

Ileal interposition with sleeve gastrectomy for treatment of type 2 diabetes mellitus

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ABSTRACT

Aim: Combination of laparoscopic ileal interposition (II) with sleeve gastrectomy (SG) is an upcoming procedure, which offers good metabolic improvement and weight reduction without causing significant malabsorption. The objective of this study was to evaluate the results of this novel procedure for control of type 2 diabetes, obesity, hypertension, and related metabolic abnormalities. **Materials and Methods:** The II and SG was performed in 43 patients (M:F = 25:18) from February 2008. Participants had a mean age of 47.2 ± 8.2 years (range 29–66 years), mean duration of diabetes of 10.1 ± 9.2 years (range 1–32 years), and mean preoperative body mass index (BMI) of 33.2 ± 7.8 kg/m². All patients had poorly controlled type 2 diabetes mellitus (DM) [mean glycated hemoglobin (HbA1C) $9.6 \pm 2.1\%$] despite use of oral hypoglycemic agents (OHAs) and/or insulin. Thirty (70%) patients had hypertension, 20 (46%) had dyslipidemia, and 18 (42%) had significant microalbuminuria. The primary outcome was remission of diabetes (HbA1C < 6.5% without OHAs/insulin) and the secondary outcomes were reduction in antidiabetic agent requirement and components of metabolic syndrome. **Results:** Mean follow-up was for 20.2 ± 8.6 months (range 4–40 months). Postoperatively, glycemic parameters (fasting and post-lunch blood sugar, HbA1C improved in all patients ($P < 0.05$) at all intervals. Twenty (47%) patients had remission in diabetes and the remaining patients showed significantly decreased OHA requirement. All patients had weight loss between 15 and 30% ($P < 0.05$). Twenty-seven (90%) patients had remission in hypertension. At 3 years, the mean fall in HbA1C (34%) was more than reduction in BMI (25%). There was a declining trend in lipids and microalbuminuria postoperatively, though it was significant for microalbuminuria only. **Conclusions:** The laparoscopic II with SG seems to be a promising procedure for control of type 2 DM, hypertension, weight reduction, and associated metabolic abnormalities. A multicenter study with larger number of patients and a longer follow-up period is needed to substantiate our preliminary findings.

Key words: Ileal interposition, metabolic surgery, sleeve gastrectomy, type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity have reached epidemic proportions in many countries throughout the

world. The global prevalence of diabetes among adults (aged 20–79 years) was estimated at 6.4% in 2010 and is projected to increase to 7.7% by 2030.^[1] Currently, India has approximately 50.8 million diabetes patients^[2] and the number is slated to increase to 80.9 million in the year 2030.^[3] The World Health Organization (WHO) stated that in 2005, an estimated 1.6 billion adults in the world were overweight and at least 400 million were obese.^[4] They also predicted that by 2015, 2.3 billion adults would be overweight and >700 million of them will be obese.^[4]

Further, diabetes and obesity are strongly linked and often coexist. When coupled together, this diabetesity^[5] imparts an additive risk and accelerates the progression of cardiovascular complications.^[6] To help curb the increasing

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burden of these diseases on the world health economy, researchers are continually exploring newer methods for achieving sustainable weight loss and remission of diabetes.^[5]

Bariatric surgery has evolved as a double-edged tool to manage obesity and related comorbidities like diabetes, hypertension, and hyperlipidemia. Following bariatric surgery, glycemic improvement starts earlier and is disproportionately more than weight reduction.^[7] Glycemic improvement is more with malabsorptive surgeries [Roux-en-Y (R-n-Y) gastric bypass and biliopancreatic diversion (BPD)] than with restrictive surgeries (gastric band).^[8] Ileal interposition in combination with sleeve gastrectomy (II + SG) is a novel procedure that offers equal metabolic benefit without causing any malabsorption.^[9] This has led to the concept of metabolic surgery. Information about this procedure is available on animals including rats, dogs, and porcine models.^[10-16] Though sufficient information is available in literature regarding the efficacy of this novel procedure (II + SG) in the treatment of T2DM,^[17-22] Indian data regarding this procedure are scarce.^[18,22] In our recently published report, we evaluated the preliminary results of II + SG treatment and demonstrated its feasibility, safety, and efficacy in T2DM.^[18] However, since those findings were based on a small study sample of 10 patients and a short-term follow-up; further long-term data including more number of patients were warranted. All over the world, this procedure is performed in obese as well as nonobese T2DM patients.^[19-21,23] We too were inspired to include selected nonobese T2DM patients in our current study. We hereby report the results of II + SG treatment in 43 T2DM patients, with a follow-up of 3 years.

