Int J Endocrinol Metab. 2011;**9**(3):374-381. DOI: 10.5812/Kowsar.1726913X.2782

KOWSAR

International Journal of
Endocrinology & Metabolism
Journal home page: www.EndoMetabol.com

Remission of Type 2 Diabetes Mellitus by Ileal Interposition with Sleeve Gastrectomy

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 05 Feb 2011
Revised: 22 Apr 2011
Accepted: 07 May 2011

Keywords:
Diabetes Mellitus
Ileal Interposition
Sleeve Gastrectomy
Hypertension
Dyslipidemia

ABSTRACT

Background: Laparoscopic leal inter Position(II) with sleeve gastrectomy (SG) is an upcoming procedure that helps to improve metabolic profile and leads to weight reduction without causing significant malabsorption, paving the way for usage of the term "metabolic surgery."
Objectives: To determine the impact of this novel procedure on glycemic control and the accompanying metabolic abnormalities of type 2 diabetes mellitus (T2DM).
Patients and Methods: The II and SG procedures were performed in 38 patients (M:F = 24:14). Despite their usage of optimum dosage of oral hypoglycemic agents (OHAs) and/or insulin, all patients exhibited poorly controlled T2DM (mean glycosylated hemoglobin [HbA1C]: 9.57 ± 2 %). The primary outcome was a remission of diabetes (HbA1C < 6.5% without OHA/insulin). Secondary outcomes included a reduced need for antidiabetic agents and a reduction in symptoms of metabolic syndrome.
Results: The mean follow up time was 11.3 ± 9 months (range: 3–32 months). Participants were 47.5 ± 8.8 years of age (range: 29–64 years), had diabetes for a mean duration of 9.7 ± 8.8 years (range: 1–32 years), and had a mean preoperative body mass index (BMI) of 32.05 ± 7.5 kg/m2. Thirty patients (79%) exhibited hypertension, 19 (50%) had dyslipidemia, and 19 (50%) harbored significant microalbuminuria. Postoperatively, glycemic parameters (fasting and post lunch blood sugars, and HbA1C) improved for all patients ($P < 0.05$) at all intervals. Eighteen patients (47%) experienced a remission in diabetes and the remaining patients received a significantly lower OHA dosage. All patients demonstrated 15–30% weight loss ($P < 0.05$). Twenty-seven patients (90%) experienced a remission in hypertension. At 2 years, the mean reduction in HbA1C (36%) was greater than the reduction in BMI (20%). A declining trend in postoperative levels of lipids and microalbuminuria became evident, although the reduction was significant for microalbuminuria only.
Conclusions: The laparoscopic II with SG procedure appears promising for gaining control of T2DM and associated morbidities. To substantiate our preliminary findings, additional long-term data that involves a larger number of patients is necessary.

▸ *Implication for health policy/practice/research/medical education:*
Ileal interposition in accompaniment with sleeve gastrectomy addresses both the foregut and hindgut hypotheses and thus provides a new paradigm for the treatment of type 2 diabetes mellitus and the associated metabolic abnormalities even in non morbidly obese subjects.

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DOI: 10.5812/Kowsar.1726913X.2782

▸ *Please cite this paper as:*
Kumar Kota S, Ugale S, Gupta N, Naik V, Krishna Kota S, Hari Kumar Kvs, Modi KD. Remission of Type 2 Diabetes Mellitus by Ileal Interposition with Sleeve gastrectomy. *In J Endcrinol Metab*. 2011;**9**(3):374-81. DOI: 10.5812/Kowsar.1726913X.2782

1. Background

Type 2 diabetes mellitus (T2DM) and obesity are diseases of epidemic proportions. The global prevalence of diabetes among adults (aged 20–79 years) was estimated to be 6.4% in 2010 and is projected to increase to 7.7% by 2030 (1). Currently, approximately 50.8 million individuals in India are diabetic (2), and this number is projected to increase to 80.9 million in 2030 (3). In 2005, the World Health Organization (WHO) stated that an estimated 1.6 billion adults in the world were overweight and at least 400 million were classified as obese. In addition, the WHO predicted that, by 2015, 2.3 billion adults would be overweight, with 700 million (30.4%) classified as obese (4). The pathogenic processes involved in the development of diabetes include autoimmune destruction of beta cells, secretion of excess insulin to compensate for increased insulin resistance, and increased production of endogenous glucose (5-7). Insulin resistance is not essential in the etiology of nonobese T2DM (8). Diabetes has been shown to persist in nonobese patients after weight loss had induced complete restoration of normal insulin sensitivity. This finding implies that impaired insulin secretion plays an essential role in T2DM (9).

