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Duodenal-Jejunal Bypass Liner to Treat Type 2 Diabetes Mellitus in Morbidly Obese Patients

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Abstract Endoscopic placement of the duodenal-jejunal bypass liner (DJBL) in morbidly obese patients induces significant weight loss. Additionally, early studies reported significant improvements in several parameters of glucose homeostasis in morbidly obese patients with T2DM. The observed glycemic control occurred soon after device placement, after a minimal weight loss, suggesting the activation of weight loss-independent anti-diabetic mechanisms of glucose normalization. This effect is associated with favorable changes in hormones involved in glucose level regulation. Recently, larger clinical studies, focused primarily on the effect of the DJBL on T2DM treatment, have corroborated initial observations not only in morbidly obese patients but in non-morbidly obese diabetic patients as well. In this article we review the evidence from preclinical animal and clinical human studies that support the efficacy of DJBL to treat T2DM in obese patients.

Keywords Type 2 diabetes mellitus · Obesity · Bariatric · Endoscopy · Gut hormones · Endoluminal · Duodenal-jejunal bypass liner

Introduction

Obesity is one of the most important risk factors for the development of type 2 diabetes (T2DM), and the common finding that obesity precedes diabetes supports a causal relationship between these two diseases [1]. As a consequence of the increasing number of individuals with obesity, the prevalence of obesity-induced diabetes has reached epidemic proportions [2]. The enormous progress made over the last few decades has increased our understanding of the role of key organs (brain, muscle, adipose tissue, and gastrointestinal tract) involved in glucose homeostasis regulation and T2DM pathophysiology. From this knowledge, new glucose-lowering agents have been developed. However, despite the large armamentarium of new and old glucose-lowering drugs, T2DM continues to be a chronic disease with no possible medical cure. In fact, a significant proportion of patients fail to achieve adequate combined target goals for glycemic, blood pressure, and lipid control [3–8]. In sharp contrast, bariatric surgery has been shown not only to be the most effective intervention to achieve long-term treatment of obesity, but it also has shown to induce adequate glycemic control in obese-T2DM patients in the absence of drugs. These phenomena called diabetes remission - defined as normal blood glucose levels after discontinuation of all glucose-lowering agents over one year – has been described consistently in severely obese T2DM patients after surgery in different studies [11, 15, 16]. A meta-analysis that reflected the data of 135,246 patients, determined that 78.1 % of severely obese diabetic patients achieved diabetes remission after surgery [9]. Nowadays, due to its impressive effects on glycemic control, bariatric surgery has been recommended as a treatment for diabetes in severely obese patients who have difficulties obtaining glycemic control using glucose-lowering agents and lifestyle changes [10, 11].

Among currently available surgical procedures for weight loss, Roux-en-Y gastric bypass (RYGB) is one of the most frequent procedures performed worldwide [12]. After RYGB, T2DM remission occurs in up to 71 % of patients [13•, 14–16, 17•]. Notably, normalization of blood glucose levels after surgical procedures such us RYGB occurs before any significant weight loss [14, 18, 19]. This early glycemic control suggests the activation of weight-loss independent mechanisms of diabetes control triggered by re-routing of nutrients and biliopancreatic secretions through the GI tract after the intestinal rearrangement that follows this surgery [20]. It has been hypothesized that nutrient exclusion from duodenum along with early delivery of partially digested nutrient into the

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mid-jejunum small bowel elicits a powerful neuroendocrine response characterized by increased levels of several gut derived peptides involved in blood glucose homeostasis and energy balance regulation. Endoscopic placement of the DJBL reproduces in isolation, these two RYGB anatomical components [21]. In line with the above-mentioned hypothesis, DJBL placement reproduces many of the effects of RYGB on weight loss and glycemic control [22–26]. In this article, we will review the association between obesity and T2DM and current available surgical procedures to treat both diseases. Then, to understand the rationale behind the DJBL concept, we will review its physiology and mechanisms of action. Finally, we will discuss the role of DJBL to treat T2DM in severely obese patients based on available clinical data.