MATERIALS AND METHODS

We started this non-randomized, prospective case series to evaluate the effects of II + SG at our center, Kirloskar Hospital, Hyderabad, India, in February 2008. The hospital's ethical committee approved the study, and all patients provided written informed consent after being informed thoroughly about the benefits and risks involved. Nonobese patients were specifically explained about potential benefits of the surgery and limited data available about this procedure for nonobese diabetic patients.^[19-21,23] Nonobese patients were included selectively on the basis of poor glycemic control despite optimum dosage of insulin \pm oral hypoglycemic agents (OHAs), good post-meal C-peptide response, and after exclusion of type 1 diabetes patients and underweight patients with body mass index (BMI) <18.5 kg/m². We report the data of all the 43 patients, who were operated upon and analyzed till July 2011.

Inclusion and exclusion criteria

The inclusion criteria were patients having T2DM of more than 1 year duration, with age between 25 and 70 years, stable weight for the last 3 months (variation in weight $<3\%$),^[19-21] BMI ≥ 18.5 kg/m², and stimulated C-peptide level >1.5 ng/ml.

The exclusion criteria were type 1 diabetes mellitus, undetectable fasting C-peptide, positive urine ketones, pregnancy, and coexisting severe hepatic, pulmonary, renal, cardiovascular, neurological, and psychiatric diseases, and obesity due to organic illness.

Subjects and preoperative evaluation

Preoperative evaluation included clinical history of T2DM, comorbidities, and complications, followed by thorough physical examination. Patients were diagnosed to have T2DM on the basis of fasting plasma glucose ≥ 126 mg/dl (fasting is defined as no caloric intake for at least 8 h) or 2-h plasma glucose of ≥ 200 mg/dl during an oral glucose tolerance test after using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or a random plasma glucose of ≥ 200 mg/dl in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.^[24] Standing height was measured using a portable stadiometer (Leicester height meter; Child Growth Foundation, UK; range 60–207 cm). Weight was measured using an electric scale (Salter, India) accurate to 100 g. BMI was calculated as weight in kilograms divided by square of height in meters.^[25] We decided a cut-off value for BMI >27 kg/m² to define obesity. Relevant biochemistry tests, urinalysis, and imaging studies (chest radiograph and ultrasound abdomen) were performed for all patients in a single laboratory accredited by national accreditation board for testing and calibration laboratories (NABL). Fully automated clinical chemistry analyzer (Olympus 2700) was used for biochemical analysis. Fasting and post-meal blood glucose was measured by hexokinase method, and cholesterol oxidase method was used for the estimation of lipid profile. Roshe E 601 analyzer was used for the assessment of serum insulin, basal and 1 hour post-meal C-peptide, thyroid profile, and microalbuminuria. Fasting serum samples were subjected to electrochemiluminescence for insulin level determination. Basal and 1 hour post-meal C-peptide and thyroid profile were measured by chemiluminescence method. Immunoturbidometry assay was utilized for detection of microalbuminuria in 24-hour urine specimen. Glycated hemoglobin (HbA1C) was checked with high-performance liquid chromatography (HPLC) method using Biorad variant D10. Patients with hypothyroidism were prescribed for thyroxine replacement. They were subjected to surgery after achievement of euthyroid state. Glomerular filtration rate was calculated

using the modified Cockcroft–Gault equation.^[26,27] Insulin resistance (IR) was assessed from the homeostasis model assessment (HOMA) formula (HOMA-IR) using fasting blood glucose and insulin.^[28]

Outcomes

The primary outcome measures

Remission of T2DM, defined as HbA1c <6.5% without requiring oral or parenteral hypoglycemic agents.

Secondary outcome measures

Improvement in glycemic parameters [HbA1C, fasting blood sugar (FBS), post-lunch blood sugar (PLBS)]

Remission or improvement in hypertension

Improvement in other metabolic parameters like lipids, microalbuminuria, and uric acid

Improvement in weight and BMI in obese patients (BMI > 27 kg/m²)

Reduction in insulin and OHA requirement for glycemic control

As per the evaluation by previous studies^[19,21] and American Diabetes Association (ADA) proposed criteria,^[29] the outcomes were planned to be monitored and analyzed at 6 months interval.

