Surgical Endoscopy (2019) 33:1553–1563
https://doi.org/10.1007/s00464-018-6443-2

Ileal interposition coupled with duodenal diverted sleeve gastrectomy versus standard medical treatment in type 2 diabetes mellitus obese patients: long-term results of a case–control study

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Received: 27 April 2018 / Accepted: 5 September 2018 / Published online: 17 September 2018

Abstract

Background Randomized controlled trials have demonstrated that bariatric surgery is effective in obtaining remission of type 2 diabetes mellitus (T2DM) in obese patients, yet no data exist in the literature from prospective studies with ileal interposition with duodenal diversion sleeve gastrectomy (II-DD-SG). The aim of this case–control study is to investigate if II-DD-SG is superior to medical treatment in T2DM obese patients.

Methods Thirty obese patients (BMI > 30) affected by T2DM were recruited for surgery (II-DD-SG) between 2008 and 2011 and were matched with an equal control group which received standard medical treatment. Anthropometric measures, glucose metabolism, cardiovascular risk factors were determined baseline and during follow-up. The primary end point was T2DM remission; reduction of body weight, BMI, and cardiovascular risk factors were secondary end-points.

Results Shortly after II-DD-SG, normalization of glucose plasma levels and glycated hemoglobin was observed followed by a significant decrease in body weight and BMI. At one-year follow-up, insulin resistance strongly declined as did insulin plasma levels. Complete remission was observed in 26 patients (86%); 2 (6.6%) had partial remission, and two (6.6%) were still diabetic. After 5 years, 17 of 25 patients on follow-up (68%) showed complete remission of T2DM and 56% had remission of cardiovascular risk factors. Only two patients receiving medical treatment showed complete remission of T2DM ($p < 0.0001$ versus II-DD-SG). No significant changes of anthropometric parameters and lipid metabolism were recorded.

Conclusions II-DD-SG is an effective surgical procedure, able to induce complete and prolonged remission of T2DM in obese patients as opposed to medical treatment.

Keywords Type 2 diabetes mellitus · Diabetes remission · Ileal interposition · Sleeve gastrectomy · Duodenal diversion

Following the first results published by Poires, in which he stated that Roux-en-Y Gastric Bypass (RY-GBP) induces remission of type 2 diabetes mellitus (T2DM) in obese patients [1], a number of following studies demonstrated that adjustable gastric banding (AGB), vertical banded gastroplasty (VBG) and bilio-pancreatic diversion (BPD) are effective too [2, 3].

More recently, sleeve gastrectomy (SG) [4–6], one anastomosis gastric bypass (OA-GBP) [6, 7], duodeno-jejunal bypass associated to SG (DJB-SG) [8], single anastomosis duodeno-ileal SG (SADI-S) [9], ileal interposition with duodenal diversion-SG (II-DD-SG) [10, 11], and SG with transit bipartition (SG-TB) [12] have also been proposed to treat T2DM.

If one considers syndemic T2DM and obesity [13], it would also seem logical to treat with the only effective

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00464-018-6443-2) contains supplementary material, which is available to authorized users.

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solution, i.e., surgery. As of 2008, AGB [14, 15], SG [16–18], RY-GBP [16–23], and BPD [22, 23] have been investigated in prospective randomized controlled trials due to their ability to lead to remission of T2DM. Contrasting results have been reported for AGB; Dixon [14] found it effective, but Ding [15] did not confirm. STAMPEDE was the only clinical trial which investigated the most frequently used bariatric intervention—sleeve gastrectomy. Schauer [16, 17] and Kashyap [18] found SG more effective than medical treatment in T2DM obese patients. Remission rate was between 26% and 37% at 1 year and 23% after 5 years. Schauer [16, 17], Ikramuddin [19], Halperin [20], Cummings [21], and Mingrone [22, 23] demonstrated that RY-GBP leads to T2DM remission in obese patients; variable remission was observed in patients (26–75%) based on study end-points, reference levels of glycated hemoglobin (HbA1c) and fasting glycemia, selection criteria and follow-up time.

BPD has shown to have the highest successful outcome – 95% after 2 years and 60% after 5 years—as described by Mingrone [22, 23]. BPD is a procedure based both on foregut (duodenal exclusion) and hindgut (early ileal chime presentation mechanisms) components, but it leads to malabsorption with marked weight reduction and high malnutrition risk as side-effects [22–24].

Ileal interposition was first proposed to treat short-bowel syndrome, since it increases transit time, through GLP-1 secretion [25] and is associated to decreased food intake and body weight. Since GLP-1 has an important incretin effect, ileal interposition was found to improve glucose and lipid metabolism, delay onset and even cure diabetes in experimental animals [26]. In human, II-DD-SG has a bariatric effect [10, 11], acts on glucose metabolism by means of foregut and hindgut mechanisms but does not lead to malabsorption and malnutrition as other surgical procedures do [27]. For these reasons, we investigated the effects of II-DD-SG on T2DM obese patients in a case–control study.