Relationship between Obesity and T2DM, and its Variations

Obesity is a state of excessive adipose tissue mass whose degree of severity can be conveniently estimated by body mass index (BMI), which correlates reasonably well with total body fat. One of the most important risk factors for T2DM development is obesity. In fact 90 % of all T2DM patients are obese (BMI>30) or overweight (BMI>25-30) [1, 27]. As a consequence of this relationship, the risk of T2DM rises with increasing body weight at all ages [28, 29]. The progressive increase in the total amount of adipose tissue is associated with increased insulin resistance (IR) [30–32], which along with a relative defect in insulin secretion and hyperglycemia are the principal features of T2DM. In addition to total body fat content, the distribution of adipose tissue in specific anatomic locations affects the risk of IR. Indeed, visceral abdominal obesity increases IR and incidence of T2DM more commonly than subcutaneous or peripheral obesity [33, 34]. However, only a small fraction of obese-insulin resistant individuals will develop T2DM [35, 36]. In obese-insulin resistant individuals normal glucose levels are maintained by hypertrophy and hyperplasia of the pancreatic islets. Beta-cell (β-cell) mass and insulin release is increased by 50 % and levels four- to five-fold higher, respectively compared to lean control individuals [37]. Obesity-induced diabetes develops when β-cell failure (decreased β-cell mass and/or function) occurs [38]. However, in some populations the risk of T2DM occurs at lower levels of BMI and is particularly true for Asian populations. When compared to Western populations, Asians have lower rates of overweight and obesity using the standard BMI-based definitions (see above). For example, in a sample of Chinese T2DM patients 50 % were normal weight [39], and in Asian adults with diabetes diagnosed before 40 years, a lean non-autoimmune phenotype was found in a significant proportion of patients [40–42]. Despite this lower BMI, the prevalence of diabetes is similar or higher than those found in Western countries [43]. These differences can be explained by genetically-based alterations in body fat distribution, changes in diet and lifestyle, as well as decreased β-cell function [44]. Fat accumulation in Asians is more commonly abdominal (which increases IR and incidence of T2DM); they have a lower amount of muscle mass and an increased insulin resistance when compared to Western individuals [45–47]. In addition, Asians have a defective β-cell response to increased insulin resistance, even with modest increases in body weight [39, 48]. Despite these variations, the association between BMI and obesity-associated diseases still occurs, however at a lower threshold. These unique features led to the development of a consensus statement, to diagnosis and management of obesity, and metabolic syndrome for Asian individuals [49].

Because of the important role of the adipose tissue – total amount and distribution – on IR and T2DM development, weight loss by any means is an important goal for obese diabetic patients, due to its beneficial effects on glycemic control [50, 51]. Considering the key features of diabetes, the ideal treatment should promote and maintain weight loss over time, prevent β-cell loss, and improve β-cell function. The Look AHEAD study demonstrated that patients with intensive lifestyle intervention lost more weight than diabetes support and education group at 1 year with 11 % vs 2 % of diabetes remission, respectively [52]. Bariatric surgery has demonstrated to be the intervention closest to the ideal treatment in severely obese patients, not only inducing significant weight loss but also improving and restoring β-cell function in a weight-loss independent fashion. Clinically, available data supports a role of these interventions to treat T2DM not only on severely obese individuals but also in non-severely obese patients with T2DM and BMI between 30-35 kg/m2 [53].

