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REVIEW ARTICLE

Metabolic Surgery and Diabesity: a Systematic Review

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Abstract
Bariatric surgery is used to induce weight loss (baros = weight). Evidence has shown that bariatric surgery improves the comorbid conditions associated with obesity such as hypertension, hyperlipidemia, and type 2 diabetes mellitus T2DM. Hence, shifting towards using metabolic surgery instead of bariatric surgery is currently more appropriate in certain subset of patients. Endocrine changes resulting from operative manipulation of the gastrointestinal tract after metabolic surgery translate into metabolic benefits with respect to the comorbid conditions. Other changes include bacterial flora rearrangement, bile acids secretion, and adipose tissue effect. The aim of this systematic review is to examine clinical trials regarding long-term effects of bariatric and metabolic surgery on patients with T2DM and to evaluate the potential mechanisms leading to the improvement in the glycaemic control.

Keywords Diabesity · Type 2 diabetes mellitus · Obesity · Metabolic surgery

Introduction

The increasing pandemics of type 2 diabetes mellitus (T2DM) and obesity are closely related and represent an important worldwide public health problem [1]. Obesity is an independent risk factor for the development of T2DM [2], leading to the term "diabesity" or obesity with accompanying T2DM. Bariatric surgery is the term referred to gastrointestinal surgery for weight control (baros = weight), whereas metabolic surgery refers to the use of surgery to primarily and purposely treat T2DM and/or metabolic syndrome. Metabolic surgery is gaining popularity as the procedure of choice for treatment of morbid obesity and T2DM, with results suggesting that weight loss and resolution of comorbidities, including T2DM, are better than those with other standard approaches (drugs) [2]. Moreover, bariatric surgery, or more appropriately "metabolic surgery," has been proposed as a new treatment option for T2DM in mildly obese patients with BMI < 35 kg/m^2 who were not able to achieve glucose homeostasis with lifestyle modifications and medical treatment [3].

A wide variety of bariatric/metabolic surgical procedures have been developed over time. These surgeries were classified into restrictive, malabsorptive, or a combination of both. However, one of the four following interventions was more frequently used: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, adjustable gastric banding, and biliopancreatic diversion (BPD) with or without duodenal switch. All these procedures could be performed laparoscopically [4].

Herein, we present the possible mechanisms leading to resolution of comorbid conditions after metabolic surgery.

Lipotoxicity and Diabesity

Central obesity is closely related to insulin resistance and T2DM due to stress failure of the beta cells of Langerhans islet of the pancreas in predisposed individuals [5]. On the other hand, the adipose tissue is known to be an immune tissue having endocrine function secreting different hormones such as leptin, estrogen, resistin, and adipocytokines. The presence of "sick fat" due to pathogenic adipocyte deposit will lead to lipotoxicity resulting in cardiovascular disease and mortality

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[6]. Therefore, weight loss after bariatric/metabolic surgery reduces metabolically active sick fat and ameliorates the metabolic disease with remission or improvement of T2DM.

Role of Gastrointestinal Tract in Diabetes Mellitus

In the past, the gastrointestinal tract (GI tract) was not noted as being part of the etiology of T2DM in conjunction to the liver, muscle, adipose tissues, and pancreatic B cells. However, one should mention that the GI tract is the first organ to transmit information concerning nutrient load via hormonal and neural pathways. Moreover, many studies including findings that have been reported using animal models [7] demonstrated resolution or improvement of T2DM after duodenal-jejunal bypass without losing weight, suggesting that manipulation of the GI tract evoked weight independent antidiabetic mechanisms [8], hence the possible role that the GI tract may play in the control of glucose levels.

Genetics and Obesity

Neuropeptide Y (NPY) represents one of the most abundant and potent orexigenic peptide found in the hypothalamus where the feeding regulation system is located. It was discovered by Tatemoto et al. in 1982 [9] and used to stimulate food intake with a preferential effect on carbohydrate intake. Fluctuations in plasma insulin and leptin levels are key factors that promote NPY expression and activity. In fact, decreased level of insulin and leptin, i.e., after starvation, causes a markedly increase and release of NPY expression [10] leading to increase in appetite and consequently food intake. This is supported by Sindelar et al. [11] and He et al. [12] who proved that the increased feeding response in mice having glucoprivation with a metabolic blocker is lacking when NPY antibodies are administered or NPY gene is deleted. Besides, it is well known that the adjustment of the NPY system is disturbed in obese rats, in part due to a diminished sensitivity to leptin [13], while other factors are still unknown [14]. In addition, once compared to normal mice, NPY protein expression is markedly increased in obese mice [15], suggesting that NPY expression variant is a probable explanation of stubborn hyperphagia and consequently obesity.