Materials and methods

Study design

Our article describes, retrospectively, data obtained from a case–control study that compared surgical treatment (II-DD-SG) to standard medical management in T2DM obese patients conducted at the L. Sacco Hospital, Department of General Surgery and Internal Medicine, University of Milan, from January 2008 to April 2011. The Ethics Committee of the Hospital had approved a specific study protocol for II-DD-SG on December 20, 2007 (NCT 092/2007).

Participants were recruited at the Endocrinology Unit of the Department of Internal Medicine. All patients received detailed information about the surgical treatment of obesity-associated T2DM and the potential advantages of hindgut manipulation by II-DD-SG. Only those who accepted this surgical treatment and signed the specific informed consent were admitted to the surgical arm.

The sample size estimated was based on the null hypothesis that II-DD-SG is able to induce T2DM remission in 80% of these obese patients (as reported in previous literature [10, 11]), whereas medical treatment is effective in only 10% of these patients. Based on these estimates, we determined that 30 patients for each of the two groups would provide a power of more than 99% to detect differences between them.

Inclusion criteria were patient aged between 20 and 65, body mass index (BMI) > 30 Kg/m^2, a diabetes history of more than 2 years, stable weight over the previous three months, fasting glucose plasma levels > 110 mg/dL, HbA1c plasma levels > 6.5% (before or during antidiabetic therapy). Exclusion criteria were the presence of secondary diabetes or latent adult diabetes (LADA), diagnosis of cancer or inflammatory bowel diseases, pregnancy, previous major abdominal surgery, psychological contraindications to bariatric surgery, severe medical complications including diabetes complications (renal failure, retinopathy, autonomic neuropathy, diabetic foot syndrome), and increased operative risk.

The control group (standard medical treatment) was composed of T2DM obese patients on treatment at our Endocrinology Unit in a 1:1 ratio with the surgical group; patients which best matched the inclusion criteria were included in the control group after signature of the informed consent.

Medical treatment

All patients were treated by a multidisciplinary team composed of an endocrinologist, a dietitian and a nurse. Visits were conducted at baseline, 1, 3, 6, and 12 months during the first year then every six months until the fifth year. Therapeutic intervention consisted in the following:

Hypocaloric–hypolipidic diet; prescribed caloric intake: 1400 Kcal/day for female patients and 1,600 Kcal/day for male patients.

Increased physical activity; prescribed a brisk walk for more than 150 min a week.

Oral antidiabetic drugs and/or insulin; as needed, in order to reach a HbA1c threshold level < 6.5% (primary end point of the treatment).

Lipid lowering treatment; in patients with LDL cholesterol levels > 100 mg/dL and or triglyceride levels > 200 mg/dL in order to achieve threshold values (100 mg/dL for LDL cholesterol and 150 mg/dL for triglycerides) [28].

Antihypertensive drugs; in patients with blood pressure > 140/90 mm Hg, in order to achieve values < 130/85 mm Hg.

Surgical treatment

All candidates for surgery were evaluated at baseline by a multidisciplinary team which included an endocrinologist, a dietitian and a psychiatrist. Following surgery, multivitamin, iron, calcium citrate, and vitamin D supplementation was offered. Follow-up visits were at 3, 6, and 12 months in the first year after surgery; then every 6 months until the fifth year.

II-DD-SG was performed laparoscopically using Ethicon EndoSurgery (Cincinnati, USA) devices. The procedure used [27, 29] (Fig. 1) was adapted from that described by De Paula [30] and consisted in the following:

Sleeve gastrectomy using a 36 Fr gastric tube and complete section of the right gastric vessels. Following duodenal section using a linear stapler, the sleeved stomach was passed through the mesocolon into the submesocolic space.

Preparation of the interposed ileal tract was completed by sectioning the ileum 50 and 200–220 cm above the ileo-cecal valve.

Isoperistaltic gastro-ileal (proximal) anastomosis and ileo-jejunal (distal) anastomosis were performed.

A final anastomosis between the distal jejunum (measured above the ileo-cecal valve) and the distal tract of the ileum was performed.

All the anastomoses were performed using a linear stapler (blue or white cartridge, as needed). The meso-ileal spaces were closed by continuous sutures (Prolene 2/0). The total length of the alimentary limb was 400 cm, with a common tract of approximately 230–250 cm.

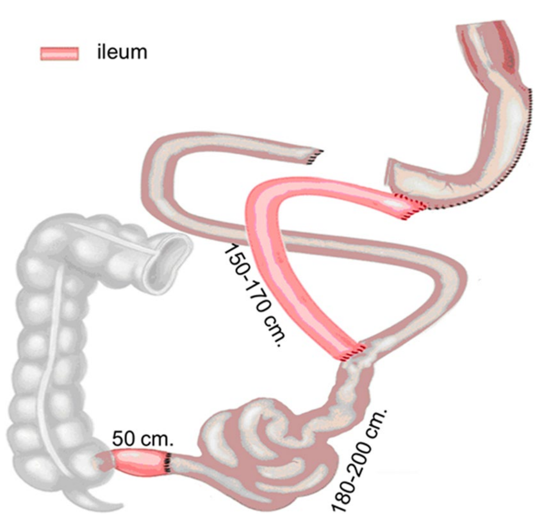

Fig. 1 Ileal interposition with duodenal diverted sleeve gastrectomy

Data collection and evaluation criteria

The following data were collected baseline and at the different follow-up time-points:

Body weight (Kg) and BMI (Kg/m^2);
Blood pressure: (mmHg);
Blood samples for HbA1c (%), fasting glucose plasma levels (FPG) (mg/dL), serum total cholesterol and LDL cholesterol (mg/dL), and serum triglycerides (mg/dL). LDL cholesterol was calculated with the Friedewald equation [31].