DJBL Mimics the Physiology of RYGB

Because of the profound effects of RYGB on body weight regulation and glucose control, identification of the anatomical components and physiological mechanisms of action mediating its effects has become a high research priority. Evidence from rodent models of bariatric surgery have suggested that two of these anatomical components – duodenal exclusion [54, 55], and accelerated delivery of partially digested nutrients to mid-jejunum [56–58] - are essential anatomical components responsible for the physiological effects of the RYGB. Evidence suggests that nutrient exclusion from the duodenum and proximal jejunum prevents the generation of intestinal dysfunctional neuroendocrine signals that promote T2DM [54, 55, 59]. In addition, after RYGB partially digested nutrients that are delivered into mid-jejunum increase postprandial circulatory levels of the incretin, glucagon like peptide 1 (GLP-1), which may mediate the antidiabetic effects of surgery through its well-known action on glucose-stimulated insulin secretion and glucoregulatory properties [60].

During the last years, evidence from human and animal studies have shown that mechanisms of weight loss after RYGB are physiological and cannot be explained only by reduced food intake, and/or nutrient malabsorption. Weight loss after RYGB results from the additive effects of reduced food intake, and increased total (TEE) and resting (REE) energy expenditure in diet-induced obese (DIO) rats [61, 62]. In contrast, weight loss after isolated gastric procedures such as vertical sleeve gastrectomy (VSG) primarily results from decreased food intake, as this procedure does not increase energy expenditure [63]. These findings have been recently supported by results obtained in humans [64]. In terms of diabetes control, diabetic remission after RYGB in morbidly obese patients occurs before any significant weight loss has occurred, suggesting the existence of weight loss-independent mechanism of glycemic control [13•, 17•, 18]. Moreover, the better glycemic control effect observed after RYGB in comparison to the glycemic control obtained after a comparable weight loss obtained with diet, supports the weight-loss independent effect of RYGB on diabetes control [65]. Among proposed mechanisms of glycemic control, increased levels of the incretin, hormone glucagon like peptide-1 (GLP-1), have been considered to play an essential role in mediating this effect [65, 66]. Conversely, glycemic control after isolated gastric procedures like adjustable gastric banding (AGB) parallels the induced weight loss, and GLP-1 levels remain unchanged after the surgery [67], indicating that weight-loss dependent mechanisms are primarily mediating improvement of glycemic control [16].

The EndoBarrier is a 60 cm long highly flexible nutrient-impermeable tube that is anchored at its proximal end in the duodenal bulb. After endoscopic placement of the device, ingested nutrients flow through the device lumen and do not contact duodenal mucosa, keeping biliopancreatic secretions external to the device, ultimately reproducing the nutrient exclusion component of the RYGB procedure [68]. Additionally, ingested nutrients are delivered into the mid-jejunum earlier (Fig. 1). With respect to device placement individuals are usually admitted in the morning of device placement after overnight fasting. Implantation is performed under general anesthesia with endotracheal intubation under endoscopic and fluoroscopic guidance [16]. Access to the stomach and duodenum is achieved by a standard gastroscopy through which a guide wire is advanced into the duodenum. The encapsulated device on a custom catheter is tracked over the guide wire into the duodenum. The capsule at the distal end holds the sleeve and anchor. The catheter has a non-traumatic ball end, which is advanced through the intestine deploying the sleeve behind itself. After full extension of the sleeve, the anchor is deployed in the duodenal bulb 0.5 cm distally from the pylorus. Device placement at our center has an average length of 24 minutes [25]. For device explantation, patients follow the same indication before the procedure as described above. Removal is carried out in patients under general anesthesia, using a custom grasper that grasps the anchor. A foreign body retrieval hood at the tip of the endoscope is used to incorporate the device to avoid any damage of the stomach or esophagus on the way out. The rate of early device removal differs from study to study and ranges from 16-40 % [23, 25, 26, 69–72]. Recently, in our last 40 consecutives patients treated with DJBL early removal dropped to 7 % after 1 year of treatment [73]. Among reasons for early removal the most frequent is symptomatic or asymptomatic device migration, persistent abdominal pain, device related upper gastrointestinal hemorrhage, and device obstruction. In our experience, these adverse events can be successfully managed through endoscopic device explantation.