Finally, this NPY system is in close interaction with many others brain modulators such as ghrelin, glucocorticoids, and orexins in order to regulate feeding behavior [13] via complex mechanisms. Figure 1 shows a simplified schematic presentation of NPY system feeding regulation.

Gastrointestinal Vagal Nerve Fibers and Obesity

Gastrointestinal (GI) vagal nerve afferent fibers are abundant in the proximal gut and represent an important link between the digestive tract and the central nervous system (CNS) as it

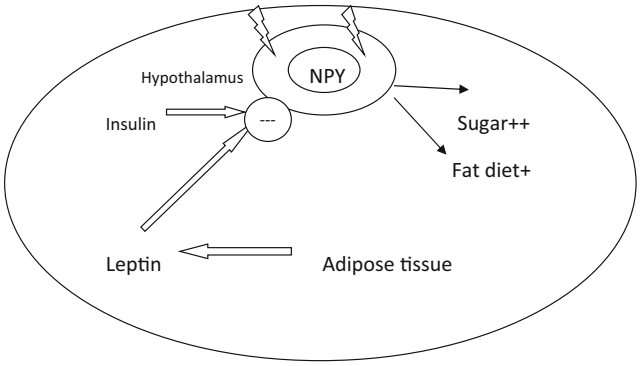

Fig. 1 Neuropeptide Y (NPY) role and obesity. Gene expression defect of NPY affect feeding behavior [13]. The normal decrease of NPY after increased leptin and insulin is lacking

is the first organ to spread and pass information regarding food intake. These afferent nerves are involved in the regulation of satiety and food intake. Besides, they represent an important pathway in the development of obesity as described and noted by many experimental animal studies [16] as well as by other published papers [17]. The stimulation of vagal afferent nerves in response to mechanical (i.e., gastric distention) or chemical stimuli (gastric peptide: ghrelin, leptin and intestinal hormones: cholecystokinin CCK, glucagon-like peptide GLP-1, peptide YY [PYY]) is well established and leads to an increase in vagal afferent activity, hence reducing food intake. However, diet-induced obesity has been proven to change vagal afferent nerves response to chemical and mechanical stimuli. On the other hand, high fat intake decreases the vagal nerve ability to respond to the stimulus, hence impairing the satiety signals and promoting weight gain [18].

Incretin Definition

Incretins are intestinal hormones that stimulate postprandial insulin secretion. The two major gut hormones that have been identified as incretins are gastric inhibitory peptide or glucose-dependant insulin-tropic polypeptide (GIP) secreted via the K cells in the duodenum and glucagon-like peptide-1 (GLP-1) secreted from the L cells in the ileum [19]. Both GIP and GLP-1 are secreted in response to the different macronutrients—carbohydrates, fats, and proteins noting that carbohydrate and fat are being the more potent—and controlled by complex mechanisms that are still not completely understood. Incretins mediate pleiotropic glycemic and extra glycemic actions: GLP-1 stimulates insulin secretion and biosynthesis and ameliorate postprandial glycemic homeostasis, improving beta cells proliferation and survival, increase glyconeogenesis in the liver and skeletal muscle, and lipogenesis in adipose tissue [20, 21]. On the other hand, GIP stimulates beta cell proliferation and inhibits beta cell apoptosis [21]. In addition, it has an effect on the adipose tissue as well, stimulating lipoprotein lipase activity and incorporation of fatty acids.

Proximal or Foregut or Upper Gastrointestinal Hypothesis

This hypothesis proposes that excluding the duodenum and upper part of the jejunum results in the inhibition of anti-incretins leading to abnormal glycemic control [2]. In fact, anti-incretins control incretin-driven responses to prevent postprandial hypoglycemia and uncontrolled β cell proliferation [22]. This evidence was supported by Rubino et al. [23] which who showed that duodenojejunal bypass was accompanied with improvement of T2DM in nonobese rats, whereas a simple gastrojejunal anastomosis did not improve diabetes. This leads us to the conclusion that excluding the proximal intestine from nutrient flow would improve glucose tolerance and that a putative diabetogenic signal originating in the foregut might be involved in the pathophysiology of T2DM [24].