The following data were collected baseline and 1 year after surgery:

Insulin plasma levels (μU/mL);
C-peptide (ng/ml)
Fasting and 120 min after oral glucose load (75 g) glycaemia;
Insulin resistance; measured with the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) [32].

The primary end point was the achievement of T2DM remission, evaluated according to the guidelines of the American Diabetes Association [33]:

Partial remission: HbA1c < 6.5% and FPG 100–125 mg/dL, no active pharmacological treatment;
Complete remission: HbA1c < 6% and FPG < 100 mg/dL lasting at least 1 year in the absence of active pharmacological treatment;
Prolonged remission: HbA1c < 6% and FPG < 100 mg/dL, for at least 5 years in the absence of active pharmacological treatment.

Criteria considered as secondary end-points were as follows:

BMI < 30 Kg/m^2, HbA1c < 6%, blood pressure < 135/85 mmHg, total cholesterol < 154 mg/dL, LDL cholesterol < 77.22 mg/dL, triglycerides < 194 mg/dL. Patients that obtained these values were considered to have achieved an optimal metabolic state [34];
Antihypertensive, antidiabetic, and lipid lowering drug use was expressed as number of the patients on treatment in the two groups;
Occurrence of drug treatment complications and of adverse events;

Early complications of surgery, classified according to Clavien–Dindo [35];

Mechanical and metabolic late complications.

Statistical analysis

Categorical variables were considered as frequencies and the difference between times within each treatment group and between treatment groups at given evaluation time-points were evaluated using the Exact Test of Fisher (one or two tails, as appropriate).

Continuous variables were reported as mean values ± standard error of the mean (S.E.M.) according to normal distribution. Differences between time-points and groups were evaluated using analysis of variance (ANOVA) and Student-*t* test (one or two tails as appropriate). Differences with $p < 0.05$ were considered significant.

Results

The major prognostic factors of diabetes remission, i.e., FPG, HbA1c, family history of diabetes, presence of complications, use of insulin, HOMA-IR, insulin and C-peptide levels were comparable in the two groups (Table 1).

No patients dropped out in the first year; five patients (16.6%) in each treatment group had dropped out at the five-year follow-up.

Bariatric effects (Fig. 2)

Body weight and BMI of II-DD-SG patients fell sharply in the first 6 months following surgery and continued to decrease up to 2 years post intervention. A slight body weight increase was evident after 3 years, yet at the 5-year follow-up evaluation, only 2 patients had BMI > 30 Kg/m^2. Waist circumference significantly decreased from 120.8 ± 2.8 cm to a minimum of 92 ± 2.2 cm ($p < 0.0001$)

Table 1 Baseline characteristics of patients in the two treatment groups

	II-DD-SG ($n = 30$)	Medical therapy ($n = 30$)	p Value*
Age (years)	50.6 (± 1.9)	55.0 (± 1.5)	0.074
Gender			
Male	8 (26.7%)	8 (26.7%)	1.000
Female	22 (73.3%)	22 (73.3%)	
Weight (Kg)	114.8 (± 4.8)	107.2 (± 2.8)	0.177
BMI (Kg/m^2)	43.0 (± 1.5)	41.9 (± 1.2)	0.569
Family history of diabetes			
Yes	17 (56.7%)	14 (46.7%)	0.606
No	13 (43.3%)	16 (53.3%)	
Duration of diabetes (years)	4.4 (± 0.6)	4.4 (± 0.7)	1.000
Sequelae of diabetes			
Yes	2 (6.7%)	1 (3.3%)	1.000
No	28 (93.3%)	29 (96.7%)	
Diabetes medications			
Oral hypoglycemic agents	24 (80.0%)	26 (86.7%)	0.731
Insulin	6 (20.0%)	4 (13.3%)	
Fasting blood glucose (mg/dL)	154.6 (± 6.4)	155.8 (± 7.8)	0.906
HbA1c (%)	7.7 (± 0.1)	7.5 (± 0.2)	0.375
Baseline insulin (uUI/mL)	16.1 (± 1.6)	13.1 (± 0.9)	0.108
Baseline C peptide (ng/mL)	4.0 (± 0.3)	3.7 (± 0.7)	0.695
HOMA-IR	6.4 (± 0.8)	4.7 (± 0.6)	0.095
Total cholesterol (mg/dL)	212.8 (± 9.3)	186.1 (± 11.1)	0.07
HDL cholesterol (mg/dL)	43.5 (± 1.6)	45.4 (± 3.5)	0.623
LDL cholesterol (mg/dL)	133.8 (± 8.8)	122.1 (± 13.0)	0.459
Triglycerides (mg/dL)	177.7 (± 13.7)	145.6 (± 12.7)	0.091
Systolic blood pressure (mmHg)	132.5 (± 2.1)	138.9 (± 6.4)	0.346
Diastolic blood pressure (mmHg)	85.8 (± 1.7)	81.1 (± 2.2)	0.096