Incretins, which include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play a major role in insulin secretion. Impaired incretin activity interferes with normal early-phase insulin secretion processes (0–20 min) in T2DM. Defective late-phase plasma insulin amplification in response to GIP-induced glucose (20–120 min) has also been observed, whereas GLP-1 has been shown to enhance the late-phase plasma insulin response markedly (10). The loss of early-phase insulin secretion results in insufficient suppression of glucagon secretion, free fatty acid secretion, and hepatic glucose output, all of which trigger continuous delivery of glucose in the circulation (11). In diabetes patients, GIP secretion is typically normal, whereas GLP-1 secretion is reduced; however, apart from the variation in secretion, the effect of GLP-1 is preserved and the effect of GIP is severely impaired (12).

Bariatric surgery, particularly gastric bypass (13), and malabsorptive surgeries (Roux-en-Y [R-n-Y] gastric bypass and biliopancreatic diversion [BPD]), are effective for achieving long-term control of obesity and T2DM (14). Various hypotheses have been proposed to explain glycemic control in 84–97% of diabetic patients who have undergone these surgeries, including exclusion of the duodenum (foregut hypothesis) and early delivery of partially digested chyle to the distal ileum, stimulating the release of GLP-1 (hindgut hypothesis) (15). Recent reports have described improved glucose homeostasis after bariatric surgery that was weight loss independent (16, 17). Bariatric surgery is an excellent method for controlling diabetes and co-morbid ailments, and has thus led to the concept of metabolic surgery (18).

De Paula *et al.* (19) reported on a technique named "neuroendocrine break," which consists of a sleeve gastrectomy (SG) in coordination with ileal interposition (II), and the process resulted in complete resolution of T2DM in morbidly obese patients. By combining the II and SG procedures, both the foregut and hindgut hypotheses are addressed. Although sufficient evidence is available in the literature regarding the efficacy of this novel procedure (II + SG) for treating T2DM (19- 24), data from the Indian population is scarce (20, 21). This procedure has been performed in obese and nonobese T2DM patients all over the world (22-25).

2. Objectives

To evaluate and report the results of II + SG treatment in 38 T2DM patients.

3. Patients and Methods

The present study included 38 patients subjected to II + SG in the Department of Laparoscopic Surgery, Kirloskar Hospital, Hyderabad, India. The hospital's ethical committee approved the study, all patients were informed thoroughly about the benefits and risks involved, Subsequently the patients provided written, informed consent. The potential benefits and the limited available data on this surgical procedure were explained specifically to nonobese diabetic patients.

3.1. Inclusion and Exclusion Criteria

To meet inclusion criteria, patients had T2DM for at least 1 year, were 25 to 70 years in age, maintained a stable weight for the previous 3 months (less than 3% weight variation) (22-24), and exhibited stimulated C-peptide (> 1.5 ng/mL). Exclusion criteria included type 1 diabetes, undetectable fasting C-peptide, positive urine ketones, pregnancy, coexisting severe hepatic, pulmonary, renal, cardiovascular, neurological, or psychiatric diseases, and obesity due to organic illness.