Distal or Hindgut or Lower Gastrointestinal Hypothesis

This hypothesis proposes that the rapid delivery of nutrients to the ileum stimulates secretion of the GLP-1 [25], which is found in high density in the ileum. This will lead to increased insulin release and the subsequent decrease of glucose level [26]. This hypothesis is supported by the results observed after "ileal interposition," in which a segment of ileum is surgically interposed into the proximal intestine, near the duodenum-jejunum boundary, leading to increased GLP-1 release after meal and improves metabolic outcomes [27]. However, suppression of glucose production and stimulation of glucose disappearance were not altered in Roux-en-Y gastric bypass (RYGB) subjects after administration of a competitive antagonist of GLP-1, therefore questioning the hindgut hypothesis and the role of incretins as the sole explanation to the improvement of diabetes after surgery [28, 29].

Ghrelin

Ghrelin is an orexigenic hormone mainly secreted from the gastric fundus and is known to inhibit insulin secretion in humans [30]. Ghrelin level is markedly decreased after sleeve gastrectomy and after RYGB [31]. However, published studies have shown a fluctuation in ghrelin levels after RYGB where levels can be elevated, normal, or decreased. This is explained by a probable difference in circadian fluctuations of ghrelin level or due to the technical resection or isolation of the gastric tube [32]. But undoubtedly, the diabetogenic effect of ghrelin [30] may have an important role after sleeve gastrectomy.

Bile Acids

Bile acids are digestive juices which participate in the absorption of fat, lioposoluble vitamins, and contribute to the enterohepatic circulation. They are known to have an impact on glucose and lipid metabolism and to be implicated with insulin resistance, diabetes, and metabolic syndrome [33]. Bile acids interact with nuclear hormone receptor farnesoid X receptor (FXR) in the liver and with the membrane receptor G protein-coupled bile acid receptor (TGR5) in the enteroendocrine L cells, promoting insulin signaling activation [34], inhibiting gluconeogenesis [35], and releasing of GLP-1 [36]. This evidence supports the hindgut hypothesis. Many published studies showed that bile acid levels are elevated after sleeve gastrectomy and RYGB which could help in improving of metabolic control and diabetes after bariatric surgery [37].

However, Steinert et al. [38] showed that, while the elevated level of GLP-1 after surgery is noted. We could suggest that bile acids may explain these complex metabolic effects seen after bariatric surgery. Even if the data is conflicting, the rerouting of nutrients due to the iatrogenic alteration of the physio-anatomy after RYGB contributes to the improvement of glycemic control [2]. Manipulation of bile acid homeostasis might be an attractive approach for resolution of T2DM.

Bacterial Flora

The gut of humans is mostly dominated by two groups of bacteria, Bacteroidetes and Firmicutes [39]. The number of Firmicutes was notably higher than the number of Bacteroidetes in the gut of obese humans and mice and vice versa for the lean mice [40–43]. Interestingly, insulin sensitivity improvement after transferring intestinal microbiota from lean donors to recipients [41] and the shifting population of the flora seen after RYGB [42] have led to confirm the role of the ecological relationship of the gut microbiota in diabesity evolution. Moreover, after RYGB, a decrease in the Firmicutes/Bacteroides ratio was found in conjunction to an increase in the bile-tolerant Proteobacteria [44]. However, the presence of elevated amount of bile acids in the ileum leads to the growth of proteobacter which in turn promote a decrease in secondary bile acids leading to elevated serum primary bile acids. This might explain that even if the precise pathophysiology of gut microbiome in obesity remains incompletely understood [45], this complex relationship between microbiote and bile acids after rerouting of the intestinal anatomy promotes together the metabolic effects seen after bariatric surgery.

Moreover, gut microbiota is known to induce breakdown of certain substances leading to the formation of short-chain fatty acids (SCFAs) which could lead via certain mechanisms [46] to the release of GLP-1 and PYY that can therefore act on

vagal afferent nerves to increase satiety, as noted earlier. Knowing that high fat diet and excess caloric intake cause switching in the resident gut microbiota, this could also highlight the important role of gut microbiota in refractory obesity.

Intestinal Gluconeogenesis

The potential role of intestinal gluconeogenesis (IG) in the metabolic benefits seen after gastric bypass surgery has been well established. The activation of hepatoportal glucose sensor after IG decreases food intake and suppresses hepatic glucose production, which in turn improves glucose homeostasis [47]. This is supported by Kim et al. and Sun et al. who demonstrated that glucose homeostasis is due to enhancing intestinal gluconeogenesis in rats after RYGB [47, 48]. In fact, intestinal gluconeogenesis is able to change the hypothalamic activity via vagal reflex arc and consequently decrease food intake, and this could participate in the satiety after gastric bypass [49]. This glucoregulatory role of intestinal senses and endogenous glucose production via a gut-brain-liver network is implicated in the early control of glycaemia following duodenojejunal bypass surgery as reported by Breen et al. [50] in a diabetic rat model. Together, these studies suggest that after RYGB, hepatic gluconeogenesis is suppressed and intestinal gluconeogenesis is stimulated, which may improve glucose homeostasis.