Procedure

The operation was performed under general anesthesia with a standard six-port laparoscopic technique. The surgical procedure involved creation of a 170-cm segment of ileum, starting at 30 cm proximal to the ileo-cecal junction. This segment was interposed into jejunum, which was divided between 20 and 50 cm from the ligament of Treitz. All three anastomoses were performed side by side with an endo-GIA stapler (Ethicon Endo-surgery, Cincinnati, OH, USA) with a 45-mm white cartridge, and the stapler openings were closed by hand with a 3-0/3 polydioxanone suture in two layers. The mesenteric gaps were closed with non-absorbable 3-0 polypropylene sutures to prevent internal herniation. A variable sleeve gastrectomy was performed after devascularization of the greater curvature from the antrum to the fundus area. Figure 1 depicts diagrammatic representation of the procedure. The lumen of the stomach was adjusted by a 32–58 French calibrator (Romsons International, New Delhi, India) that was placed along the lesser curvature. The endo-GIA stapler with 60-mm cartridges was used for resection. Nonobese patients were subjected to only fundectomy, leaving a good volume of residual stomach for normal food intake.

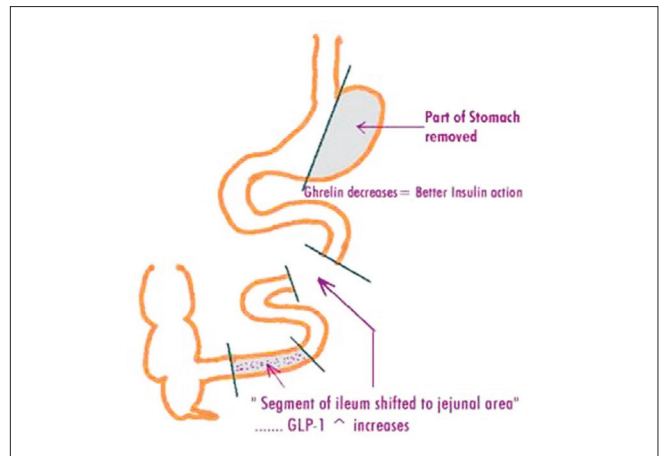


Figure 1: Diagram of ileal interposition with sleeve gastrectomy

Postoperative follow-up

Postoperatively, the diabetes and hypertension medications were adjusted according to the plasma glucose and blood pressure record levels, respectively. The patients were kept on a liquid diet for 5–7 days, followed by semisolid diet for another 7 days, and finally a solid diet, always in small quantities. The patients were discharged between the fourth and sixth postoperative days with vitamin supplements. Routine upper gastrointestinal endoscopy was done after 1 month of surgery. They were asked to come for follow-up visits at 1, 3, 6, and 9 months, and every 6 months thereafter.

Statistical analysis

All outcome measures were evaluated prospectively from the sixth month onward at every visit. 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 by Student's *t*-test. The categorical data were analyzed by using two-tailed Fisher's exact test in view of the small sample size. Even though the sample size was small in later periods of follow-up, we were stimulated to do the statistical analysis with an intention to compare the outcomes among different group of patients. *P* values less than 0.05 were considered significant.

RESULTS

A total of 43 patients underwent II + SG (18 females and 25 males). Their baseline demographic parameters are given in Table 1. Preoperatively, 21 patients required ≥ 2 OHAs and 22 required insulin \pm OHA for glycemic control.

The mean operative time was 3.9 ± 0.9 hours and the mean postoperative hospital stay was 4.1 ± 0.8 days.

No intraoperative complications were noted and none of the patients required conversion to open surgery. Postoperatively, 7 patients had difficulty in swallowing for the initial 2 weeks. About 25% of the patients (12/43) had nausea and loss of appetite for the initial 1 month. No major surgical complications were noted in any of the patients.

Mean follow-up period was 20.2 ± 8.6 months (range 4–40 months). The postoperative follow-up data are summarized in Table 2. Compared to BMI, there was a higher decrease in HbA1C at all intervals (mean decline in BMI 25% vs. mean fall in HbA1C 34%) [Figure 2].

Diabetes and hypertension remission data

At 6 months, 20/42 (47%) patients were off any OHAs and no one required insulin in contrast to 21 patients in preoperative period requiring OHAs and 12 patients requiring insulin in addition to OHAs ($P = 0.005$ and 0.0001 , respectively). Fifteen out of 42 (36%) required only

metformin and 7/42 (14%) required ≥ 2 OHAs.

Thirty-six patients had completed 1-year follow-up: 22 were off OHAs ($P = 0.003$), 10 subjects required only metformin, 3 required ≥ 2 OHAs, and only 1 patient required insulin in addition to OHAs ($P = 0.002$).

Eleven out of 14 patients at 2 years follow-up were off OHAs ($P < 0.0001$) and 3 required only metformin for glycemic control ($P = 0.006$).

Among the 5 patients who had completed 3 years follow-up, 3 were off any medications ($P = 0.004$), 1 subject required only metformin ($P = 0.0001$), and another subject required a combination of glimeperide and metformin for glycemic control ($P = 0.003$).