3.2. Subjects and Preoperative Evaluation

The preoperative evaluation included a clinical history of T2DM, comorbidities, and complications, followed by a thorough physical examination. Patients were diagnosed with T2DM if their fasting plasma glucose was ≥ 126 mg/dL (fasting was defined as no caloric intake for 8 h), their 2-h plasma glucose was ≥ 200 mg/dL during an oral glucose tolerance tolerance test after consuming a glucose load (anhydrous glucose, 75 g) dissolved in water, or the patient presented with classic symptoms of hyperglycemia (random plasma glucose ≥ 200 mg/dL) (26). The standing height of each patient was measured using a portable stadiometer (Leicester height meter, UK; range, 60–207 cm). Weight was measured with an electric scale (Salter, India), accurate to 100 g. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared (27). We defined obesity as patients' BMI of > 27 kg/m^2. Relevant biochemistry tests, urinalyses, and imaging studies (chest radiograph and ultrasound of the abdomen) were performed on all patients in a single laboratory that had received approval by the National Accreditation Board for Testing and Calibration Laboratories (NABL). A fully automated clinical chemistry analyzer (Olympus 2700) was used to conduct biochemical analyses. Fasting and post-meal blood glucose were measured by the hexokinase method; the cholesterol oxidase method was used to estimate the lipid profile. A Roshe E 601 analyzer was used to assess serum insulin, C-peptide (basal and 1 h post meal), thyroid profile, and microalbuminuria. To determine insulin levels, fasting serum samples were subjected to electrochemiluminiscence. C-peptide and thyroid profiles (basal and 1 h post meal) were measured by the chemiluminiscence method. The immunoturbidometry assay was used to detect microalbuminuria in a 24-h urine specimen. Glycated hemoglobin ($HbA1_C$) was examined using the high performance liquid chromatography (HPLC) method with Biorad variant D10. Patients with hypothyroidism were prescribed thyroxine replacement and were subjected to surgery after the euthyroid state was achieved. The glomerular filtration rate was calculated using the modified Cockgroft-Gault equation (28, 29). Insulin resistance (IR) was assessed using the homeostasis model assessment (HOMA) formula (HOMA-IR) with fasting blood glucose and insulin (30).

3.3. Outcomes

The primary outcome measure was T2DM remission, defined as HbA1c < 6.5% without oral or parenteral hypoglycemic agents. Secondary outcomes measures included iimproved glycemic parameters ($HbA1_C$, fasting blood sugar and post lunch blood sugar), rremission or improved hypertension, iimproved metabolic parameters (e.g., lipids and microalbuminuria), decreased weight and BMI (obese patients), and rreduced insulin and oral hypoglycemic agent (OHA) requirements.

3.4. Procedure

The operation was performed under general anesthesia via a standard 6-port laparoscopic technique. The surgical procedure involved the creation of a 170-cm segment of ileum that started 30 cm proximal to the ileocecal junction. This segment was interposed into the jejunum, which was divided between 20 and 50 cm from the ligament of Treitz. All 3 anastomoses were performed side-by-side with an endo-GIA stapler (Ethicon Endo-surgery, Cincinnati, OH, USA) fitted with a 45-mm white cartridge. The stapler openings were closed by hand with a 3 = 0 polydioxanone suture in 2 layers. A variable sleeve gastrectomy was performed after the larger curvature from the antrum to the fundus area was devascularized. *Figure 1* depicts a diagrammatic representation of the procedure. The lumen of the stomach was adjusted using a 32–58 French calibrator (Romsons International, New Delhi, India), which was placed along the smaller curvature. The endo-GIA stapler with 60-mm cartridges was used for the resection process. Nonobese patients were subjected to fundectomy only, and a sufficient volume of residual stomach remained for normal food intake.

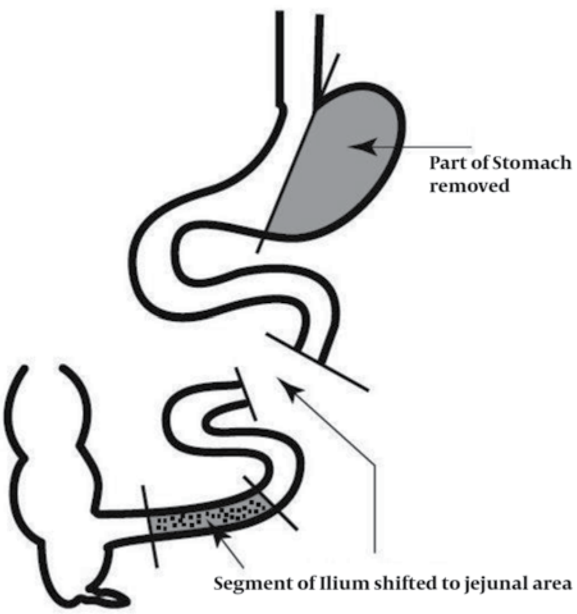

Figure 1. Diagram of Ileal Interposition with Sleeve Gastrectomy

3.5. Postoperative Follow Up

Diabetes and hypertension medications were adjusted postoperatively according to plasma glucose and blood pressure records. The patients maintained a liquid diet for 5–7 days, followed by a semisolid diet for 7 days, and finally a diet that included solids (to be consumed in small quantities). The patients were discharged between the fourth and sixth postoperative days with vitamin supplements. A routine upper gastrointestinal endoscopy was conducted 1 month after surgery. Patients were asked to return for follow up at 1, 3, 6, 9, 12, 18, and 24 months.