To study the contribution of these two anatomical components in isolation, a diet-induce obese rat model of an endoluminal sleeve (ELS) device was developed. Duodenal placement of the ELS in DIO-rats induced an average body weight loss of 20 %. Weight loss was accompanied by a decrease in food intake without evidence of reduced nutrients absorption. In addition to the weight loss effect, ELS-treated rats had a significant improvement in different parameters of glucose homeostasis such as fasting glycemia, fasting insulin, and oral glucose tolerance among others parameters [74]. More interestingly, full duodenal exclusion with an ELS device increased total and resting EE, augmented circulating concentrations of glucagon-like peptide-1 (GLP-1), and improved glucose homeostasis by both weight loss-dependent and independent mechanisms [24]. Recently, the effect of the DJBL on fasting and nutrient stimulated levels of different gut derived peptides and hormones involved in glucose and energy balance regulation was characterized in a group of obese-T2DM treated with the DJBL 22. The average BMI and HbA1c was 37.0±1.3 kg/m2 and 8.4±0.2 %, respectively. Plasma levels of GLP-1, GIP, and glucagon were determined at baseline, one week, 24 weeks after DJBL placement, and one week after device explant. After 24 weeks of DJBL treatment, mean weight loss was 12.7±1.3 kg, which corresponds with an average percentage of excess body weight loss (%EBWL) of 29.8±3.5 % (all $p<0.01$). Fasting glucose levels decreased from 11.6±0.5 mml/L to 8.6±0.5 mml/L after 24 weeks of treatment. Similarly, glucose levels during the oral nutrient stimulation test were significantly lower compared to baseline values as demonstrated by a 23 % reduction in the area under the curve (AUC) (baseline 1999±85 vs. week 24 1538±72, $p<0.05$). Also, HbA1c decreased to 7.0±0.2 % ($p<0.01$) with respect to baseline levels. Accordingly, insulin resistance determined by HOMA-IR also improved as shown by a decrease from 14.6±5.8 to 6.3±1.8. DJBL treatment, did not affect fasting GLP-1 levels. In contrast, GLP-1 levels after oral nutrient stimulation augmented as demonstrated by a 35 % increase in the AUC

