Leslie DB, Dorman RB, Serrot FJ, et al. Efficacy of the Roux-en-Y gastric bypass compared to medically managed controls in meeting the American Diabetes Association composite end point goals for management of type 2 diabetes mellitus. Obes Surg. 2012;22:367–74.
41. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg. 2013;23:93–102.
42. Dixon JB, Chuang LM, Chong K, Chen SC, Lambert GW, Straznicky NE, et al. Predicting the glycemic response to gastric bypass surgery in patients with type 2 diabetes. Diabetes Care. 2013;36:20–6.
43. Sánchez-Pernaute A, Herrera MA, Pérez-Aguirre ME, Talavera P, Cabrerizo L, Matía P, et al. Single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S). One to three-year follow-up. Obes Surg. 2010;20:1720–6.
44. Scopinaro N, Adami GF, Papadia FS, Camerini G, Carlini F, Briatore L, et al. The effects of biliopancreatic diversion on type 2 diabetes mellitus in patients with mild obesity (BMI 30–35 kg/m^2) and simple overweight (BMI 25–30 kg/m^2): a prospective controlled study. Obes Surg. 2011;21: 880–8.
45. Sánchez-Pernaute A, Rubio MA, Pérez Aguirre E, Barabash A, Cabrerizo L, Torres A. Single-anastomosis duodenoileal bypass with sleeve gastrectomy: metabolic improvement and weight loss in first 100 patients. Surg Obes Relat Dis. 2012 [Epub ahead of print].