Continuous variables are expressed as means ± standard errors of the mean

*Fisher exact test was used for categorical variables and Student *T* test for continuous variables

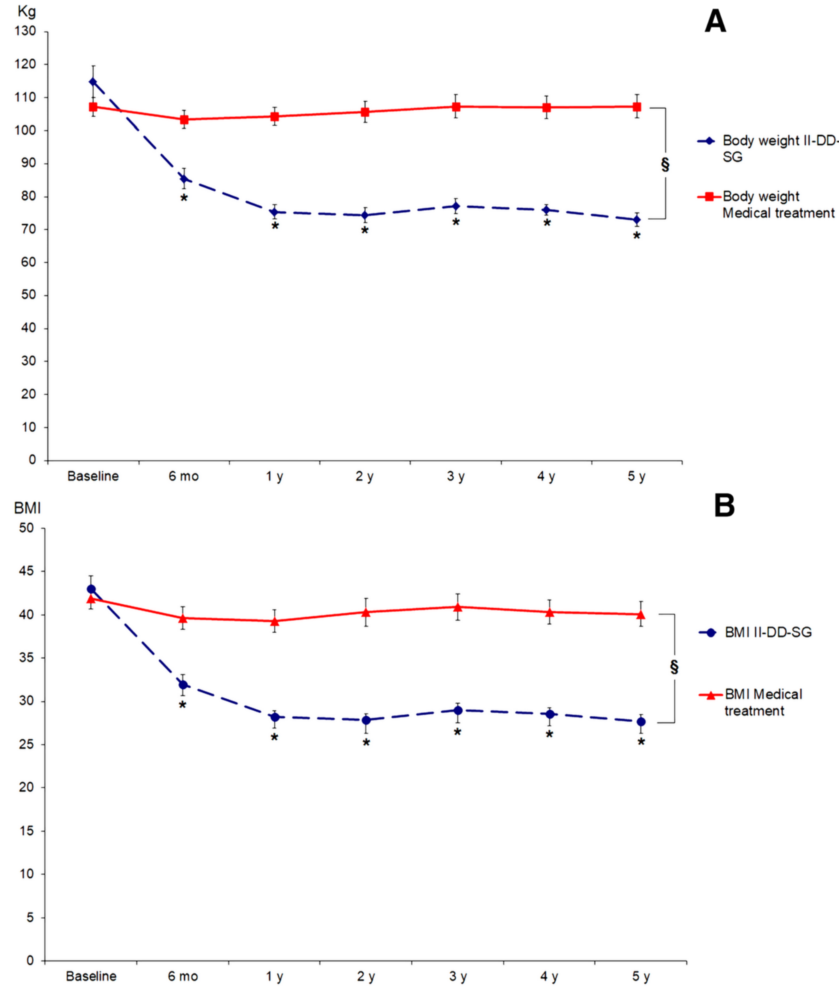

Fig. 2 Anthropometric changes after treatment with II-DD-SG versus medical therapy (*$p < 0.05$ considering the difference with the baseline value within the same group; §$p < 0.0001$ considering the difference between groups)

after 2 years, with a slight increase at the next planned follow-up.

Patients that followed counseling and standard medical treatment showed a slight decrease in body weight and BMI after 2 years starting from the sixth month follow-up. After 5 years, only 2 patients had a weight decrease > 10% of the initial body weight and 1 patient a weight decrease > 5%.

Effects on glucose homeostasis and T2DM remission

Six months after II-DD-SG, mean FPG fell from 154.6 ± 6.4 to 89.6 ± 2.4 mg/dL and mean HbA1c from 7.7 ± 0.1% to 5.6 ± 0.2%; these results remained stable and statistically significant over time until the fifth-year post-surgery ($p < 0.0001$ for different time-points of the II-DD-SG group and between the two groups for each time-point, Fig. 3). At the 1-year follow-up visit (Table 2), mean insulin plasma concentration fell from 16.1 ± 1.6 uUI/mL to 3.2 ± 0.4 uUI/mL ($p < 0.0001$) and HOMA-IR decreased from 6.4 ± 0.8 to 1.5 ± 0.3 ($p < 0.0001$). Twenty-three patients had normal FPG and HbA1c, 5 patients had values classified as subnormal (FPG 100–125 mg/dl, HbA1c 6–6.5%) and two patients were still diabetic. Eighteen patients stopped the assigned pharmacological treatment for containment of glucose plasma levels in the first week following surgery. After 1 year, according to ADA criteria, 16.6% partial remission rate ($n = 5/30$) and 76.6% complete remission rate ($n = 23/30$) was observed; T2DM persisted in 2 patients (6.6%). Five years after surgery, the number of patients with complete remission fell to 68% (17/25), whereas partial remission rate decreased to 20% of total remaining, and 3 out of 25 patients were classified as diabetic. Complete prolonged remission rate was as high as 68%.

