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Ileal Interposition with Sleeve Gastrectomy for Control of Type 2 Diabetes

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Abstract

Background: Bariatric surgery offers the best solution in management of obesity and related metabolic ailments, paving the way for a concept termed metabolic surgery. We report the results of a novel surgical procedure on glycemic control and metabolic syndrome in poorly controlled type 2 diabetes.

Methods: Ten patients (four men, six women) underwent laparoscopic surgical procedure of sleeve gastrectomy and ileal interposition. All patients had diabetes for more than 3 years with poor control despite use of oral hypoglycemic agents (OHAs) and/or insulin. The primary outcome was remission of diabetes (hemoglobin A1c $<7\%$ without OHAs/insulin), and secondary outcomes were change in OHA requirement, components of metabolic syndrome, insulin resistance, and microalbuminuria.

Results: We report the preliminary postoperative follow-up data of 9.1 ± 5.3 months (range, 2–16 months). Participants had a mean age of 48.2 ± 9 years (range, 34–62 years), duration of diabetes of 11 ± 5.7 years (range, 4–25 years), and preoperative body mass index of $33.8 \pm 6.5\,kg/m^2$. Seven patients had diabetes remission, and the remaining three showed significantly decreased OHA requirement. All participants had weight loss ranging between 15% and 30% and had remission of hypertension. Microalbuminuria (96.8 ± 19.1 vs. 46.7 ± 10.1 mg/L, $P = 0.03568$) and insulin resistance as assessed by homeostasis assessment model of insulin resistance (5.2 ± 2.1 vs. 1.8 ± 0.9, $P = 0.0005$) decreased significantly after surgery.

Conclusions: Our preliminary observations demonstrated the feasibility, safety, and efficacy of this novel surgical procedure in type 2 diabetes. Further long-term data from more patients are necessary to confirm these findings.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) have reached epidemic proportions, and the scientific world is exploring new methods of tackling this diabesity.[1] The Asian population has higher insulin resistance (IR) at the same body weight than the Western population.[2] Surgical procedures offer the best treatment for obesity along with beneficial effects on hyperglycemia, hypertension, and dyslipidemia.[3] Remission of diabetes is reported more in procedures that affect the entero-insular axis than pure restrictive procedures.[4] Recent reports have identified improvement in glucose homeostasis after bariatric surgery that is independent of weight loss.[5,6] Reduced incretin effect coupled with IR contributes significantly towards diabetes in nonobese individuals. Bariatric surgery in these nonobese patients also offers excellent benefits on control of diabetes and co-morbid ailments, leading to change in the concept as "metabolic surgery."[7]

With increasing number of bariatric surgeries performed, modifications have been explored to minimize the associated malabsorption and morbidity. Ileal interposition is a novel procedure that involves shift of an ileal segment proximally into the jejunum. This procedure coupled with sleeve gastrectomy results in effective glycemic control.[8] This procedure does not involve bypass or diversion of food from the digestive hormones, thus minimizing the malabsorption. We started a prospective observational study to determine the effects of this novel procedure for treatment of poorly controlled T2DM in overweight or obese patients.

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We report here the clinical data and postoperative results in the initial 10 patients.

Patients and Methods

We started a prospective study to evaluate the effects of ileal interposition with sleeve gastrectomy for treatment of T2DM in overweight or obese patients in January 2008. The hospital's ethical committee approved the study, and all patients provided written informed consent. Of a total of 12 patients who were operated up to now, we report the preliminary data of first 10 patients. The patients were subdivided into two groups based on the duration of follow-up: Group A with follow-up of more than 10 months ($n = 5$) and Group B with follow-up of less than 10 months ($n = 5$).

The inclusion criteria were patients having T2DM of 3 years or more in duration with optimum prescribed therapy with hemoglobin A1c (HbA1c) >8%, age between 30 and 75 years, body mass index (BMI) of 25–45 kg/m^2, stable weight for the last 3 months, and post-meal C-peptide level >1.5 ng/mL. The exclusion criteria were duration of diabetes more than 25 years, post-meal C-peptide levels <1 ng/mL, pregnancy, chronic kidney disease (glomerular filtration rate <60 mL/min), coexisting severe hepatic/neurological/psychiatric disorder, and obesity due to nonendocrine illness.