To resume, the initiation of intestinal gluconeogenesis takes place after protein diet [49] and after gastric bypass [51]. This contributes to the satiety effect seen after protein intake, a useful method to help losing weight. On the other hand, intestinal gluconeogenesis is in relation with the hypothalamus, the center of feeding and energy homeostasis, via the portal glucose signal and would lead to decreased satiety and inhibit the glucose production in the liver, thereby modulating glucose homeostasis.

Figure 2 indicates the role of intestinal gluconeogenesis in refractory diabesity.

Effects of Metabolic Surgery on Diabetes: Physiology and Strategy

Type 2 diabetes mellitus (T2DM) is a chronic disease leading to macrovascular and microvascular complications including myocardial infarct, stroke, blindness, neuropathy, and renal failure. Worldwide, diabetes is increasing rapidly at a serious grave rate and causing 3.4 million deaths per year [52]. However, the global diabetes health burden is estimated to reach 522 million in 2030 [53]. The mechanism of glycemic control is still incompletely understood, and recent evidence support the role of bariatric and metabolic surgery in inducing the remission of diabetes or reducing the need for medications, with durable long-term results in morbidly obese patients [54, 55]. Several mechanisms have been implicated in the remission of T2DM after anatomic modification of the GI tract. These different metabolic procedures allows nutrient load to reach the ileum more rapidly than usual and at the same time bypassing much of the stomach, duodenum, and part of the jejunum. However, the purely restrictive procedures are thought to achieve glycemic control through weight loss and caloric restriction without an entero-hormonal effect. Although it has been postulated that an increase in glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) [56] in addition to rapid gastric emptying [57, 58] and decreased level of ghrelin [59] after sleeve gastrectomy seem to play a role in the resolution of diabetes, Ryan et al. found that neither ghrelin nor GLP-1 was found to play a role in weight loss after sleeve gastrectomy whereas bile acids were identified as important [60]. Thus, the mechanisms are still in a gray zone and further studies are needed to elucidate the exact mechanism of the physiologic remission of diabetes after sleeve gastrectomy which may be a combination between a hormonal and a weight loss through caloric restriction mechanisms, whereas with respect to the malabsorptive or hybrid procedures, hormonal changes have been implicated in glucose homeostasis. The concept of "entero-insular axis" was developed in 1969 by Unger and Eisentraut [61] where they highlighted the close relationship between intestines and insulin via the link with pancreatic B islet cells of Langerhans.

Moreover, metabolic improvements and glucose tolerance in association to reduced plasma insulin and increase in GLP-1 were comparable after RYGB and sleeve gastrectomy in rats [62]. In addition to the improvement of hepatic insulin sensitivity via an independent weight loss phenomenon [63] and the improvement in skeletal insulin sensitivity related to weight loss [64], it leads to a progressive decline in glucose levels directly after bariatric/metabolic surgeries.

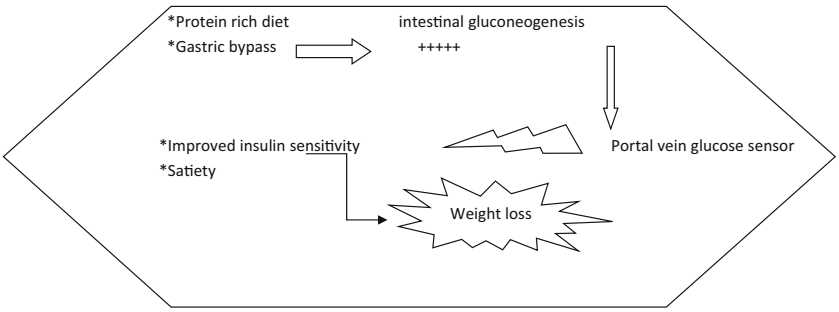

Fig. 2 Role of intestinal gluconeogenesis. Intestinal gluconeogenesis inhibits hepatic gluconeogenesis, hence improving glucose homeostasis [51]