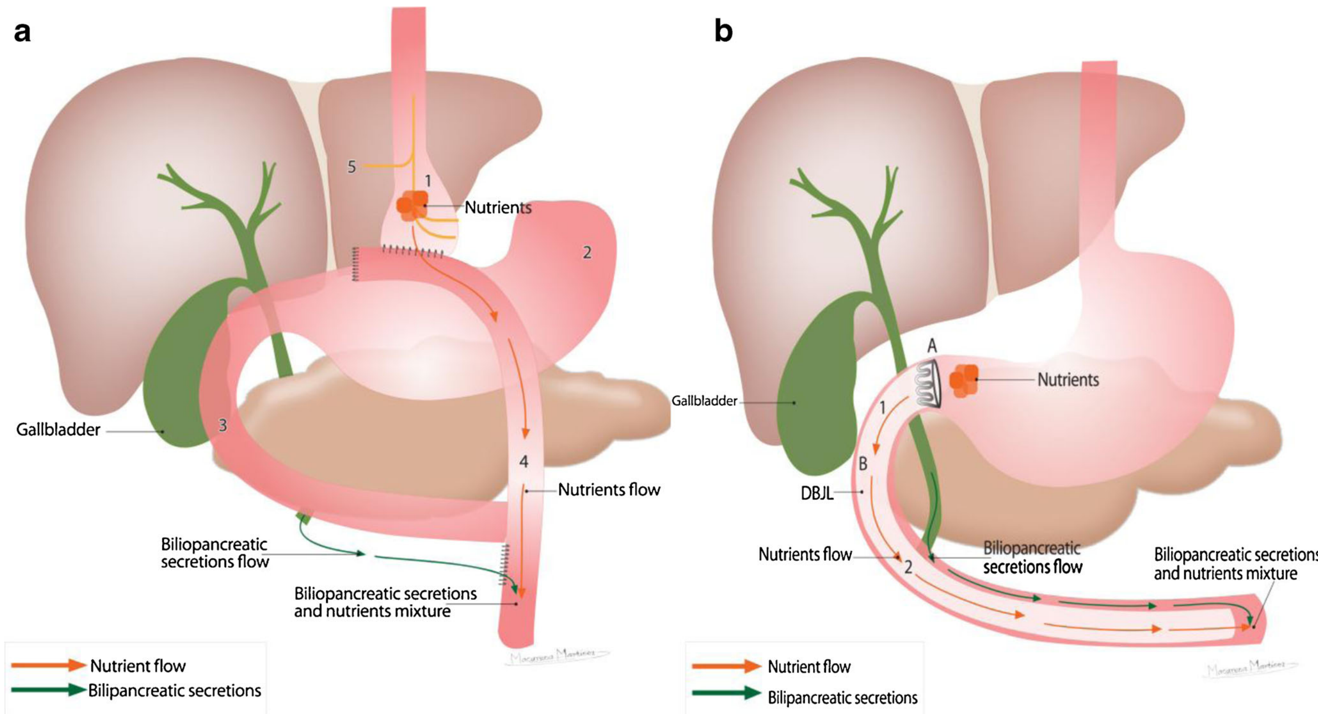

Fig. 1 DJBL mimics Roux-en-Y gastric bypass. **1a,** Roux-en-Y gastric bypass is comprised of two primary anatomical manipulations, the creation of the gastric pouch (GP) and the rearrangement of the intestine in a Roux-en-Y configuration. These two primary manipulations translate into the creation of five individual anatomical components: 1) isolation of the gastric cardia; 2) nutrient exclusion from distal stomach; 3) nutrient exclusion from duodenum and proximal jejunum; 4) early contact of partially digested nutrients with jejunum; and 5) partial vagotomy. **1b,** DJBL consist of a proximal anchor (a), and the nutrient-impermeable highly flexible tube (b). After implantation of the ELS, a physical barrier is created among ingested nutrients and proximal intestinal lumen, preventing contact between ingested nutrient and duodenal and proximal jejunal mucosa (1). Meanwhile, biliopancreatic secretions remain external to the device lumen (2) and mix with ingested food at the distal end of the ELS (3)

analysis (baseline 4440±249 vs. week 24 6008±429 $p<0.01$). Moreover, levels of the glucose raising hormone glucagon decreased after DJBL treatment. Interestingly, this study showed that the above-described endocrine changes occurred only one week after DJBL placement, when a minimal weight loss has occurred. These findings, indicate that isolated nutrient exclusion from duodenum and/or early delivery of partially digested nutrients into the mid-jejunum after DJBL placement is sufficient to reproduce not only the neuroendocrine changes observed after RYGB but also most of its effects on weight loss and glucose control independently of body weight loss.

Weight Loss Effect of DJBL

Early studies demonstrated the efficacy of DJBL to induce a significant weight loss in morbidly obese patients. After 12 weeks of DJBL placement, patients with an initial BMI between 42-46 km/m2 exhibited an average percentage of excess body weight loss (%EBWL) that ranged from 11.9-23.6 % [69, 70, 72, 75]. The body weight lost after DJBL placement is superior to the body weight loss obtained with diet as shown in a couple of studies. DJBL-treated patients had a greater weight loss compared to patients under diet restriction as demonstrated by an average %EBWL of 19-22 % and %EBWL of 5.3-6.9 %, respectively [70, 75]. Studies with a longer follow-up have shown that weight loss effect of DJBL can be greater. Recently, two studies have evaluated the results of DJBL treatment after 52 weeks of treatment. In a single-arm prospective open-label study the average %EBWL in 24 patients that completed the study was 47±4.4 % [25]. Similarly, in a group of 22 morbidly obese patients the weight loss effect after 52 weeks of treatment was 39±3.9 % [26]. Combined, these results show that DJBL placement in morbidly obese patients is an effective intervention to treat obesity as a minimally invasive approach.