In the group with standard medical treatment at the 6-month follow-up, patients showed a slight decrease of FPG (from 155.8 ± 7.8 to 146.5 ± 5.3 mg/dL, $p = 0.348$) and HbA1c (from 7.5 ± 0.2% to 7.3 ± 0.2%, $p = 0.486$). At the 1-year follow-up, insulin (from 13.1 ± 0.9 to 7.7 ± 0.7 uUI/mL, $p = 0.0002$), as well as HOMA-IR (from 4.7 ± 0.6 to 2.3 ± 0.1, $p < 0.0001$) were reduced, but decreases were less pronounced compared to surgical patients. Results remained stable over time and none of the patients had stopped

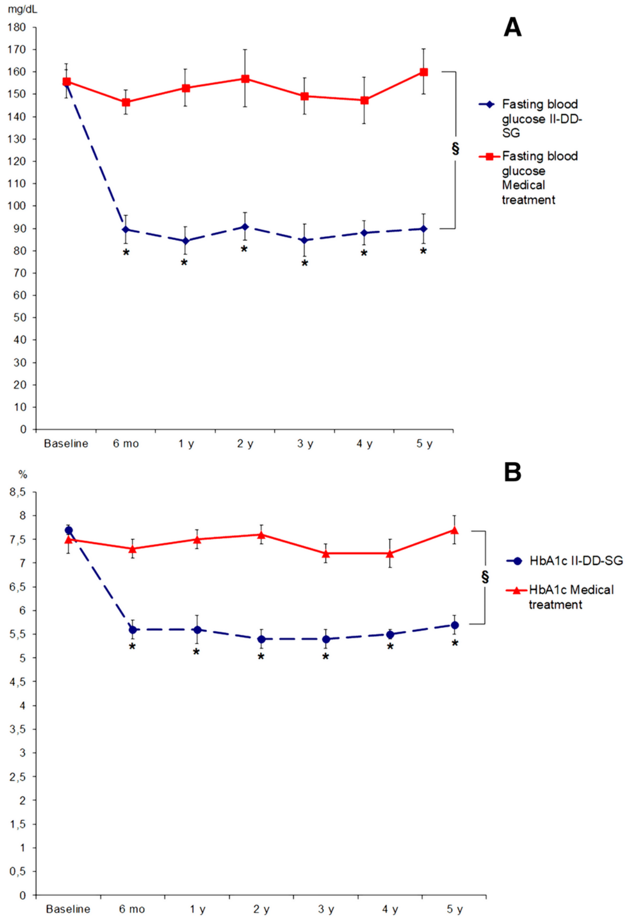

Fig. 3 Glucose metabolism changes after treatment with II-DD-SG versus medical therapy ($^{*}p<0.05$ considering the difference with the baseline value within the same group; $^{§}p<0.0001$ considering the difference between groups)

medication at the 1-year follow-up time point. At 5 years, 2 patients had normal FPG and HbA1c values, 3 patients had subnormal values and 20 patients had pathological values. Complete prolonged remission (under treatment) was achieved in 8% of the patients.

Effects on cardiovascular risk factors

At baseline, all patients enrolled in the study had the following risk factors for complications [34] (Table 3): HbA1c > 6% (100% of the patients), BMI > 30 Kg/m^2 (100%), blood pressure > 135/85 mmHg (66%), total cholesterol > 154 mg/dL (88%), LDL cholesterol > 77 mg/dL (96.6%), triglycerides > 194 mg/dL (63.3%).

Six months after II-DD-SG, only 3 patients had complete normalization of all cardiovascular risk factors whilst HbA1c and BMI were normalized in 23.3% and 33%, respectively.

One year after surgery, 23 (76.6%) patients had HbA1c < 6% but only 11 (36%) LDL cholesterol < 77.22 mg/dL. Complete normalization of cardiovascular risk factors occurred in 8 patients (26.6%) alone. Four years post-surgery, 14 out of 28 patients (50%) were free of cardiovascular risk factors. Complete remission persisted in all these patients also at the last follow-up visit 5 years post-surgery.

In the medical treatment group, none of the patients had complete persistent remission of cardiovascular risk factors (up to and including the last follow-up visit at 5 years). HbA1c, BMI, blood pressure, and lipid metabolism markers remained stable. This must be also interpreted in the light of the fact that medical treatment was started before entering in the trial.

Surgical complications and side-effects of treatment

Two patients had major postoperative complications after II-DD-SG (6.6%) respectively, bleeding from the SG suture line and anastomotic leak at the gastro-ileal anastomosis. Both were stabilized and recovered following a second procedure (Clavien Dindo grade IIIb). Three minor complications (10%) were observed; 2 wound infections and 1 wound hematoma. At the reference time point at five years post-surgery, one additional complication, intestinal occlusion due to a hernia through a mesenteric defect, was observed and corrected by surgical closure of the defect.

No patients showed malnutrition or changes in vitamin B12, folic acid, vitamin D, total protein and albumin plasma levels; all patients, though, had received daily vitamin and trace element supplementation. Incidence of diarrhea in the medical and surgery treated group was similar (13.7% vs. 16.6%). Symptomatic hypoglycemia was occasionally reported in 23 patients (76%) after medical treatment whilst none of the patients in the II-DD-SG group reported such episodes. Progression of concomitant pathological states, present before trial start, such as neuropathy and retinopathy, progressed from minor to major in three patients after medical treatment and in 1 patient who received surgery.