Recovery in hypertension was seen in 25/28 (90%) patients at 3 months, 16/20 (80%) patients at 6 months, 8/10 (80%) patients at 1 year, 7/10 (70%) patients at 18 months, 5/6 (83%) patients at 2 years, and 3/3 (100%) patients at 3 years follow-up. At all intervals, recovery in hypertension was statistically significant ($P < 0.0001$).

Table 1: Baseline data of the study group

N (men/ women)	43 (25/ 18)
Obese patients (BMI > 27 kg/ m ²)- N (%)	30 (70%)
Non obese patients (BMI ≤ 27 kg/ m ²)- N (%)	13 (30%)
Hypertension- N (%)	30 (70%)
Dyslipidemia- N (%)	20 (46%)
Microalbuminuria- N (%)	18 (42%)
Age (years)	47.2± 8.2 (29-66)
Duration of DM (years)	10.1± 9.2 (1-32, median- 7.5 years)*
BMI (Kg/ m ²)	33.2± 7.8
HbA1C (%)	9.6 ± 2.1
Fasting C-peptide (ng/ ml)	2.8 ± 1.3
Post meal C peptide (ng/ ml)	4.8± 2.8
HOMA-IR	22.3 ± 3.7
LDL-Cholesterol (mg/ dl)	114.7± 33.6
Triglyceride (mg/ dl)	198.2± 157.7 (median- 210)*
Microalbuminuria (mg/ 24 hours)	95.2 ± 64. 8 (median- 28)*

Data expressed as N or mean ± SD (range), *Median data is mentioned as SD is high, N: Number of patients, SD: Standard deviation, BMI: Body mass index, HbA1C: Glycosylated hemoglobin, HOMA-IR: Homeostasis Model assessment-Insulin resistance, LDL: Low Density Lipoprotein

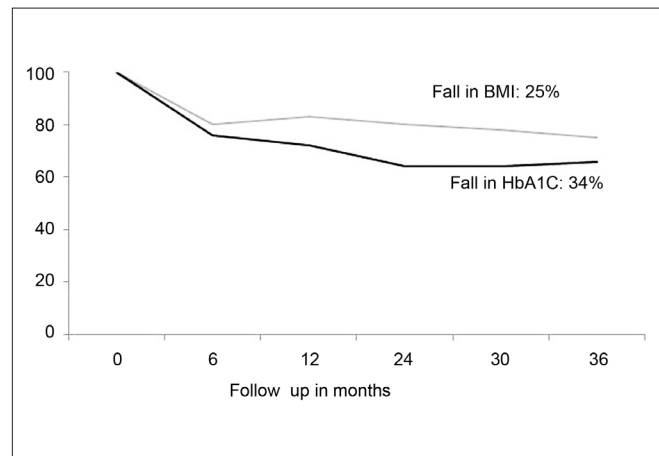


Figure 2: Postoperative comparison of percentage fall in BMI and HbA1C

Table 2: Post operative metabolic parameters in 43 patients

Parameter follow up	FBS (mg/ dl)	PLBS (mg/ dl)	HbA1C (%)	BMI (kg/m ²)	Cholesterol (mg/ dl)	LDL-C (mg/ dl)	Trigly. (mg/ dl)	Micralb. (mg/24hr)
Preop	184.8 ± 50.2	292.6 ± 85.5	9.6 ± 2.1	33.2 ± 7.8	189.1 ± 44.7	114.7 ± 33.6	198.2 ± 157.7	95.2 ± 64.8
3 mth	*103.2 ± 22.4	*152.1 ± 61.1	*6.8 ± 1.2	*27.9 ± 5.2	*157.9 ± 30.2	*91.4 ± 19.5	*129.3 ± 105.2	*52.3 ± 61.4
6 mth	*120.6 ± 34.3	*144.4 ± 32.2	*7.6 ± 1.8	*25.6 ± 4.1	168.8 ± 34.8	*89.44 ± 22.7	*121.7 ± 85.2	*34.6 ± 39.3
12 mth	*102.9 ± 26.3	*139.3 ± 41.1	*7.1 ± 1.2	*26.5 ± 4.1	169.5 ± 39.4	*95.3 ± 25.6	*143.6 ± 103.1	*33.5 ± 25.8
18 mth	*119.6 ± 20.9	*198.8 ± 32.2	*7.3 ± 1.2	*26.8 ± 3.9	179.5 ± 36.1	111.5 ± 21.2	186.6 ± 144.1	*25.7 ± 13.4
24 mth	*109.5 ± 28.7	*152.1 ± 38.1	*6.4 ± 1.1	*25.5 ± 3.9	189.6 ± 22.4	110.5 ± 12.7	*101.6 ± 38.3	*34.5 ± 22.9
30 mth	*114.5 ± 20.2	*156.4 ± 39.9	*6.9 ± 1.3	*25.9 ± 4.0	176.4 ± 24.1	108.9 ± 20.1	175.6 ± 121.3	*43.5 ± 15.9
36 mth	*119.6 ± 21.3	*162.1 ± 40.2	7.2 ± 1.5	*26.6 ± 3.8	194.5 ± 25.2	112.4 ± 21.1	188.7 ± 109.3	38.5 ± 27.5