Preoperative evaluation included history of T2DM and complications, physical examination for suitability of surgery, blood tests, urinalysis, and imaging studies. Fasting samples were analyzed for glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), serum creatinine, and plasma insulin. Post-meal samples were taken for estimatation of C-peptide and plasma glucose. The morning urine sample was used for estimation of microalbuminuria, and glomerular filtration rate was calculated using the modified Cockgroft-Gault equation. IR was derived from the homeostasis model assessment (HOMA) formula (HOMA-IR) using fasting blood glucose and insulin.

The operation was performed under general anesthesia with a standard six-port laparoscopic technique. The surgical procedure involves creation of a 170-cm segment of ileum, starting at 30 cm proximal to the ileocecal junction. This segment is 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 a endo-GIA stapler (Ethicon Endo-surgery, Cincinnati, OH) with a 45-mm cartridge, and the stapler openings were closed by hand with a 3/0 polydioxanone suture in two layers. The sleeve gastrectomy was performed after devascularization of the greater curvature from the antrum to the fundus area. 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

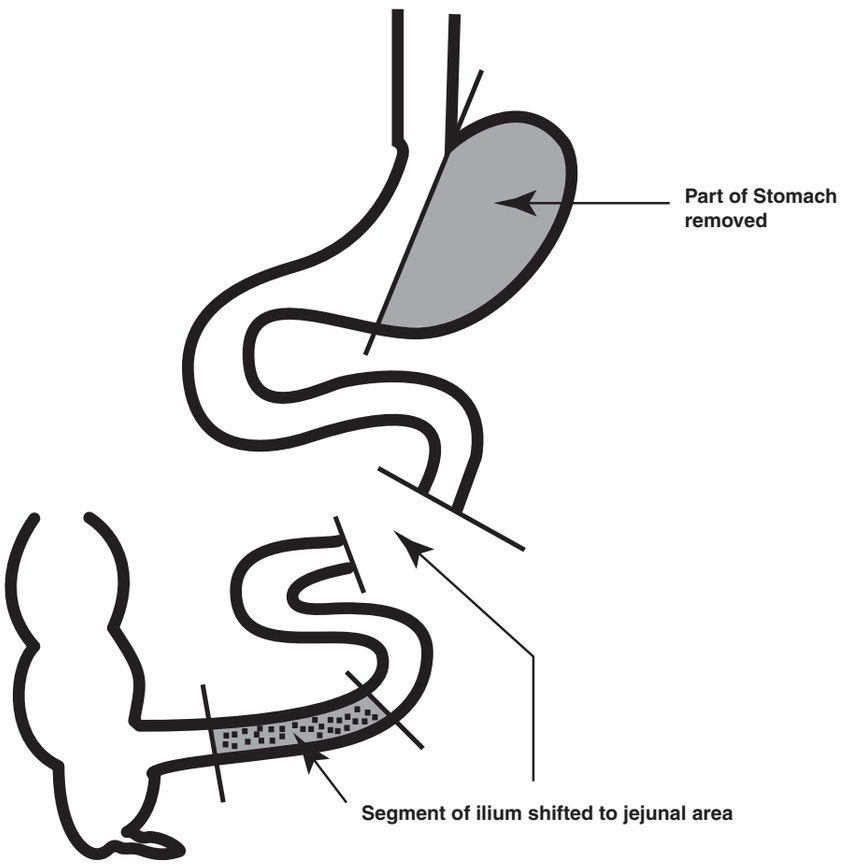

FIG. 1. Ileal interposition with sleeve gastrectomy.

Table 1. Clinical Data and Drug Requirement of Patients Before (Preop) and After (Postop) Surgery