46. Gill RS, Birch DW, Shi X, Sharma AM, Karmali S. Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review. Surg Obes Rel Dis. 2010;7:707–13.
47. Abbatini F, Capoccia D, Casella G, Soricelli E, Leonetti F, Basso N. Long-term remission of type 2 diabetes in morbidly obese patients after sleeve gastrectomy. Surg Obes Relat Dis. 2012, pii: S1550-7289(12)00340-1.
48. Benaiges D, Flores Le-Roux JA, Pedro-Botet J, Chillarón JJ, Renard M, Parri A, et al. Sleeve gastrectomy and Roux-en-Y gastric bypass are equally effective in correcting insulin resistance. Int J Surg. 2013;11:309–13.
49. Vidal P, Ramón JM, Goday A, Benaiges D, Trillo L, Parri A, González S, Pera M, Grande L. Laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy as a definitive surgical procedure for morbid obesity. Mid-term results. Obes Surg. 2013;23:292–9.
50. Vidal J, Ibarzabal A, Romero F, Delgado S, Momblán D, Flores L, et al. Type 2 diabetes mellitus and the metabolic syndrome following sleeve gastrectomy in severely obese subjects. Obes Surg. 2008;18:1077–82.
51. Lee WJ, Chong K, Ser KH, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Arch Surg. 2011;146:143–8.
52. Hamza N, Abbas MH, Darwish A, Shafeekb Z, Newa J, Ammori BJ. Predictors of remission of type 2 diabetes mellitus after laparoscopic gastric banding and bypass. Surg Obes Relat Dis. 2011;7:691–6.
53. American Diabetes Association. Diagnosis and classification of diabetes mellitus (position statement). Diabetes Care. 2013;36 Suppl. 1:S67–74.
54. Ramos-Levi AM, Cabrerizo L, Matía P, Sánchez-Pernaute A, Torres AJ, Rubio MA. Which criteria should be used to define type 2 diabetes remission after bariatric surgery? BMC Surg. 2013;13:8, http://dx.doi.org/10.1186/1471-2482-13-8.
55. Lee WJ, Chong K, Chen JC, et al. Predictors of diabetes remission after bariatric surgery in Asia. Asian J Surg. 2012;35: 67–73.
56. Deitel M. Update: why diabetes does not resolve in some patients after bariatric surgery. Obes Surg. 2011;21: 794–6.
57. Dixon JB, Hur KY, Lee WJ, Kim MJ, Chong K, Chen SC, et al. Gastric bypass in Type 2 diabetes with BMI <30: weight and weight loss have a major influence on outcomes. Diabet Med. 2013;30:127–34.
58. Rubino F, Schauer PR, Kaplan LM, Cummings DE. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. Annu Rev Med. 2010;61: 393–411.
59. Rubino F, R'bibo SL, del Genio F, Mazumdar M, McGraw TE. Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. Nat Rev Endocrinol. 2010;6:102–9.
60. Navarrete Aulestia S, Leyba J, Navarrete LLS, García Caballero M, Sánchez N, Pulgar V, et al. Roux-en-Y gastric bypass for treatment of patients with DM type 2 and BMI of 30 to 35 kg/m^2. Nutr Hosp. 2012;27:1160–5.
61. Li Q, Chen L, Yang Z, Ye Z, Huang Y, He M, et al. Metabolic effects of bariatric surgery in type 2 diabetic patients with body mass index of 35 kg/m^2. Diabetes Obes Metab. 2012;14: 262–70.
62. Gómez-Ambrosi J, Silva C, Galofré JC, Escalada J, Santos S, Millán D, et al. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. Int J Obes. 2012;36:286–94.
63. Lee WJ, Chong K, Ser KH, Chen JC, Lee YC, Chen SC, et al. C-peptide predicts the remission of type 2 diabetes after bariatric surgery. Obes Surg. 2012;22:293–8.
64. Ramos-Leví AM, Matía P, Cabrerizo L, Barabash A, Torrejón MJ, Sánchez-Pernaute A, Torres AJ, Rubio MA. C-peptide levels predict type 2 diabetes remission after bariatric surgery. Nutr Hosp. 2013 [in press].
65. Miras AD, Chuah LL, Lascaratos G, Faruq S, Mohite AA, Shah PR, Gill M, Jackson SN, Johnston DG, Olbers T, le Roux CW. Bariatric surgery does not exacerbate and may be beneficial for the microvascular complications of type 2 diabetes. Diabetes Care. 2012;35:e81.
66. Heneghan HM, Cetin D, Navaneethan SD, Orzech N, Brethauer SA, Schauer PR. Effects of bariatric surgery on diabetic nephropathy after 5 years of follow-up. Surg Obes Relat Dis. 2013;9:7–14.
67. Johnson BL, Blackhurst DW, Latham BB, Cull DL, Bour ES, Oliver TL, Williams B, Taylor SM, Scott JD. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. J Am Coll Surg. 2013, pii: S1072-7515(12)01409-3.
68. Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA, Seeley RJ. All bariatric surgeries are not created equal: insights from mechanistic comparisons. Endocr Rev. 2012;33:595–622.
69. Jiménez A, Casamitjana R, Flores L, Viaplana J, Corcelles R, Lacy A, et al. Long-term effects of sleeve gastrectomy and Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus in morbidly obese subjects. Ann Surg. 2012;256:1023–9.
70. Pontiroli AE, Pizzocri P, Librenti MC, Vedani P, Marchi M, Cucchi E, et al. Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: a three-year study. J Clin Endocrinol Metab. 2002;87:3555–61.
71. Sjöström CD, Lissner L, Wedel H, Sjöström L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes Res. 1999;5:477–84.
72. Orci L, Chilcott M, Huber O. Short versus long Roux-limb length in Roux-en-Y gastric bypass surgery for the treatment of morbid and super obesity: a systematic review of the literature. Obes Surg. 2011;21:797–804.
73. Stefanidis D, Kuwada TS, Gersin KS. The importance of the length of the limbs for gastric bypass patients—an evidence-based review. Obes Surg. 2011;21:119–24.
74. Marinari GM, Papadia FS, Briatore L, Adami G, Scopinaro N. Type 2 diabetes and weight loss following biliopancreatic diversion for obesity. Obes Surg. 2006;16:1440–4.
75. Kadera BE, Lum K, Grant J, Pryor AD, Portenier DD, De Maria EJ. Remission of type 2 diabetes after Roux-en-Y gastric bypass is associated with greater weight loss. Surg Obes Relat Dis. 2009;5:305–9.
76. Chikunguwo SM, Wolfe LG, Dodson P, Meador JG, Baugh N, Clore JN, et al. Analysis of factor associated with durable remission of diabetes after Roux-en Y gastric bypass. Surg Obes Relat Dis. 2010;6:254–9.
77. DiGiorgi M, Rosen DJ, Choi JJ, Milone L, Schrope B, Olivero-Rivera L, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long term follow-up. Surg Obes Relat Dis. 2010;6:249–53.
78. Dorman RB, Serrot FJ, Miller CJ, et al. Case-matched outcomes in bariatric surgery for treatment of type 2 diabetes in the morbidly obese patient. Ann Surg. 2012;255:287–93.
79. Kashyap SR, Schauer P. Clinical considerations for the management of residual diabetes following bariatric surgery. Diabetes Obes Metab. 2012;14:733–9.
80. Picot J, Jones J, Colquitt JL, Loveman E, Clegg AJ. Weight loss surgery for mild to moderate obesity: a systematic review and economic evaluation. Obes Surg. 2012;22: 1496–506.
81. Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M, et al., Heinberg LJ, Kushner R, Adams TD, Shikora S, Dixon JB, Brethauer S. Clinical practice guidelines for

the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient-2013 update: cosponsored by American Association of Clinical Endocrinologists, the obesity society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis. 2013;9:159–91.

82. Ramos-Levi AM, Sánchez Pernaute A, Cabrerizo L, Matia P, Barabash A, Hernández C, et al. Remission of type 2 diabetes mellitus hould not be the foremost goal after bariatric surgery. Obes Surg. 2013, http://dx.doi.org/10.1007/s11695-013-1032-x.