

ORIGINAL ARTICLE

Resolution of type 2 diabetes after gastrectomy for gastric cancer with long limb Roux-en Y reconstruction: a prospective pilot study

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Purpose: It is unclear whether metabolic surgery is effective in non obese type 2 diabetes mellitus (T2DM) and the result after gastrectomy and conventional reconstruction for gastric cancer with non obese T2DM are not satisfactory for improvement of T2DM. Prospective single-arm pilot study with long limb Roux-en Y reconstruction after gastrectomy was evaluated on its safety and efficacy as a potential cure for T2DM in patients with non obese gastric cancer. **Methods:** Fifteen patients with non obese T2DM and gastric cancer were enrolled. After gastrectomy, the gastrointestinal tract was reconstructed by Roux-en Y gastrojejunostomy or esophagojejunostomy. The biliopancreatic and Roux limb were 100 to 120 cm long each. **Results:** There was no surgery-related mortality, but four cases experienced complications (26.7%). Before surgery, the mean body mass index was 25.2 ± 3.4 kg/m² and mean glycated hemoglobin (HbA1c) was $7.7 \pm 1.4\%$ with antidiabetic medications. The mean BMI decreased to 21.7 ± 3.1 kg/m² ($P < 0.05$) and the mean HbA1c decreased to $6.3 \pm 0.8\%$ ($P < 0.05$) 6 months after surgery. At the end of the study (follow-up duration, 12.5 ± 5.5 months), HbA1c decreased to $< 6\%$ in 11 patients (78.6%) without any antidiabetic medications. There were no patients who had anemia, and/or malnutrition after surgery except one patient who died due to recurrence four months after surgery. **Conclusion:** Long limb Roux-en Y reconstruction after gastrectomy is feasible and has the potential to cure T2DM in non obese gastric cancer patients. A randomized controlled trial is needed to confirm this result.

Key Words: Type 2 diabetes mellitus, Roux-en-Y anastomosis, Gastrectomy, Stomach neoplasms

INTRODUCTION

The care of patients with type 2 diabetes mellitus (T2DM) should focus not only on glucose control but also on management of complications such as heart disease, dyslipidemia, obesity, and cancer. However, the prevalence of adult diabetes has been rising globally [1,2] and

the economic and social burdens of diabetes threaten the world's health systems [3,4].

It has been demonstrated that metabolic surgery resolves T2DM in morbidly obese patients [5-7]. In contrast, whether metabolic surgery is effective in nonmorbidly obese patients still remains to be solved. Moreover, Asian people develop T2DM at a younger age with a lesser de-

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gree of obesity, and tend to have the complications and die earlier [8,9].

As life expectancy is increased, the number of patients with gastric cancer and T2DM is increased as well. It was noticed that gastric resection induce the resolution of T2DM in non-morbidly obese patients [10-12].

Recently, we studied the outcome of T2DM after gastrectomy and conventional reconstruction in non obese gastric cancer patients [13]. The study was a large-series retrospective study including about 400 patients and only 15.1% were resolved from T2DM after operation, which were not satisfactory. This prompted us to develop a effective reconstruction method for diabetic control after gastrectomy in gastric cancer patients with non obese T2DM. We grafted the bariatric type operation, long-limb Roux-en Y reconstruction into gastric cancer surgery. This study aimed to investigate the safety and efficacy of long limb Roux-en Y reconstruction after gastrectomy in non obese gastric cancer patients.

METHODS

Study design

This was a prospective pilot study to evaluate the safety and efficacy of long limb Roux-en Y reconstruction after gastrectomy as a potential cure for T2DM in non obese gastric cancer patients. The study was based on a protocol determined by the Departments of Surgery and Endocrinology of Gangnam Severance Hospital and was approved by the Institutional Review Board of this hospital (# 3-2009-0152). Each patient was informed of the investigational nature of the trial and received detailed information regarding the study protocol. All patients provided written informed consent before their enrollment in the trial. The study was also registered on the ClinicalTrials.gov website (<http://www.clinicaltrials.gov/>) (NCT01373346).