Patient	Duration (years)		Complications	Follow-up (months)	Daily medications for T2DM and HTN		BMI (kg/m^2)		HbA1c	
	DM	HTN			Preop	Postop	Preop	Postop	Preop	Postop
1 (56/F)	12	8	Neuropathy	16	MF 1,500 mg, glibenclamide 15 mg, pioglitazone 30 mg, amlodipine 5 mg	None	29.2	24	9.9	6.7
2 (42/F)	4	3	Neuropathy, PVD	16	Gliclazide 240 mg, MF 1,500 mg, atenolol 25 mg	None	30.7	21.5	15.8	5.6
3 (56/M)	10	1	Neuropathy	13	MF 1,000 mg, glibenclamide 20 mg, acarbose 100 mg, pioglitazone 30 mg, enalapril 5 mg, amlodipine 5 mg	None	33	22	9.3	5.9
4 (50/F)	10	4 months	PVD	12	Glimepiride 8 mg, rosiglitazone 4 mg, MF 1,000 mg, ramipril 5 mg	None	30.5	27	11.7	6.8
5 (42/F)	7	2	Neuropathy	11	Glimepiride 4 mg, MF 1,500 mg, premix insulin 56 U, telmisartan 40 mg	None	42.2	28.5	8.2	5.7
6 (34/M)	8	4	PDR, neuropathy	8	Glimepiride 8 mg, MF 1,000 mg, premix insulin 14 U, telmisartan 40 mg	None	25.5	21	8.5	7
7 (42/F)	10	10	None	7	MF 1,000 mg, glibenclamide 10 mg, premix insulin 60 U, losartan 50 mg, amlodipine 10 mg, glargine insulin 36 U	None	45.4	34	8.5	6.8
8 (56/M)	9	9	Neuropathy	4	MF 2,000 mg, glimepiride 2 mg, atenolol 50 mg, premix insulin 46 U, acarbose tablet 100 mg	MF 500 mg	31	24.8	10.3	6.8
9 (42/F)	15	6	Neuropathy	2	MF 1,500 mg, pioglitazone 15 mg, ramipril 5 mg, premix insulin 82 U, glargine insulin 35 U	Sitagliptin 100 mg, MF 500 mg	40	34	8.7	7.4
10 (62/M)	25	10	PVD	2	MF 1,500 mg, glibenclamide 15 mg, pioglitazone 30 mg, ramipril 5 mg, premix insulin 70 U	MF 1,000 mg	30.4	26	9.9	8.5

DM, diabetes mellitus; HTN, hypertension; MF, metformin; PDR, proliferative diabetic retinopathy; PVD, peripheral vascular disease.

cartridges was used for resection. The schematic representation of the surgery is depicted in Figure 1. F1

The primary outcome measure was remission of T2DM, defined as HbA1c <7% without requiring oral or parenteral hypoglycemic agents. Secondary outcomes include change in oral hypoglycemic agent (OHA) requirement, IR, microalbuminuria, and components of metabolic syndrome. Postoperatively the diabetes and hypertension medications were adjusted as appropriate according to the blood pressure record and plasma glucose levels. Postoperatively 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 sixth and eighth postoperative day with follow-up visits at 1, 3, 6, 9, and 12 months, with the intent for follow-up also at 18 and 24 months. All outcome measures were evaluated prospectively from the first month onward at every visit.

The continuous data were presented as mean with standard deviation. Student's *t* test was used for statistical analysis, and a significance level of less than 0.05 was considered significant.

Results

T1 T2 The clinical details and postoperative follow-up of the 10 patients are summarized in Tables 1 and 2. Participants had a mean age of 48.2 ± 9 years (range, 34–62 years), duration of diabetes of 11 ± 5.7 years (range, 4–25 years), and preoperative BMI of $33.8 \pm 6.5\,kg/m^2$. The mean operative time was 5.4 ± 1.1 hours, and all patients were discharged after 1 week of hospitalization with vitamin supplements. They were on liquid nutritional supplements initially, and semisolid food was introduced thereafter. Two patients had difficulty in swallowing rapidly for the initial 2 weeks, which improved later on in the early postoperative period. However, none of the patients had any serious complications intraoperatively and postoperatively in this short follow-up. Routine upper gastrointestinal endoscopy after 1 month of surgery did not reveal any abnormality.