3.6. Statistical Analysis

All outcome measures were evaluated at every visit prospectively from the third month onward. Online Graphpad Quickcalcs software (Graphpad. Software Inc., La Jolla, CA, USA, available at http://www.graphpad.com/quickcalcs/index.cfm) was used for statistical calculations. Continuous data were analyzed using the student's t test.

Because of the small sample size, categorical data were analyzed by the two-tailed Fisher's exact test. A *P value* of less than 0.05 was considered significant.

4. Results

A total of 38 patients, whose baseline demographic characteristics are listed in *Table 1*, underwent II + SG. For preoperative glycemic control, 17 patients required ≥ 2 OHAs and 21 required insulin ± OHA. The mean follow up period was 11.3 ± 9 months (range: 1–26 months). The postoperative follow up data is summarized in *Table 2*. Compared with BMI, there was a greater decrease in HbA1c at all intervals (mean decrease in BMI of 20% versus a mean decrease in $HbA1_C$ of 36%, *(Figure 2)*.

Table 1. Study Group Baseline Data

	Results	CV, %
Patient, No.	38	-
men	24	-
women	14	-
Obese patients (BMI > 27 kg/ m²), No (%)	29 (67)	-
Nonobese patients (BMI ≤ 27 kg/m²), No (%)	14 (33)	-
Hypertension, No (%)	30 (79)	-
Dyslipidemia, No (%)	19 (44)	-
Microalbuminuria, No (%)	19 (44)	-
Age, y, Mean ± SD (range)	47.5 ± 8.8 (29–64)	18.5
Duration of DM, y, Mean ± SD (range)	9.7 ± 8.8 (1–32)	90.7
BMI, kg/m² [a]	32.05 ± 7.5	23.4
HbA1c, % [a]	9.57 ± 2	20.9
Fasting C-peptide, ng/mL [a]	2.8 ± 1.3	46.4
Post-meal C-peptide, ng/mL [a]	4.6 ± 2.6	56.5
HOMA-IR [a]	20.3 ± 3.5	17.3
LDL Cholesterol, mg/100 ml [a]	102.7 ± 34.6	33.7
Triglyceride, mg/100 ml [a]	184.2 ± 176.8	95.9
Microalbuminuria, mg/24 h [a]	77.2 ± 124.8	161.6