*P value <0.05 (student's t test), Data expressed as mean ± SD values, BMI: Body mass index, FBS: Fasting blood sugar, PLBS: Post lunch blood sugar, LDL-C: Low density lipoprotein cholesterol

Overall, at the end of 3 years, 20/43 (47%) patients and 27/30 (90%) patients went in remission for diabetes and hypertension, respectively. In group of patients with BMI >35 kg/m², 10/12 (82%) patients had remission in diabetes, i.e. maintaining HbA1C <6.5% without any antidiabetic medication, and 10/10 (100%) patients had remission in hypertension. Glycemic control with HbA1C <7% was achieved in 78% patients.

Postoperatively, improvement in other metabolic parameters like lipids and microalbuminuria was observed; however, it was statistically significant only for microalbuminuria and not for lipids.

Analysis of outcome in patients classified as per preoperative BMI, duration of diabetes, and stimulated C-peptide

We divided the patients into two groups according to three 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 depicts the comparison of

postoperative glycemic improvement in both groups at all intervals. Table 4 highlights the remission data in diabetes and hypertension in all the groups at all intervals.

DISCUSSION

Our current report demonstrates the beneficial effects of this novel procedure in 43 patients in controlling T2DM, hypertension, obesity, and related metabolic abnormalities. This is an extension of our previous data of II + SG in 10 diabetic patients.^[18]

Combination of foregut and hindgut theories explains the improvement in diabetes and weight loss after this surgery.^[30] All patients had considerable weight loss ranging between 15 and 30%. Diabetes control was good following surgery, with complete remission in 18/39 (47%) patients and the rest of the patients showing more than 80% reduction in diabetes drug requirement. Hypertension remitted in 27/30 (90%) patients. This remission persisted in all patients during follow-up. There was significant reduction in microalbuminuria postoperatively. Declining

Table 3: Postoperative glycemic improvement (HbA1C) in patients classified as per their preoperative BMI, duration of diabetes and stimulated C-peptide levels

Follow up in Months	HbA1C					
	BMI <27 kg/m ² (n=13)	BMI >27 kg/m ² (n=30)	DM duration <10years (n=25)	DM duration >10 years (n=18)	Stimulated C-peptide <4 ng/ml (n=19)	Stimulated C-peptide >4 ng/ml (n=24)
0	9.1 ± 1.9	9.7 ± 1.9	9.3 ± 2.2	9.8 ± 1.3	10.2 ± 1.7	9.1 ± 2.1
3	7.1 ± 1.3*	6.5 ± 0.9*	6.9 ± 1.5*	6.9 ± 0.8*	7.7 ± 1.2*	6.7 ± 0.9*
6	7.6 ± 0.7	7.6 ± 1.9*	7.1 ± 1.2*	7.2 ± 1.9*	8.5 ± 1.9	6.7 ± 1.4*
9	7.6 ± 0.8	7.1 ± 1.9*	7.2 ± 0.9*	9.3 ± 2.4	8.8 ± 2.3	7.4 ± 0.7*
12	7.6 ± 0.3	7.4 ± 1.5*	6.5 ± 1.0*	8.9 ± 2.5	8.5 ± 1.3	6.5 ± 0.9*
18	7.2 ± 0.3	7.7 ± 1.4*	7.0 ± 1.8	8.1 ± 1.2	8.9 ± 0.7	6.9 ± 1.6*
24	7.3 ± 0.9	6.3 ± 1.2*	6.1 ± 0.9*	7.6 ± 1.2	8.5 ± 1.2	6.3 ± 1.2*
30	7.8 ± 0.2	6.5 ± 1.1*	6.5 ± 0.8*	7.9 ± 1.1	8.9 ± 1.2	6.5 ± 1.8 *
36	7.1#	6.8 ± 1.4	6.1 ± 1.2 *	8.0#	7.8#	7.8 ± 1.2