Discussion

An important part in the algorithm of treatment for T2DM obese patients has been metabolic surgery based on surgical study results obtained at the end of the last century and prospective controlled randomized study results published in the last ten years [36].

Two different meta-analyses [2, 3] reported good results obtained by bariatric interventions which lead to T2DM remission through reduction of insulin resistance and body weight. Furthermore, RY-GBP and BPD lead to important hormone changes in the gastro-intestinal tract [24, 25], with

Table 2 Variables related to glucose metabolism after treatment with II-DD-SG versus medical therapy

Follow-up time	II-DD-SG	Medical therapy	*p* Value*
Baseline			
Fasting blood glucose (mg/dL)	154.6 (±6.4)	155.8 (±7.8)	0.906
HbA1c (%)	7.7 (±0.1)	7.5 (±0.2)	0.375
HbA1c ≤ 6%	0/30 (0.0%)	0/30 (0.0%)	1.000
HbA1c ≤ 6.5%	0/30 (0.0%)	0/30 (0.0%)	1.000
Insulin (uUI/mL)	16.1 (±1.6)	13.1 (±0.9)	0.108
HOMA-IR	6.4 (±0.8)	4.7 (±0.6)	0.095
6 Months			
Fasting blood glucose (mg/dL)	89.6 (±2.4)	146.5 (±5.3)	< 0.0001
HbA1c (%)	5.6 (±0.2)	7.3 (±0.2)	< 0.0001
HbA1c ≤ 6%	23/30 (76.7%)	1/30 (3.3%)	< 0.0001
HbA1c ≤ 6.5%	27/30 (90.0%)	8/30 (26.7%)	< 0.0001
Insulin (uUI/mL)	6.6 (±1.1)	8.8 (±0.6)	0.084
HOMA-IR	1.5 (±0.3)	2.8 (±0.2)	0.0006
1 Year			
Fasting blood glucose (mg/dL)	84.5 (±2.2)	152.9 (±8.3)	< 0.0001
HbA1c (%)	5.6 (±0.3)	7.5 (±0.2)	< 0.0001
HbA1c ≤ 6%	23/30 (76.7%)	0/30 (0.0%)	< 0.0001
HbA1c ≤ 6.5%	28/30 (93.3%)	3/30 (10.0%)	< 0.0001
Insulin (uUI/mL)	3.2 (±0.4)	7.7 (±0.7)	< 0.0001
HOMA-IR	0.7 (±0.1)	2.3 (±0.1)	< 0.0001
2 Years			
Fasting blood glucose (mg/dL)	90.8 (±6.2)	157.1 (±12.8)	< 0.0001
HbA1c (%)	5.4 (±0.2)	7.6 (±0.2)	< 0.0001
HbA1c ≤ 6%	24/29 (82.8%)	1/25 (4.0%)	< 0.0001
HbA1c ≤ 6.5%	27/29 (93.1%)	4/25 (16.0%)	< 0.0001
3 Years			
Fasting blood glucose (mg/dL)	84.8 (±3.2)	149.2 (±8.2)	< 0.0001
HbA1c (%)	5.4 (±0.2)	7.2 (±0.2)	< 0.0001
HbA1c ≤ 6%	26/29 (89.7%)	1/25 (4.0%)	< 0.0001
HbA1c ≤ 6.5%	27/29 (93.1%)	7/25 (28.0%)	< 0.0001
4 Years			
Fasting blood glucose (mg/dL)	88 (±1.5)	147.3 (±10.5)	< 0.0001
HbA1c (%)	5.5 (±0.1)	7.2 (±0.3)	< 0.0001
HbA1c ≤ 6%	23/28 (82.1%)	2/25 (8.0%)	< 0.0001
HbA1c ≤ 6.5%	27/28 (96.4%)	8/25 (32.0%)	< 0.0001
5 Years			
Fasting blood glucose (mg/dL)	89.8 (±2.6)	160.2 (±10.2)	< 0.0001
HbA1c (%)	5.7 (±0.2)	7.7 (±0.3)	< 0.0001
HbA1c ≤ 6%	17/25 (68.0%)	2/25 (8.0%)	< 0.0001
HbA1c ≤ 6.5%	24/25 (96.0%)	6/25 (24.0%)	< 0.0001

Continuous variables are expressed as means ± standard errors of the mean

*Fisher exact test was used for categorical variables and Student *T* test for continuous variables. Two-way ANOVA for fasting blood glucose and HbA1c confirmed $p < 0.0001$ within each group for different times and between groups for each time

a decrease of ghrelin and increase of incretins and other enterokines [37]. The Swedish Obesity Subjects study demonstrated that surgery is able to prevent the onset of T2DM [38] and avoid micro- and macrovascular complications [39]. These effects on T2DM and the ability of surgery to reduce the burden of dyslipidemia and blood hypertension have decreased the risk of cardiovascular complications in T2DM obese patients and increased their life span [40].