Endoscopic Treatment of T2DM with the DJBL

In addition to the weight loss effect of DJBL treatment, earlier studies revealed improvement in several parameters of glucose homeostasis in morbidly obese T2DM patients treated with the DJBL [69, 70, 75]. However, these initial reports were not designed to specifically study the effect of the DJBL on T2DM treatment and included a limited number of diabetic patients. Despite these limitations, the results were encouraging. In the first human experience with DJBL, four out of 12 patients had T2DM. After 12 weeks, three of the four patients experienced diabetes remission and one patient failed to improve glycemic control [69]. A second study also included four patients with T2DM. Of these patients, three were randomized to the DJBL. After 12 weeks of treatment, two patients had lower HbA1c levels compared to their baselines and decreased their use of glucose-lowering drugs. One patient was able to discontinue all medications after 12 weeks of treatment [70]. Finally, in another study, eight T2DM-patients were randomized to the DJBL arm, and two patients were randomized to the diet arm. On average, T2DM duration was estimated in 3.6 years (range 1-10 years). After 12 weeks of DJBL placement, T2DM-patients exhibited lower fasting glucose levels with a drop from 11.1±4.3 to 9.3±3.8 mmol/L. Similarly, Hb1A1c decreased from 8.8±1.7 % to 7.7±1.8 % of DJBL treatment. These changes were accompanied by reductions in glucose-lowering drugs in six patients. While one patient was able to discontinue all his glucose-lowering medications, however one T2DM patient was not able to decrease their pharmacological therapy [75]. The first study focused primarily on evaluating the effect of DJBL on insulin-resistance in a group of morbidly-obese T2DM patients, including 54 individuals receiving treatment for up to 26 weeks. Additionally, investigators also determined the effect of DJBL on weight loss and glycemic control [76]. At the end of the study, all T2DM patients experienced significant reductions on HbA1c levels. However, T2DM-patients with a poor initial glycemic control, as demonstrated by baseline HbA1c levels above 9 %, were not able to decrease HbA1c below 7 %, indicating that a longer treatment may be necessary to improve glycemic control in patients with a more advanced disease.

Together, these observations provided initially encouraging results for a potential role of the DJBL in treating obese patients with T2DM. However, the reduced number of treated patients, defined criteria for diabetes remission and/or improvement, short term studies, and limited characterization of T2DM status at the time of the implant reduces these data to interesting observations. Therefore, longer studies, with a larger number of T2DM patients primarily designed to determine the effectiveness of DJBL as a potential treatment of diabetes, are needed to establish its efficacy to treat T2DM.

In the first 52 week study, a total of 22 morbidly-obese T2DM with a baseline age and BMI of 46.2±10.5 years and 44.8±7.4 kg/m^2 were enrolled in a 52-week, prospective, open- label clinical trial [26]. Of these patients, 13 completed the 52 week study with a mean duration of the implant period for all subjects of 41.9±3.2 weeks. At the end of the study, significant reductions in several parameters of glucose homeostasis were observed. Fasting glucose and Hb1Ac levels decreased from 179±68 to 142±57 mg/dl ($p<0.05$) and from 8.9±1.7 to 6.6±1.4 % ($p<0.05$) respectively. Similarly, fasting insulin levels were reduced from 19.5±14.7 to 9.4±10.5 lU/mL ($p<0.05$). The average %EBWL was 39±0.9 after 52 weeks of treatment. The improvement in glycemic control was also accompanied by a substantial reduction in levels of total cholesterol, LDL, and triglycerides.