Patients were eligible for the study if they had a history of T2DM over 6 months, a body mass index (BMI) < 30 kg/m², and underwent curative resection for gastric cancer. Patients were required to have their C-peptide above 1 ng/mL. Candidates were excluded if they had anti-glutamic acid decarboxylase antibody and/or islet cell antibody,

and had a history of recently receiving medications such as dipeptidyl peptidase-IV inhibitors or glucagon-like peptide-1 analogues. The enrollment continued from February 2010 through May 2011. Baseline weight/height, vital signs, oral glucose tolerance test score, and levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), C-peptide, and serum insulin were measured before surgery and again regularly after surgery. Insulin resistance was measured by the insulin sensitivity index [14] homeostasis model assessment (HOMA)-insulin resistance [15] and quantitative insulin sensitivity check index (QUICKI) [16] using a web calculator (<http://mmatsuda.diabetes-smc.jp/MIndex.html>, <https://sas1.unibas.ch/11calculators-QUICKI.php>). Insulin secretion was measured by HOMA-derived beta-cell function (HOMA-B) (HOMA-B = 225 × 18/fasting insulin × fasting glucose) [17].

The safety of this procedure was evaluated by mortality and morbidity rates. Because the procedure was not so different from conventional gastric cancer surgery except the length of Roux limb and biliopancreatic limb, the rate of Roux stasis or A-loop syndrome was specifically evaluated.

Operative procedure

All patients underwent radical gastrectomy under general anesthesia and D1 + lymph node dissection was applied into early gastric cancer and D2 lymph node dissection in advanced gastric cancer [18].

The gastrointestinal tract was reconstructed by Roux-en Y gastrojejunostomy or esophagojejunostomy with antecolic fashion. The jejunum was divided at approximately 100 to 120 cm distal to the ligament of Treitz and the distal limb of the jejunum was then anastomosed along the proximal gastric greater curvature or esophagus. The jejunojunctionostomy was performed approximately 100 to 120 cm distal from the gastrojejunal or esophagojejunal anastomosis (Fig. 1).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (range). Demographic and baseline characteristics were summarized descriptively, and the changes in the observation parameters at baseline and endpoint were analyzed using the Wilcoxon signed rank test. A two

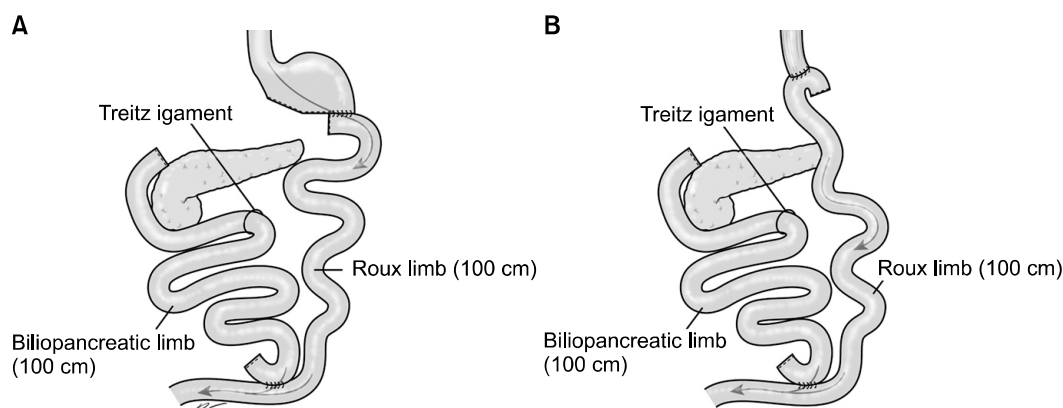


Fig. 1. Long limb Roux-en Y anastomosis. After gastrectomy, the gastrointestinal tract was reconstructed by Roux-en Y gastrojejunostomy (A) or esophagojejunostomy (B). The biliopancreatic and Roux limb were 100 to 120 cm long each.