[a] All data are as Mean ± SD

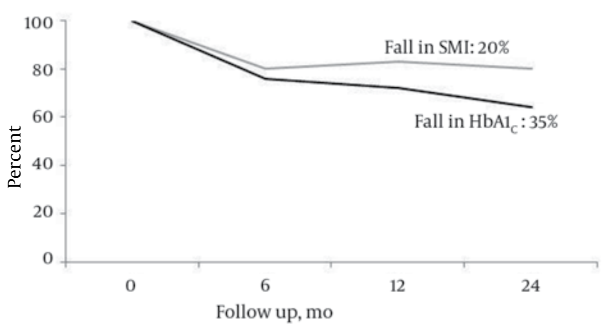

Figure 2. Postoperative Comparison of Percentage (%) Fall in BMI & HbA1C

4.1. Diabetes and Hypertension Remission Data

At 6 months, 15/29 patients (52%) were not using any OHAs and no patients required insulin, whereas in the preoperative period,18 patients required OHAs and 21 patients required insulin in addition to OHAs ($P = 0.001$ and 0.002, respectively). Seven out of 29 patients (24%) required metformin alone, and 4/29 patients (13%) required ≥ 2 OHAs. Sixteen patients have completed the 1-year follow up; 8 were not using OHAs ($P = 0.004$) and only 1 patient required insulin in addition to OHAs ($P = 0.002$). At the 2-year follow up, 4 out of 6 patients were not using OHAs ($P < 0.0001$) and 1 required metformin alone for glycemic control ($P = 0.001$). A recovery from hypertension was observed in 25/28 patients (89%) at 3 months, 16/20 patients (80%) at 6 months, 8/10 patients (80%) at 1 year, 7/10 patients (70%) at 18 months, and 5/6 patients (83%) at 2 years. For all intervals, the recovery from hypertension was statistically significant ($P < 0.001$). Overall, 18/38 (47%) and 27/30 (90%) went into remission for diabetes and hypertension, respectively, after 2 years. In patients with a BMI > 35 kg/m², 10/12 (82%) experienced a remission in diabetes and 10/10 (100%) experienced remission in hypertension. Postoperatively, improvements were observed in other metabolic parameters like lipids and microalbuminuria; however, only the latter was statistically significant. The mean length of the operation was 5.2 ± 1.1 hours. Postoperation, 6 patients experienced difficulty swallowing for 2 weeks. About 25% of the patients (12/43) experienced nausea and loss of appetite for 1 month. No major surgical complications were observed.

4.2. Analysis of Patient Outcomes

We divided the patients into 2 groups according to 3 preoperative parameters: BMI < 27 kg/m² versus > 27 kg/m²; stimulated C-peptide (1 hour post meal) < 4 ng/mL versus > 4 ng/mL; and duration of diabetes ≤ 10 years versus > 10 years. *Table 3* compares postoperative glycemic improvements observed in both groups and at all intervals. *Table 4* highlights the diabetes and hypertension remission data in all groups and at all intervals.

5. Discussion

Our current report demonstrates, in 38 patients, the beneficial effects of the novel II + SG procedure for controlling T2DM, hypertension, obesity, and related metabolic abnormalities. Taken in combination, the foregut and hindgut theories explain the resulting improved diabetes and weight loss after this surgery (31). All patients experienced weight loss that ranged from 15% to 30%. Complete remission of T2DM was observed in 18/38 patients (47%), and the remaining patients demonstrated a greater than 80% reduction in antidiabetic medication requirements. Hypertension remitted in 27/30 patients (90%). A significant reduction in postoperative microalbuminuria was observed with a declining trend in lipid parameters.

The definition of obesity as it relates to BMI varies in different parts of the world. According to WHO guidelines, obesity is defined as > 30 kg/m² (32). The cut-off BMI value

Table 2. Postoperative Metabolic Parameters in 38 Patients

Parameter [c]	FBS [a], mg/100 mL	PLBS [a], mg/100 mL	HbA1c [a], %	BMI [a], kg/m²	Cholesterol, mg/100 mL	LDL-C [a], m/100 mL	Triglycerides, mg/100 mL	Micralbuminuria, mg/24 h
Preoperative	180.8 ± 49.1	281.7 ± 83.3	9.57 ± 2	32.05 ± 7.5	177.1 ± 43.7	102.7 ± 34.6	184.2 ± 176.8	77.2 ± 124.8
3 mo	107.1 ± 25.2 [b]	158.1 ± 64.9 [b]	6.96 ± 1.1 [b]	26.91 ± 5.0 [b]	158.7 ± 29.1 [b]	90.4 ± 21.5 [b]	128.3 ± 95.3 [b]	48.7 ± 61.4 [b]
6 mo	121.5 ± 34.3 [b]	146.4 ± 31.9 [b]	7.57 ± 1.82 [b]	25.62 ± 4.3 [b]	172 ± 33.9	101.4 ± 30.7	131.6 ± 82.6 [b]	38.6 ± 39.3 [b]
12 mo	98.9 ± 27.1 [b]	134.2 ± 43.2 [b]	7.3 ± 1.4 [b]	26.47 ± 3.8 [b]	169 ± 41.4	95 ± 29.6 [b]	146 ± 132.1 [b]	31.5 ± 25.8 [b]
18 mo	123.8 ± 19.3 [b]	198 ± 34.2 [b]	7.4 ± 1.2 [b]	26.42 ± 3.8 [b]	175 ± 36.4	111 ± 22.5	186 ± 164.1	18.7 ± 13.4 [b]
24 mo	109.5 ± 28.7 [b]	147 ± 37.4	6.2 ± 1.2	25.48 ± 4.1 [b]	192.6 ± 12.1	120.6 ± 13.6	101.6 ± 38.3	35 ± 23.9

[a] Abbreviations: BMI, Body mass index; FBS,Fasting blood sugar; PLBS, Post lunch blood sugar; LDL-C, Low density lipoprotein cholesterol
[b] *p* value < 0.05 (student's t test)
[c] All data are as Mean ± SD