*P value <0.05 (student's t test), Data expressed as Mean ± SD values, #statistical analysis could not be done because of availability of limited number of patients, DM: Diabetes mellitus

Table 4: Diabetes and Hypertension remission data in patients under different groups

Month	Patients with remission in Diabetes						Patients with remission in hypertension					
	BMI>27 kg/m ²	BMI<27 kg/m ²	DM duration <10 years	DM duration >10 years	Stimulated C-pep > 4 ng/ml	Stimulated C-pep <4 ng/ml	BMI >27 kg/m ²	BMI <27 kg/m ²	DM duration <10 years	DM duration >10 years	Stimulated C-pep >4 ng/ml	Stimulated C-pep <4 ng/ml
3	15/ 29	5/13	16/ 25	4/17	15/24	5/18	20/21*	5/7*	14/15*	11/13*	18/19*	7/9*
6	17/ 29*	3/13*	17/25*	3/17	16/24*	4/ 18	13/15*	3/5*	10/11*	6/9*	11/13*	5/7*
12	18/ 26*	4/10	16/ 23*	6/13	17/25*	5/11	7/8*	½	7/8*	½	7/8*	½
18	11/ 16*	1/6	10/ 15*	2/7	9/14*	3/8	6/8*	½	5/7*	2/3*	6/8*	½
24	9/10*	2/4*	8/10*	3/4*	9/11*	2/3	5/5*	0/1	5/5*	0/1	5/6*	0/0
30	3/5	1/3	4/6	0/2	4/5	0/3	5/5*	0/0	4/4*	1/1*	5/5*	0/0
36	2/3	1/2	2/2*	1/3	3/3*	0/2	3/3*	0/0	3/3*	0/0	3/3*	0/0

*P value < 0.05 (Two tailed Fisher's exact test), Data expressed as number of patients in remission / total patients, BMI: Body mass index, DM: Diabetes mellitus

trend was seen in lipid parameters, even though it was statistically not significant. Overall surgical complication rate was low, with 25% patients having nausea and about 12% patients having throat discomfort while swallowing.

Definition of obesity as per BMI varies in different parts of the world. As per the WHO guidelines, obesity is defined as $>30 \text{ kg/m}^2$.^[31] Cut-off value of BMI to define obesity in Asians is lower. It is $>28 \text{ kg/m}^2$ in China^[32] and $>25 \text{ kg/m}^2$ in Japan.^[33] The Asia Pacific guidelines mention a cut-off of $>27.5 \text{ kg/m}^2$ to define obesity.^[34] We chose to take a BMI cut-off of $>27 \text{ kg/m}^2$ for diagnosis of obesity in our study population, looking at the available Asian data varying within different countries. The consensus statement for diagnosis of obesity for Indians with BMI $>25 \text{ kg/m}^2$ was published later in February 2009.^[35] But we stuck to the BMI cut-off of $>27 \text{ kg/m}^2$, as was decided initially. A steady decline in weight and BMI was found in all patients. There was significant reduction of weight from baseline to the tune of 22, 27, 30, and 32% at intervals of 6 months, 1 year, 2 years, and 3 years, respectively. Correspondingly, similar decline in BMI was also seen [Table 2] (23, 18, 22, and 25% reduction at intervals of 6 months, 1 year, 2 years, and 3 years, respectively). A greater declining trend was seen in patients with higher BMI. Overall, other studies evaluating similar procedure have reported reduction in BMI to the tune of 18–27%,^[19,21,22] which is comparable to our study.

There was remarkable glycemic improvement in all patients. The improvements in glycemic parameters (FBS, PLBS, and HbA1C) were statistically significant during follow-up at all the intervals [Table 2]. De paula *et al.* have demonstrated normalization of HbA1C $<6\%$ in 47.4% and $<7\%$ in 86.9% cases, compared to 47% (HbA1C $< 6.5\%$) and 78% (HbA1C $< 7\%$) cases in our series.^[19] This difference can be explained by different metabolic milieu in our study population characterized by higher IR in Indian subjects as compared to westerners. Postoperative glycemic improvement was disproportionately more than weight loss, indicating weight loss independent benefits of the metabolic surgery [Figure 2]. Based on this and available literature,^[36,37] patients with BMI $<27 \text{ kg/m}^2$ were also subjected to this procedure and showed improvement in glycemic control with substantial reduction in antidiabetic agent requirement [Table 3]. In our patients' subgroup with BMI $>35 \text{ kg/m}^2$, 82% patients had complete remission in diabetes. Tinoco *et al.* have also demonstrated statically significant reduction in fructosamine levels as a glycemic parameter, which we did not include as routine biochemical glycemic parameter in our patients.^[21]