Table 1 Bariatric surgery and diabetes: literature review results

	Procedure	Following time (years)	HbA1c (%)	Remission rate	Remarks
Adams et al. [74]	418 RYGB (93 T2DM) 417 nonsurgical obese control (106 T2DM	6	< 6.5	62% complete remission.	Better control of bypass than nonsurgical group
	321 population-based control (92 T2DM)				Mean BMI 45.9
Sjostrom et al. [75]	641 band, VBG, RYGB 627 matched controls	10	ND	36% 13%	Mean BMI 41
Arterburn et al. [76]	4434 RYGB	5	< 6	68% complete 9% partial	Retrospective cohort
Cohen et al. [66]	66 RYGB	6	< 6.5	88% complete 11% partial	30 < BMI < 35
Lakdawala et al. [77]	52 RYGB	5	< 7	58% complete	30 < BMI < 35
				38% partial	96% improvement
					Of metabolic status
Heneghan et al. [78]	52 RYGB, LSG, LAGB	5	< 6.5	44% complete 33% partial	Mean BMI 49 ± 8.7
Sultan et al. [79]	95 LAGB	5	< 6	40% complete 40% partial	Mean BMI 46.3
Scopinaro et al. [76]	312 BPD	10	ND	97%	
Pontiroli et al. [76]	23 BPD 78 LAGB	5.5	ND	100% 66%	
	37 control			None	
Marceau et al. [76]	1356 DS (377 T2DM)	7	ND	92%	
Cummings et al. [80]	Lifestyle modification (20) RYGB (23)	1		5.9% 60%	30 < BMI < 45
Schauer et al. [81]	Medical therapy alone (50)	1		12% 42%	BMI 36.0 ± 3.5
	RYGB(50)			37%	
	LSG (50)				
Ikramuddin et al. [82]	LS + medical therapy (60) RYGB (60)	1	< 7	32% 75%	BMI 30.0–39.9

Effect of bariatric surgery on T2DM [76]

BPD biliopancreatic diversion, *LAGB* laparoscopic gastric band, *RYGB* Roux-en-Y gastric bypass, *LS* lifestyle modification, *LSG* laparoscopic sleeve gastrectomy, *DS* duodenal switch, *ND* not defined

In brief, a combination of weight dependant and independent mechanisms is the key of regulating glucose homeostasis.

Add to this, in one observational study, metabolic surgery improves glucose control for up to 20 years albeit beneficial effect diminishes over years [65]. However, the majority of patients sustain a glycemic control for at least 5 years as shown in many randomized control trials (RCT) [66, 67].

According to RCT, among the different metabolic surgeries that are available, the highest rate of glucose control is achieved by biliopancreatic diversion followed by Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric band [68].

Table 2 Better glycemic control after bariatric surgery: a predictive score

Variable	P 0	O 1	I N 2	T 3
*A*ge	≥ 40	< 40		
*B*MI (kg/m^2)	< 27	27–34.9	35–41.9	≥ 42
C-peptide (mmol/L)	< 2	2–2.9	3–4.9	≥ 5
*D*uration of T2DM	> 8	4–8	1–3.9	<1

ABCD scoring system: the total possible values range from 0 to 10 [88]

Impact of Bariatric Surgery, Conventional Therapy, and Diabetes

A lot of published studies have established the benefit of bariatric/metabolic surgery in the remission or improvement of diabetes and other cardiovascular risks, hence ameliorating metabolic syndrome [3].

Besides, surgery is far more effective than medical conventional treatment for the short- and long-term controls of obese patients with type 2 diabetes and should be considered in the

Table 3 Better glycemic control after bariatric surgery: a predictive score

ABCD score	Complete remission HbA1c < 6%	Partial remission HbA1c < 6.5%
0	5.9%	5.9%
1	5.0%	20.0%
2	26.3%	38.6%
3	31.9%	42.0%
4	52.5%	67.8%
5	55.4%	75.0%
6	61.7%	78.3%
7	77.0%	92.3%
8	85.2%	96.3%
9	87.1%	87.1%
10	93.3%	93.3%

Results according to ABCD score [88]. Highest score is associated with better results

treatment algorithm for this disease [69, 70]. In a large meta-analysis, Buchwald et al. [71] showed better diabetes remission in patients who underwent procedures with a greater impact on weight loss such as biliopancreatic diversion/ duodenal switch (BPD/DS), RYGB rather than those who underwent restrictive surgeries and that diabetes improvement was noted for 2 years at least, whereas other studies suggest a similar positive impact on diabetes control with sleeve gastrectomy and gastric bypass [72].