Table 3. Postoperative Glycemic Improvement (HbA1c) in Patients Classified as Per Their Preoperative BMI, Duration of Diabetes and Stimulated C-peptide Levels

	HbA1C [a]					
	BMI < 27 kg/m², (n = 14)	BMI > 27 kg/m², (n = 29)	DM duration < 10 years [c], (n = 26)	DM [b] duration > 10 years [c], (n = 17)	Stimulated C-peptide < 4 ng/mL, (n = 18)	Stimulated C-peptide > 4 ng/mL, (n = 25)
0 mo	9.1 ± 1.8	9.7 ± 1.9	9.3 ± 2.2	9.8 ± 1.3	9.9 ±1.7	9.2 ± 2.1
3 mo	7.1 ± 1.4 [c]	6.8 ± 0.9 [c]	6.8 ± 1.2 [c]	6.9 ± 0.8 [c]	7.3 ± 1.2 [c]	6.7 ± 0.9 [c]
6 mo	7.7 ± 0.7	7.6 ± 2.2 [c]	7.1 ± 1.0 [c]	8.0 ± 2.3 [c]	8.6 ± 1.9	6.7 ± 1.4 [c]
9 mo	7.5 ± 0.8	8.4 ± 2.0 [c]	7.3 ± 0.7 [c]	9.4 ± 2.3	8.9 ± 2.3	7.4 ± 0.7 [c]
12 mo	7.4 ± 0.1	7.3 ± 1.6 [c]	6.5 ± 1.0 [c]	8.4 ± 2.3	8.5 ± 1.1	6.5 ± 0.9 [c]
18 mo	7.3 ± 0.3	7.7 ± 1.6 [c]	7.1 ± 1.8	8.6 ± 1.1	8.9 ± 0.7	6.9 ± 1.6 [c]
24 mo	7.3 [d]	6.3 ± 1.2 [c]	5.6 ± 0.4 [c]	7.6 [d]	8.4 [d]	6.3 ± 1.2 [c]

[a] All data are as Mean ± SD
[b] Abbreviations: DM, Diabetes mellitus"
[c] *P* value < 0.05 (student's t test),
[d] Statistical analysis could not be done because of availability of limited number of patients.

that defines obesity in Asians is lower; for example, China (33) uses > 28 kg/m² and Japan uses > 25 kg/m² (34). The Asia Pacific guidelines note a cut-off of > 27.5 kg/m² to define obesity (35). We chose to use a BMI cut-off of > 27 kg/m² to diagnose obesity in our study population, which encompassed available Asian data spanning several countries. The consensus statement for the diagnosis of obesity for Indians with BMI > 25 kg/ m² was published later, in February 2009 (36); however, we used the BMI value of > 27 kg/m², as decided initially. A steady decline in weight and BMI was observed in all patients. Significant weight reduction was apparent, compared with baseline, of 21%, 27%, and 30% at the 6-month, 1-year, and 2-year intervals, respectively. A corresponding, similar decline in BMI also was observed (*Table 1*) with 23%, 18%, and 23% reduction at 6-month, 1-year, and 2-year intervals, respectively. A greater declining trend was observed in patients with higher BMIs. Other studies that used similar procedures have reported reduced BMI at a rate of 18–27% (20, 22, 24), which is comparable to our study results.

Remarkable glycemic improvement was seen in all patients, with statistically improved glycemic parameters (fasting and post lunch blood sugars and $HbA1_C$) evident during follow up at all intervals *(Table 2)*. The values for glycemic parameters were higher at 6 months, which may be attributed to patients' reluctancefor titrations of the medicines, despite clear advice, and/or lapses in follow up. Improvements in postoperative glycemic control were disproportionately greater than weight loss, indicating that weight loss has benefits that are independent of metabolic surgery *(Figure 2)*. On the basis of the available literature (22, 37, 38), patients with a BMI < 27 kg/m² were also subjected to this procedure and demonstrated improved glycemic control with a substantial reduction in antidiabetic agent requirements *(Table 2)*. In the patient subgroup with a BMI > 35 kg/m², 82% experienced complete remission from diabetes.