Thirteen out of 43 of our patients were nonobese. Recent

studies have confirmed that II with SG is effective even in nonobese diabetic patients with BMI of 23–34 kg/m^2 to improve their glycemic and metabolic parameter.^[19,20,23] The key strengths of these studies were the safety and efficacy of the surgery in treating patients with T2DM with a lower BMI and the possibility of other achievements beyond glycemic control. They showed sustained glycemic improvement with preservation of beta cell function and cardiovascular benefits. Possible mechanisms explaining the benefits of this procedure in nonobese subjects could be as follows:

- Calorie restriction induced decreased stimulation of duodenum, leading to attenuated secretion of unknown culprit foregut factor (Rubino's factor).^[38]
- Earlier exposure of food to ileum, leading to better incretin response.^[39]
- Ileal brake – Food entering into ileum modulates gastric and intestinal motility to reduce food intake and absorption.^[40]
- Enhanced postoperative serum bile acid levels have been proposed to play a role in improved insulin sensitivity (correlated with high adiponectin levels) and increased incretin-induced insulin secretion.^[41]

As per the 2010 ADA guidelines, cure / remission of diabetes is defined as HbA1C $<5.6\%$.^[42] From the beginning, we maintained HbA1C $<6.5\%$ (without requiring any medication for diabetes control) as a reasonable criterion for remission in diabetes. There was no specific HbA1C related definition for remission in diabetes when we started our study; therefore, maintaining HbA1C $<6.5\%$ without requiring pharmacotherapy was taken as a remission criterion postoperatively. There were higher values for glycemic parameters at 6 months [Table 2]. This could be attributed to reluctance on patient's side to up-titrate the medicines in spite of clear advice and/ or to follow-up lapses.

Hypertension is a major risk factor for cardiovascular disease and microvascular complications such as retinopathy and nephropathy.^[43] Sugerma *et al.*^[44] demonstrated that hypertension was controlled in approximately 70% of morbid obese patients who underwent a gastric bypass. De paula *et al.* have found a remission in hypertension in 83.3% patients.^[19] In our series, 27/30 (90%) patients had subsidence of hypertension after surgery and remission persisted throughout the follow-up of 3 years. The beneficial effect on hypertension could be related to weight loss and improved insulin sensitivity.

The surgical technique used in this study is designed essentially for diabetes control and utilizes both the foregut and hindgut mechanisms.^[35] The SG component of II +

SG restricts calorie intake and reduces ghrelin (a potent orexigenic substance that contributes significantly toward impaired glucose homeostasis);^[45] it also speeds up gastric transit of food, reaching the ileal segment faster. Glucagon-like peptide 1 (GLP-1), the incretin responsible for the first phase of insulin secretion, is defective in T2DM.^[46] In the ileal interposition component of II + SG, rapid stimulation of interposed ileal segment by ingested food leads to augmented GLP-1 secretion. Only fundectomy was carried out in nonobese patients for the metabolic benefits of ghrelin withdrawal. Postprandial 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 also influences glucose metabolism by inhibiting glucagon secretion, decreasing hepatic gluconeogenesis, delaying gastric emptying, promoting satiety, suppressing appetite, and stimulating glycogenesis.^[47-53]

Microalbuminuria is an independent predictor of cardiovascular risk in diabetes patients^[54] and the surgery resulted in a trend toward improvement in microalbuminuria in all participants. Statistically significant reduction in microalbuminuria was noticed at all intervals except at 30 and 36 months; possibly lesser number of patients on follow-up at that interval was the limiting factor [Table 2]. De paula *et al.* reported that prevalence of microalbuminuria reduced from 20.5 to 10% postoperatively.^[19]

Tschiya *et al.*^[55] demonstrated that ileal transposition to the upper jejunum affected lipid and bile salt absorption, attenuating cholesterol absorption and transport, possibly by promoting premature absorption of bile salts. In the study by De paula *et al.*, the low density lipoprotein (LDL) level of less than 100 mg/dl and triglyceride levels lower than 150 mg/dl were achieved in 66 and 71% patients, respectively.^[19] Our patients did not show significant improvement in lipid parameters as observed in earlier studies. The reasons for this could be liberal usage of statins by almost all patients prior to surgery, leading to normal baseline preoperative lipid parameters. High mean cholesterol values at 24 and 36 months [Table 2] could be attributed to reluctance on the part of patients to use statins contrary to advice.