Remission of diabetes was seen in all five patients from group A and in two patients from group B. The remaining three patients of group B had a significant decrease in OHA requirement. Two patients were on single-drug therapy for diabetes, and only one patient (with shortest follow-up of 2 months) was on two-drug therapy. There was significant improvement in other secondary outcomes measured as well. Hypertension was seen in all patients preoperatively requiring single-drug therapy. Blood pressure normalized in all patients postoperatively without using antihypertensive medication. Participants from both the groups had significant weight loss ranging from 15% to 30% of excess weight. However, patients from group A showed a greater percentage loss of weight than group B patients. The lipid parameters, including LDL-C, TG, and HDL-C, did not change significantly in both groups postoperatively. One patient in group A was treated with fenofibrate 145 mg daily postoperatively for high TG. Microalbuminuria was present preoperatively in eight of 10 patients and showed insignificant improvement after surgery in both the groups. All patients had evidence of IR as assessed by HOMA-IR, which decreased significantly after surgery (8.5 ± 3.2 vs. 1.8 ± 0.4, $P = 0.0091$) in group A but not in group B (10.3 ± 13.7 vs. 3.3 ± 1.3, $P = 0.3176$). One patient from group B had a history of proliferative retinopathy, treated with photocoagulation, and showed marked improvement in retinopathy postoperatively. We did not assess for autonomic neuropathy routinely in all our patients.

Discussion

Our preliminary report demonstrates the beneficial effects of this novel procedure in control of T2DM. To the best of our knowledge, this is the first report from our country about laparoscopic surgical procedure for control of T2DM. Diabetes control was excellent following surgery with complete remission in seven patients. Remission was observed in all patients with long duration of follow-up (group A) and in two out of five patients with short follow-up (group B). There was significant change in HbA1c in both the groups. Glucagon-like peptide hormone produced from ileal L cells is the key hormone in mediating the diabetes improvement and weight loss after bariatric surgery. DePaula et al.[9] have reported 87% resolution in diabetes with similar surgery in a group of 23 patients followed up for less than a year. Our data showed remission of diabetes in seven and significant improvement in the remaining three patients from group B. The lack of remission of diabetes in the remaining three patients could be due to the short follow-up period and high IR in our patients. Patients from group B showed significant improvement in

Table 2. Clinical and Biochemical Data Before (Preop) and After (Postop) Surgery

	Group A (n = 5)			*Group B* (n = 5)		
Parameter	*Preop*	*Postop*	P *value*	*Preop*	*Postop*	P *value*
Body weight (kg)	81.6 ± 15.8	61.4 ± 8	0.0092	101.2 ± 16.5	83.6 ± 13.9	0.0227
BMI (kg/m^2)	33.1 ± 5.3	24.6 ± 3.1	0.0103	34.5 ± 8.1	27.9 ± 5.8	0.0071
FBS (mg/dL)	208.4 ± 48.3	97.8 ± 8.9	0.0039	196.6 ± 26.6	134.2 ± 15.6	0.0108
PLBS (mg/dL)	308.6 ± 46.9	125 ± 27.3	0.0002	285.4 ± 47.3	186.8 ± 20	0.0058
HbA1c (%)	10.9 ± 2.9	6.1 ± 0.5	0.0256	9.2 ± 0.8	7.3 ± 0.7	0.0102
HOMA-IR	8.5 ± 3.2	1.8 ± 0.4	0.0091	10.3 ± 13.7	3.3 ± 1.3	0.3176
TG (mg/dL)	359.6 ± 434	205.6 ± 189	0.2392	201 ± 83.8	130.8 ± 42.2	0.1495
HDL-C (mg/dL)	43.6 ± 7.4	41 ± 7.8	0.2763	37.4 ± 4.2	37 ± 5.6	0.8355
LDL-C (mg/dL)	121 ± 28.3	94.2 ± 37.2	0.0910	101.8 ± 24.3	93.4 ± 17.2	0.3894
Microalbuminuria (mg/L)	190 ± 271	53 ± 59.7	0.2303	70 ± 36.9	24.9 ± 10.1	0.0835

Data are mean ± SD values. Group A had a mean follow-up of 13.6 months (range, 11–16 months), and Group B had a mean follow-up of 4.6 months (range, 2–8 months). FBS, fasting blood sugar; PLBS, plasma blood sugar.

glycemic profile despite a short follow-up period, indicating weight loss-independent benefits of the metabolic surgery.