Recent studies have confirmed that the use of II with SG is effective in nonobese diabetic patients (BMI of 23–34 kg/m²), improving glycemic and metabolic parameters (22, 23, 25). The key strengths of these studies are that the surgery was safe and efficacious for treating T2DM patients with a lower BMI, and it potentially leads to other benefits beyond glycemic control. These studies showed sustained glycemic improvement with preservation of beta-cell function, and enhanced cardiovascular benefits. Several possible mechanisms may explain the benefits of this procedure in nonobese subjects:

a) Calorie restriction induces decreased stimulation of the duodenum, which leads to attenuated secretion of

Table 4. Postoperative Glycemic Improvement (HbA1c) in Patients Classified as Per Their Preoperative BMI, Duration of Diabetes and Stimulated C-peptide Levels

Time, mo	BMI > 27 kg/m²	BMI < 27kg/ m²	DM duration < 10 years	DM duration > 10 years	Stimulated C-peptide > 4 ng/mL	Stimulated C-peptide < 4 ng/mL
Patients With Remission in Diabetes [b]						
3	6/27	2/10	7/22	1/15	7/21	1/16
6	9/19 [a]	3/10 [a]	8/18[a]	4/11	10/16 [a]	2/13
12	7/11 [a]	1/5	7/11 [a]	1/5	7/9 [a]	1/7
18	6/10 [a]	0/1	5/8 [a]	1/3	6/8 [a]	0/3
24	4/5 [a]	1/1 [a]	4/5 [a]	1/1 [a]	5/6 [a]	0/0
Patients With Remission in Hypertension [b]						
3	20/21 [a]	5/7 [a]	14/15 [a]	11/13 [a]	18/19 [a]	7/9 [a]
6	13/15 [a]	3/5 [a]	10/11 [a]	6/9 [a]	11/13 [a]	5/7 [a]
12	7/8 [a]	1/2	7/8 [a]	1/2	7/8 [a]	1/2
18	6/8 [a]	1/2	5/7 [a]	2/3 [a]	6/8 [a]	1/2
24	5/5 [a]	0/1	5/5 [a]	0/1	5/6 [a]	0/0

[a] P value < 0.05 (Two tailed Fisher's exact test)
[b] Data expressed as number of patients in remission / total patients

an unknown foregut factor (Rubino's factor) (39).

b) The earlier exposure of food to the ileum leads to an improved incretin response (40).

c) An ileal brake, i.e. food entry into the ileum, modulates gastric and intestinal motility to reduce food intake and absorption, occurs (41).

d) Enhanced postoperative serum bile acid levels may play a role in improved insulin sensitivity (correlation with high adiponectin levels) and increased incretin-induced insulin secretion (42).

Hypertension is a major risk factor for both macrovascular and microvascular complications (43). Seventy-five percent of our patients (30/43) had hypertension, and the majority (27/30 or 90%) exhibited a decrease in hypertension after surgery, and remission persisted throughout the 2.5-year follow up. The beneficial effects on hypertension may be related to weight loss and improved insulin sensitivity. Sugerman *et al.* (44) demonstrated controlled hypertension in approximately 70% of morbidly obese patients who underwent a gastric bypass.

The surgical technique used in this study used both the foregut and the hindgut mechanisms (31). The sleeve gastrectomy component of the II + SG procedure functions to restrict calorie intake, which results in reduced ghrelin secretion (a potent orexigenic substance that contributes significantly to impaired glucose homeostasis) (45). In the ileal interposition component of II+SG, the rapid stimulation of the interposed ileal segment by ingested food leads to augmented GLP-1 secretion (46). In nonobese patients, only fundectomies were conducted, to elicit the metabolic benefits of ghrelin withdrawal without significantly interfering with patient food intake. Post lunch glucose homeostasis is determined not only by stimulation of insulin secretion and suppression of hepatic glucose production, but also by the velocity of gastric emptying. GLP-1 influences glucose metabolism by inhibiting glucagon secretion, decreasing hepatic gluconeogenesis, delaying gastric emptying, promoting satiety, suppressing appetite, and stimulating glycogenesis (47).

The relative contribution of improved insulin sensitivity and insulin secretion to the overall results of these operations is difficult to quantify. As emphasized by Ferrannini and Mingrone (48) in relation to the effect of bariatric surgery in morbidly obese T2DM patients, diabetes remission results from amelioration of insulin resistance coupled withimprovement of beta-cell dysfunction. The speculated importance of preoperative initial BMI evaluations (21) and postoperative weight loss, caloric restriction, and hormonal changes as the final outcome determinants is still unclear.