The remarkable improvement of T2DM after surgical procedures like RYGB even before significant weight loss has occurred, has provided the rationale to use bariatric surgery as an effective treatment to control hyperglycemia in patients without severe obesity [15, 19, 20]. Accordingly, the effectiveness of bariatric surgery to induce diabetes remission in normal weights T2DM-animal models, and patients without severe obesity have been largely demonstrated [16, 54, 77–94]. To determine whether DJBL treatment can improve glycemic control in non-severely obese T2DM patients, 20 subjects with T2DM of less than 10 years of duration, baseline HbA1 between 7.5 % to less than 10 %, were enrolled in a prospective 52-week, single-center, open-label clinical study [23]. Sixteen (80 %) patients implanted with the DJBL completed the 52 weeks of the study. Reasons for early removal of DJBL were investigator request because of subject non-compliance to follow up, patient request due to abdominal pain. The remaining two cases of early device removal were due to device migration and/or rotation. The average pre-implant BMI in these patients was 30±3.6 kg/m2, which indicates individuals that are not severely obese. Fasting glucose levels had a significant decrease after one week of implantation from 207±61 mg/dL at baseline to 139±37 mg/dL when only a minimal weight loss of 2.2 kg on average had occurred, highlighting the weight loss independent glycemic control induced by the DJBL. Fasting glucose levels remained lower until the end of the study. After one year of treatment, fasting glucose levels had decreased to 155±52 which represented an overall reduction of 25 %. As expected, improvement in plasma glucose levels was paralleled by reduction in glycated hemoglobin levels. At the end of the study, baseline HbA1c levels declined from 8.7±0.9 % to 7.5±1.6 % at week 52. Importantly, 62.5 % (10/16) of patients at the end of the study had Hb1Ac levels below 7 % which are indicative of an appropriated glycemic control according to current guidelines [95]. This effect was not observed in the majority of patients with pre-implantation Hb1Ac levels above 9 %. In terms of glucose-lowering medications, the study reported that seven patients were able to decrease the amount of drugs needed to control their glucose levels and four patients had to augment the number or dose of medications. At the end of the study, DJBL-treated patients had lost on approximately 14 kg on average. The results of this study indicated that in the majority of patients with T2DM, placement of the DJBL yielded a significant improvement on different parameters of glucose control.

Future Directions

The field of bariatric surgery is one of constant evolution. Over the last years, the deeper understanding on the mechanisms of actions of these interventions has made to design new, less invasive, yet equally effective interventions to combat obesity and T2DM based on the physiological aspects of surgical procedures such as RYGB. Although recently developed, available evidence suggests that endoscopic treatment of obesity and T2DM with the DJBL promises to become an attractive, less invasive, and effective therapy for type 2 diabetes. One of the challenges for this device is to evaluate alternatives to extend its metabolic benefits either re-implanting the device or maintaining it for a longer period of time. Additionally, the roles of complementary pharmacological therapies that can augment the benefits of this device on weight loss and glycemic control remain to be properly studied. Finally, encouraging results obtained from observational studies need to be corroborated by properly designed randomized clinical trials that will finally establish the efficacy of DJBL to treat T2DM.

Conclusions

Available evidence strongly suggests that DJBL is effective to improve glycemic control in a significant proportion of severely obese diabetic patients, providing an attractive therapeutic alternative when more invasive interventions such as surgical procedures are not considered to be an option either due to physician recommendation, patient preference or high surgical risk. Interestingly, it seems that the majority of the glycemic control effect of the DJBL occurs independently of weight loss, which may proportion the rational basis to treat diabetic patients with a BMI 30-35. In addition to the benefits on glycemic control, a weight loss effect of DJBL has been consistently shown across different studies. However, despite these encouraging results, long-term data from randomized controlled clinical studies are needed to determine the efficacy and to establish risk/benefit profiles of this intervention in the treatment of patients with T2DM.

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Compliance with Ethics Guidelines

Conflict of Interest Rodrigo Muñoz declares that he has no conflict of interest.

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