Prior to 2007, data which compared medical and surgical treatment in prospective controlled randomized trials were

Table 3 Effects of II-DD-SG on cardiovascular risk factors

		Baseline	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years	*p* Value*
BMI ≤ 30 Kg/m^2	II-DD-SG	0/30** (0.0%)	11/30 (36.7%)	23/30 (76.7%)	24/29 (82.8%)	20/29 (69.0%)	23/28 (82.1%)	21/25 (84.0%)	< 0.0001
	Medical therapy	0/30** (0.0%)	0/30 (0.0%)	0/30 (0.0%)	0/25 (0.0%)	0/25 (0.0%)	0/25 (0.0%)	1/25 (4.0%)	
HbA1c ≤ 6%	II-DD-SG	0/30** (0.0%)	23/30 (76.7%)	23/30 (76.7%)	24/29 (82.8%)	26/29 (89.7%)	23/28 (82.1%)	17/25 (68.0%)	< 0.0001
	Medical therapy	0/30** (0.0%)	1/30 (3.3%)	0/30 (0.0%)	1/25 (4.0%)	1/25 (4.0%)	2/25 (8.0%)	2/25 (8.0%)	
Systolic blood pressure ≤ 135 mmHg	II-DD-SG	20/30** (66.7%)	25/30** (83.3%)	28/30 (93.3%)	28/29 (96.6%)	23/29 (79.3%)	24/28 (85.7%)	19/25** (76.0%)	< 0.0001
	Medical therapy	20/30** (66.7%)	21/30** (70.0%)	20/30 (66.7%)	11/25 (44.0%)	12/25 (48.0%)	14/25 (56.0%)	14/25** (56.0%)	
Diastolic blood pressure ≤ 85 mmHg	II-DD-SG	20/30** (66.7%)	24/30** (80.0%)	28/30** (93.3%)	26/29** (89.7%)	26/29 (89.7%)	20/28 (71.4%)	22/25** (88.0%)	0.025
	Medical therapy	27/30** (90.0%)	26/30** (86.7%)	30/30** (100.0%)	25/25** (100.0%)	17/25 (68.0%)	25/25 (100.0%)	25/25** (100.0%)	
Total cholesterol ≤ 154 mg/dL	II-DD-SG	3/30** (10.0%)	14/30** (46.7%)	17/30 (56.7%)	7/29** (24.1%)	20/29 (69.0%)	18/28 (64.3%)	19/25 (76.0%)	0.001
	Medical therapy	9/30** (30.0%)	7/30** (23.3%)	8/30 (26.7%)	5/25** (20.0%)	6/25 (24.0%)	5/25 (20.0%)	9/25 (36.0%)	
LDL cholesterol ≤ 77 mg/dL	II-DD-SG	1/30** (3.3%)	12/30 (40.0%)	11/30 (36.7%)	7/29** (24.1%)	11/29 (37.9%)	14/28** (50.0%)	15/25 (60.0%)	0.0002
	Medical therapy	5/30** (16.7%)	2/30 (6.7%)	3/30 (10.0%)	5/25** (20.0%)	3/25 (12.0%)	7/25** (28.0%)	2/25 (8.0%)	
Triglycerides ≤ 194 mg/dL	II-DD-SG	21/30** (70.0%)	29/30** (96.7%)	29/30 (96.7%)	27/29** (93.1%)	29/29 (100.0%)	28/28 (100.0%)	25/25** (100.0%)	0.012
	Medical therapy	26/30** (86.7%)	24/30** (80.0%)	21/30 (70.0%)	19/25** (76.0%)	18/25 (72.0%)	19/25 (76.0%)	23/25** (92.0%)	
Reduction of all cardiovascular risk factors	II-DD-SG	0/30** (0.0%)	3/30** (10.0%)	6/30 (20.0%)	7/29 (24.1%)	11/29 (37.9%)	14/28 (50.0%)	14/25 (56.0%)	< 0.0001
	Medical therapy	0/30** (0.0%)	0/30** (0.0%)	0/30 (0.0%)	0/25 (0.0%)	0/25 (0.0%)	0/25 (0.0%)	0/25 (0.0%)	

*Chi-square test was performed comparing variables between II-DD-SG and medical therapy groups for each time; only the minimum *p* value was reported

***p* Value not significant

not available. Over the last 10 years, Schauer [16, 17], Mingrone [22, 23], Kashyap [18], Ikramuddin [19], Halperin [20], and Cummings [21] have demonstrated in CCTs that BPD, RY-GBP, and SG are better than standard or intensive medical treatment. These data suggest that surgical interventions which involve hindgut manipulation and which are able to increase the postprandial secretion of incretins (like GLP-1) and enterokines [37] are more effective in T2DM patients versus restrictive interventions such as AGB. Data also indicate that even though SG acts in ameliorating ghrelin and bile acid turn-over [41], it is less effective in resolving T2DM than GBP or BPD [4–6].