Microalbuminuria is an independent predictor of cardiovascular risk in diabetes patients (49); the surgery resulted in an upward trend toward improved microalbuminuria in all participants. A statistically significant reduction in microalbuminuria was noted at all intervals except for 24 months, and this is possibly due to the lower number of patients who followed up at that interval *(Table 2)*.

Lipid management has been used to lower LDL cholesterol, raise HDL cholesterol, and lower triglycerides, thus reducing macrovascular disease and mortality in patients with T2DM, particularly in those with prior cardiovascular events (50). Tsuchiya *et al.* (51) demonstrated that ileal transposition to the upper jejunum affected lipid and bile salt absorption by attenuating cholesterol absorption and transport, possibly by promoting the premature absorption of bile salts. Our patients did not show significant improvements in lipid parameters compared with those observed in earlier studies. The reasons for this could be liberal usage of statins by almost all patients prior to the surgery, which resulted in a normal baseline for preoperative lipid parameters. The high mean cholesterol values observed at 24 months *(Table 2)* may be attributed to patient reluctance to use statins. It was observed that remission in diabetes and hypertension was higher *(Table 4)* in the group of patients with a higher preoperative BMI (> 27 kg/m²), a shorter duration of diabetes (≤ 10 years), and higher stimulated C-peptide levels (> 4 ng/mL). Improved glycemic and metabolic parameters were also seen in this group *(Table 3)*. Thus, the overall benefits of II + SG were clearly more evident in this subgroup of patients. In nonobese subjects with T2DM, defective early insulin secretion following oral glucose is the key factor that leads to hyperglycemia. This defective beta-cell function is associated with reduced early GLP-1 response. Metabolic surgery (II + SG) corrects this defect (37), and hence is beneficial in nonobese diabetic patients with a BMI < 27 kg/m² as well.

II does involve a few technical complexities, such as the need for enteroanastomosis and its potential risk for leaks, intestinal obstruction, and internal hernia. Certain suture techniques, closure of all possible internal hernia sites, and oversewing of stapler lines would probably ensure additional safety. The average operating time was similar to that required for the R-n-Y gastric bypass and BPD procedures (52, 53) and to the reported operative durations of 170–180 minutes that have been demonstrated in other similar studies on II + SG (20, 22, 24). Complications were less frequent in our series, with mainly nausea and anorexia occurring in about 25% patients and throat discomfort while swallowing in about 12% patients. These symptoms improved in 2 weeks. De Paula *et al.* (22) has reported major intraoperative complications in 7.7% of cases and postoperative complications in 10.3% of cases. We encountered a much smaller rate of complications and no mortality. Thus, II + SG appears to be a safe procedure, although it can potentially cause nutritional problems. All patients were advised to take iron, calcium, B12, and multivitamin supplementation regularly. Hypertrophy of the pancreas with nesidioblastosis (54) has been reported in post gastric bypass patients but, however, no causal relationship has been established. The proliferative effect of GLP-1 on cells has been considered, but a long-term follow up on these patients is necessary to explore this possibility. The limitations of our study included study brevity: a report from a single center with a follow up of only 2 years and a relatively small number of patients that lacked a control group. Multicentric studies on a larger number of patients with a longer follow up period would strengthen our observations. Nevertheless, the data in this current report substantiates earlier reports and adds value to the limited information available on this procedure. Another important limiting factor is the technical expertise required for the laparoscopic ileal interposition, which requires extensive training to perform.

In conclusion, we discovered that an increase in incretin hormones, due to rapid stimulation of a proximally shifted ileal segment coupled with a sleeve gastrectomy, leads to better control of hyperglycemia in T2DM patients. Based on the principle of neuroendocrine brake (19), this surgery appears to be a safe and is a potentially effective option for the management of T2DM patients. Patients with a shorter duration of diabetes, higher BMI, and higher stimulated C-peptide values would respond better. Additional multicentric long-term data from a larger number of patients is necessary to define the role of this novel surgery in patients with T2DM and related metabolic abnormalities.

Acknowledgments

None declared.

Financial Disclosure

None declared.

Funding/Support

None declared.

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