It was observed that remission in diabetes and hypertension was higher [Table 3] in the group of patients with higher preoperative BMI (>27 kg/m²), shorter duration of diabetes (≤ 10 years), and higher stimulated C-peptide levels (>4 ng/ml). Improvement in glycemic and metabolic parameters was also better in this group [Table 3]. Thus, overall benefits of II + SG were clearly more in this subgroup of patients. Tinoco *et al.* have demonstrated that pre-surgical BMI and

duration of T2DM were not the determinant factors for the post-surgical remission of T2DM.^[21] But the study mentions remission data for 1 year only. We presume that in long term, the results may simulate the trend followed by our study population. In nonobese subjects with T2DM, defective early insulin secretion after an oral glucose is the key factor leading to hyperglycemia. This defective beta cell function is associated with a reduced early GLP-1 response. Metabolic surgery (II + SG) corrects this defect,^[56] and hence is also beneficial in nonobese diabetic patients with BMI <27 kg/m². An Indian study has demonstrated similar diabetes remission rates even in patients with type 2 diabetes >10 years accompanied by significant weight loss, with a similar procedure.^[22] But that study has mentioned results only for 6 months postoperatively. Even in our study, the HbA1C results showed statistically significant reduction both in patients with duration of T2DM <10 years and in those with duration of T2DM >10 years, up to 6 months postoperatively. This early glycemic benefit might be due to calorie restriction and weight loss induced by the surgical procedure. Beyond the period of 6 months, only patients with duration of diabetes <10 years reported significant reduction in HbA1C and remission in diabetes, which might be truly reflective of weight loss independent benefits of the metabolic surgery.

The average operating time was similar to that required for R-n-Y gastric bypass and BPD procedures.^[57,58] It is also quite similar to the reported operative duration of 170–180 minutes, demonstrated by other such similar studies on II + SG.^[19,21,22] De paula *et al.* have reported 7.7% intraoperative complications including resection of an ischemic transposed ileum, cardiac arrhythmia, and hypertensive crisis. Exclusion of high-risk cases and proper preoperative control of cardiac morbidities in our study population resulted in nil intraoperative complications. Overall postoperative complication rate in our series was low with mainly nausea and loss of appetite in about 25% patients and throat discomfort in about 12% patients. These symptoms improved in a span of 2 weeks. No major long-term or delayed surgical complications were noted in any of the patients. De paula *et al.* have demonstrated 15.4% minor early postoperative complications and 21.1% late clinical complications like gout attack, prolonged emesis, urinary tract infection, and fungal esophagitis.^[19] Tinoco *et al.* have demonstrated ketoacidosis and urinary infection in 3.3% cases and diarrhea in 6.6% cases. Three months postoperatively, there was 3.3% incidence of cholecystolithiasis and bowel obstruction caused by adhesions.^[21] We found a very low rate of complications and no mortality in our study group. So, II + SG appears to be a safe procedure.

The limitations with our study were:

- a. The brevity of the study
- b. Report from single center with follow-up of only 3 years
- c. Relatively small number of patients with absence of control group
- d. Lack of study of the effects of the procedure on the diabetic complications like retinopathy and neuropathy. De paula *et al.* have demonstrated objective improvement of retinopathy in 36.4%, symptomatic improvement in neuropathy in 62.5%, and some improvement in erectile dysfunction in 62.5% cases following II + SG.^[19]
- e. Lack of evaluation for evidence of malabsorption like iron, calcium, and vitamin B12 deficiency. The more extensive the intestinal bypass, the greater are the chances of nutritional and metabolic complications.^[59-63] Theoretically, since the current procedure does not induce bypass, chances of malabsorption are less. However, iron deficiency was observed in 4.5% patients despite routine iron supplementation in the study by De paula *et al.*^[19]

However, all the patients are still being followed up and intermittently analyzed. Multicenter studies on larger number of patients with longer follow-up period would strengthen our observations. Nevertheless, the data of our current report substantiate our earlier findings and add value to the limited information available on this procedure on rats, dogs, and humans.^[10-22] Another important limiting factor is the technical expertise required for the laparoscopic II, which requires extensive training. Long-term data are needed to establish its efficacy, as some recent results have shown recurrence rate close to 50% following bariatric surgery (R-n-Y gastric bypass).^[64,65]

CONCLUSION

Augmented incretin hormones due to rapid stimulation of a proximally shifted ileal segment coupled with a sleeve gastrectomy lead to control of hyperglycemia in T2DM patients. This surgery based on the principle of neuroendocrine brake^[55] appears to be safe and a potentially effective option in the management of type 2 diabetes patients. Patients with shorter duration of diabetes, higher BMI and higher stimulated C-peptide values would respond better. Further long-term data from a larger number of patients is necessary to define the role of this novel surgery in type 2 diabetes and related metabolic abnormalities.

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