Hall et al. [73] showed less remission rate with patients having diabetes for more than 10 years and with HbA1c of more than 10%; in this study, they report better remission rate and control in patients with newly diagnosed diabetes (less than 10 years) and whose glucose level was better controlled preoperatively.

Many studies reporting long-term effect of bariatric surgery on diabetes remission are summarized in Table 1.

Moreover, emerging data have shown good outcomes after metabolic surgery in treating T2DM in obese diabetics with a BMI of less than 35 kg/m^2 [83]. Furthermore, a systematic review suggests that bariatric surgery is even better than non-surgical treatment in controlling diabetes patients with a BMI of 30–35 kg/m^2 on a short-term basis [84].

Li et al. [85] showed 80% of remission of diabetes with a HbA1c of less than 7% in patients with a BMI of less than 35 kg/m^2. Panunzi et al. [86] found that the general diabetic remission rate was identical among patients over 35 and under 35 kg/m^2 (71 and 72%, respectively).

That said is encouraging, but it means that 20 to 30% of patients with moderately elevated BMI are undergoing a surgery and all the risks it carries, without achieving the clinical benefit of glycemic control.

There is no relation between inadequate weight loss and metabolic nonresponse. Older age, long history of T2DM, high HbA1c levels, and a preoperative multidiabetic medication can be assumed to be negative predictors for glycemic control [87].

In fact, an ABCD scoring system was developed for predicting the success of T2DM treatment after metabolic surgery (see Tables 2 and 3).

And more recently, DiaRem score has been used as a valid tool to anticipate the efficacy of the clinical response of diabetes remission or cure after metabolic surgery (RYGB) [89], based on age, insulin dependence, diabetes medication use, and hemoglobin A1C levels (Table 4).

Different Surgical Modalities

The duodenal-jejunal bypass procedure, as described by Rubino et al. [23] in a work on rats, was proven to control diabetes even without weight loss, based on the foregut hypothesis. This operation is used to regulate glycaemia in nonobese patients and could be combined with a sleeve

Table 4 Better glycemic control after bariatric surgery: a newer predictive score

	0	1	2	3	4	6	10
Age (years)	< 40	40–49	50–59	60			
HbA1c level (%)	< 6.5%		6.5–6.9%		7–8.9%	9%	
Medication use	metformin			Sulfonylureas and nonmetformin insulin sensitizing agent			
Insulin dependence	No						Yes
	0–2	3–7		8–12	13–17	> 18	
Partial remission[a]	> 90%	80%		> 40%	> 20%	4–5%	
Complete remission[b]	> 80%	40%		> 20%	> 10%	–	

DiaRem scoring system with its relationship to diabetes response [89]. Scores vary between 0 and 22

[a] Partial remission is defined as follows: no medications, hemoglobin A1c (HbA1c) level less than 6.5% fasting glucose level less than 125 mg/dL, and no active treatment or procedures for at least 1 year

[b] Complete remission is defined as follows: no medications, HbA1c level less than 5.7%, fasting glucose level less than 100 mg/dL, and no active treatment or procedures for at least 1 year

gastrectomy [90] together in order to benefit from weight loss. Human experiences are encouraging [91]. Moreover, an endoscopic device inserted and fixed from the duodenum to the proximal jejunum results also in significant benefit regarding diabetes control and weight loss on a short-term basis [92].

Sleeve gastrectomy associated to transit or intestinal bipartition is also a method which control metabolic syndrome and obesity [93].

Conclusion

Metabolic surgery is a more appropriate term to define bariatric surgery aiming for treatment of comorbid conditions associated with obesity, because weight loss induced by bariatric surgery has an impact on metabolic syndrome with a marked improvement of diabetes, hypertension, dyslipidemia, and other cardiovascular comorbidities. For instance, there have been many studies which demonstrate a decrease in micro- and macrovascular risks after these procedures and Reno protective long-term effect [94].

However, although diabetes is improved and often remitted completely, the definition of remission varies depending on HbA1c threshold used. The durability and the degree of the glycemic control vary according to the different procedures and remain uncertain because if 80% of patients describe complete diabetic remission, it means that 20% did not take the expected results.

Given the efficacy, safety, and cost-effectiveness of metabolic surgery, the second Diabetes Surgery Summit (DSS-II) consensus conference recently placed surgery squarely within the overall diabetes treatment algorithm, recommending consideration of this approach for patients with inadequately controlled diabetes and a BMI as low as 30 kg/m^2, or 27.5 kg/m^2 for Asian individuals [95].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

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