All patients had considerable weight loss ranging between 15% and 30% coupled with remission in hypertension. Weight loss was seen in both the groups, but the group with longer follow-up (Group A) had a higher percentage loss of excess weight than group B patients. Insulin sensitivity improved in group A when compared with group B, suggesting the accrual of benefits with prolonged observation period after surgery. The observed beneficial effect on hypertension in all the patients is related to weight loss and improved insulin sensitivity.[10] We have not observed any complications in the form of anastomotic leak, stomal ulcers, or malabsorption features in any of our patients, although it is a short follow-up.

The foregut and hindgut theories are proposed to explain the pathogenesis of resolution of diabetes following bariatric surgery.[11] The surgical technique used in this study is designed essentially for diabetes control and utilizes both these mechanisms. The first component is sleeve gastrectomy, resulting in restriction of calorie intake and loss of ghrelin. Ghrelin is a potent orexigenic hormone and contributes significantly towards impaired glucose homeostasis.[12] The second characteristic of this surgery is ileal interposition, resulting in rapid stimulation of transposed ileal segment by ingested food leading to augmented glucagon-like peptide hormone secretion. Glucagon-like peptide hormone is the incretin hormone responsible for the first phase of insulin secretion, which is defective in type 2 diabetes.[13] Glucagon-like peptide hormone also influences glucose metabolism by inhibiting glucagon secretion, delaying gastric emptying, and stimulating glycogenesis.[14]

Microalbuminuria is an independent predictor of cardiovascular risk in diabetes patients, and the surgery resulted in a trend towards improvement in microalbuminuria in all participants. Our patients did not show significant improvement in lipid parameters as observed in earlier studies, suggesting a different metabolic milieu in our population.[9] The short postoperative follow-up period and the small number of patients are the limitations of our study. Another important limiting factor is the technical expertise required for the laparoscopic ileal interposition, which requires extensive training.

In 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 appears safe and a potentially effective option in the management of type 2 diabetes patients with excess weight. Further long-term data from a larger number of patients is necessary to define the role of this novel surgery in type 2 diabetes.

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Author Disclosure Statement

All authors have no potential financial interest or any commercial association that might have a potential conflict of interest. All authors declare that no competing financial interests exist.

References

1. Astrup A, Finer N: Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? Obes Rev 2000;1: 57–59.
2. Enas EA, Mohan V, Deepa M, Farooq S, Pazhoor S, Chennikkara H: The metabolic syndrome and dyslipidemia among Asian Indians: a population with high rates of diabetes and premature coronary artery disease. J Cardiometab Syndr 2007;2:267–75.
3. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H: Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–93.
4. Greenway SE, Greenway FL 3rd, Klein S: Effects of obesity surgery on non-insulin-dependent diabetes mellitus. Arch Surg 2002;137:1109–1117.
5. Flatt PR: Effective surgical treatment of obesity may be mediated by ablation of the lipogenic gut hormone gastric inhibitory polypeptide (GIP): evidence and clinical opportunity for development of new obesity-diabetes drugs? Diabetes Vasc Dis Res 2007;4:151–153.
6. Cohen RV, Schiavon CA, Pinheiro JS, Correa JL, Rubino F: Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22–34 kg/m^2: a report of 2 cases. Surg Obes Relat Dis 2007;3:195–197.
7. Kawamura I, Ochiai T: Current status of obesity surgery as metabolic surgery. Nippon Geka Gakkai Zasshi 2006; 107:305–311.
8. Mason EE: Ileal [correction of ilial] transposition and enteroglucagon/GLP-1 in obesity (and diabetic?) surgery. Obes Surg 1999;9:223–228.
9. DePaula AL, Macedo AL, Rassi N, Machado CA, Schraibman V, Silva LQ, Halpern A: Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less than 35. Surg Endosc 2008;22:706–716.
10. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K: Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292:1724–1737.
11. Cummings DE, Overduin J, Foster-Schubert KE: Gastric bypass for obesity: mechanisms of weight loss and diabetes resolution. J Clin Endocrinol Metab 2004;89:2608–2615.
12. Broglio F, Arvat E, Benso A, Gottero C, Muccioli G, Papotti M, van der Lely AJ, Deghenghi R, Ghigo E: Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. J Clin Endocrinol Metab 2001;86:5083–5086
13. Nauck M, Stockmann F, Ebert R, Creutzfeldt W: Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 1986;29:46–52.
14. Holst JJ: The physiology of glucagon-like peptide 1. Physiol Rev 2007;87:1409–1439.

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