Koopmans first proposed ileal interposition in the 1970s [42]; he induced ileal brake in experimental animal models with consequent reduction in food intake and body weight. Cummings investigated this technique in diabetic rodents [26] with good results. De Paula proposed two techniques of ileal interposition, with or without duodenal exclusion [10]. We think that II-DD-SG is a very effective procedure for T2DM treatment in obese patients; SG has restrictive and bariatric effects reducing insulin resistance [4, 5], duodenal exclusion preserves insulin secretion [43] and ileal interposition stimulates GLP-1 and enterokines secretion [27, 28].

Recently, ileal interposition with sleeve gastrectomy was introduced in clinical practice as a cure for obesity, metabolic syndrome and diabetes [30]. Although several studies [10, 11, 27, 30, 44, 45] have been performed to demonstrate the effectiveness of ileal interposition in association to sleeve gastrectomy and duodenal diversion, a controlled study in comparison to medical treatment of obese patients affected by T2DM was missing; our study evaluated such aspects and also investigated the effects of surgery on cardiovascular risk factors, such as dyslipidemia and blood pressure with promising results. Our results show that also II-DD-SG is better than medical treatment for obese patients affected by T2DM.

Clinical data show that II-DD-SG leads to very early remission of T2DM and resolution of the metabolic syndrome [11, 27, 44, 45]. Additionally, the number of patients requiring medical treatment falls during the first year following surgery. In our study, glucose and lipid metabolism of obese T2DM patients decreases significantly following II-DD-SG surgery against standard medical therapy in the short and long-term follow-up. According to the ADA criteria for definition of T2DM complete and prolonged remission (i.e., 5 years of complete remission persistence), more than 68% of the patients receiving II-DD-SG were disease-free 5 years post-surgery versus 8% after medical therapy. Effects on weight loss, blood hypertension and lipid metabolism are also persistent over time. The persistence of clinical and metabolic read-outs from the first to the fifth year following II-DD-SG surgery contrasts to those observed in BPD, RY-GBP, and SG in which there is a progressive decrease in therapeutic effects by 33% [22, 23], 33–50%, and 38%, respectively [16, 17].

The positive results of our study have to be interpreted with respect to others obtained using the above mentioned surgical procedures considering a number of aspects. Firstly, II-DD-SG, SG, RY-GBP, and BPD may have a different therapeutic power on T2DM, but in order to prove this hypothesis, a prospective controlled trial comparing the various surgical procedures is warranted since no compelling data exist. The Swedish Obese Subjects study demonstrated that during a 20-year follow-up period, T2DM post-surgical remission rate in obese patients reduces slowly [38]. This observation, in a large population, contrasts the results obtained by Schauer [16, 17] and Mingrone [22, 23], which showed a fast reduction of the remission rate.

A possible explanation lies in the fact that there was a high withdrawal rate following randomization (31% and 20%), leading to a spontaneous selection of the less responsive patients to the surgical procedure. This suggests the importance of the standardization of the selection criteria for metabolic surgery to compare the studies in the future.

Secondly, even though the prognostic factors collected and followed during the study were the same in the medical treatment and surgically treated group, the selection criteria were in favor of T2DM remission: our patients were generally young, heavily obese with high BMI and had clinical characteristics, such as short-term history of disease, low FPG and HbA1c levels, which were more favorable to T2DM remission. In the afore mentioned studies [16, 17, 22, 23], disease onset was longer (6–8 years) and the prognostic factors less favorable.

Thirdly, in our study, the control arm was under standard care and not intensive medical treatment. This is due to the fact that at the beginning of our study, innovative drugs such as GLP-1 or its analogues were not available as standard care in Italy and were not administered to patients in that arm.

To correctly define the role of surgery in the context of treatment of T2DM in obese patients, we must consider the risk–benefit ratio, which includes but is not limited to postoperative complications and long-term nutritional side-effects. Although the rate of postoperative complications following bariatric surgery is low and mortality is even less [46], the more complex the surgical technique, the higher the risk of complications. Also, in the light of the fact that diabetic patients have a higher risk of infection [47] and vascular complications [48]. This should speak against II-DD-SG as a therapeutic option in T2DM obese patients, but our results coupled with those of Celik [44] and De Paula [49] demonstrate low risk of complications and mortality. Finally, clinical signs of malabsorption and malnutrition after II-DD-SG were not observed since all patients received nutritional support during the whole follow-up period.

We conclude that II-DD-SG is a good surgical option for T2DM obese patients; there were no major surgical complications, no malabsorption and more than 68% of patients had complete remission on the long-term. Even though we included in our study patients with favorable remission characteristics in the surgical arm, the prolonged remission rate and the favorable prognosis of cardiac risk factors are evident from the results obtained and reported. Nevertheless, further studies are needed to compare sleeve gastrectomy, Roux-en-Y Gastric By-Pass, BPD and, in our opinion, II-DD-SG as surgical options to treat T2DM obese patients with the primary objective of obtaining the highest long-term remission rate.

Funding None declared.

Compliance with ethical standards

Disclosures Prof. Diego Foschi, Dr. Luca Sorrentino, Dr. Igor Tubazio, Dr. Consuelo Vecchio, Dr. Tarcisio Vago, Dr. Maurizio Bevilacqua, Dr. Andrea Rizzi, Prof. Fabio Corsi have no conflicts of interest or financial ties to disclose.

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