Table 1. Preoperative demographic data of 15 patients

Characteristic	Value
Duration of type 2 diabetes mellitus (mo)	136.9 ± 102.4
Antidiabetic medication	
Insulin	1 (6.7)
Insulin + oral	1 (6.7)
Oral	13 (86.7)
Serum insulin level (μIU/mL)	8.1 ± 6.8
Serum C-peptide level (ng/mL)	2.2 ± 1.2

Values are presented as mean ± standard deviation or number (%).

sided P-value of 0.05 was considered statistically significant. All statistical analyses were performed using of PASW ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

A total of 15 non obese T2DM patients with gastric cancer were enrolled. There were 10 males and 5 females and their mean age was 62.1 ± 8.7 years. The baseline demographic data are presented in Table 1. Four patients received total gastrectomy and 11 patients received subtotal gastrectomy. Eleven patients received laparoscopic operation

The mean surgical time was 265.5 ± 84.8 minutes. There was no surgery-related mortality, but four patients experienced complications; one experienced anastomotic stricture that was recovered with conservative management, one experienced anastomosis site kinking managed with

temporary stent insertion and one had myocardial infarction treated with percutaneous transluminal coronary angioplasty with stent insertion. There was one wound complication. There were no patients who were complaints of Roux stasis or A-loop syndrome. Final pathologic results revealed that nine patients were early gastric cancer and six patients were advanced. Four patients received chemotherapy. During the follow-up period, there was one patient who had poorly differentiated neuroendocrine carcinoma and died due to recurrence four months after surgery, but the blood glucose level was well controlled (HbA1c < 6.0%) without medication. In the remained patients, there was no evidence of recurrence in the regular check-up at 6 months after operation. Also, there was no stricture or jejunal ulcer in the follow-up endoscopic examination.

The patient who died of recurrence was excluded from the efficacy evaluation. Six months after surgery (n = 14), the mean BMI was significantly decreased to 21.7 ± 3.1 kg/m² from 25.2 ± 3.4 kg/m² (P < 0.05). The preoperative mean HbA1c was 7.7 ± 1.4% with antidiabetic medications and the mean HbA1c was also significantly down to 6.3 ± 0.8% (P < 0.05).

At the end of the study, the follow-up duration was 12.5 ± 5.5 months (6.0 to 21.7 months). HbA1c < 6% without any antidiabetic medications were observed in 11 patients (78.6%). A total of four patients who received total gastrectomy and seven patients (70%) who received subtotal gastrectomy were included. All of four patients who re-

Table 2. Outcome of patients showing HbA1c < 6% without the antidiabetic medication after surgery (n = 11)

	Preoperative	After surgery (6 mo)	P-value ^{a)}	The end of study	P-value ^{b)}
ISI	5.7 ± 3.0	14.0 ± 6.1	0.028	12.7 ± 7.3	0.075
HOMA-IR	1.9 ± 1.9	0.9 ± 0.7	0.033	0.8 ± 0.6	0.026
QUICKI	0.4 ± 0.1	0.4 ± 0.0	0.169	0.5 ± 0.1	0.017
HOMA-B	8.7 ± 6.9	13.4 ± 8.9	0.169	17.8 ± 12.3	0.047
Hemoglobin (g/dL)	13.3 ± 1.8	12.6 ± 1.8	0.091	13.0 ± 1.7	0.507
Albumin (g/dL)	4.4 ± 0.4	4.2 ± 0.6	0.139	3.9 ± 0.7	0.011
Triglyceride (mg/dL)	117.7 ± 55.5	98.1 ± 62.9	0.510	88.6 ± 66.8	0.368
Cholesterol (mg/dL)	139.0 ± 32.4	123.3 ± 27.4	0.233	123.4 ± 34.5	0.287

Values are presented as mean ± standard deviation.

HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; HOMA-B, homeostasis model assessment-derived beta-cell function.

^{a)}Preoperative versus postoperative 6 months values. ^{b)}Preoperative versus the end of study values.

ceived chemotherapy discontinued anti-diabetic medication after operation. Although improvement of insulin sensitivity was unstable, insulin secretion was significantly improved ($P < 0.05$) (Table 2). The FPG levels of 2 patients (14.3%) were between 6.1 and 7.0 mmol/L and their HbA1c were well controlled (between 6% and 7%) with or without medications. Only one patient had HbA1c above 7%, but the FPG and 2-hour plasma glucose levels were significantly decreased after surgery. There were no patients who had anemia, and/or malnutrition after surgery. Even though the albumin levels were decreased at the end of study compared to the preoperative levels, they were still within normal range. Also, the levels of serum triglyceride and serum cholesterol decreased after operation, but remained in normal range.

DISCUSSION

Calorie restriction and/or weight loss are one of many effective ways to control T2DM in morbidly obese patients. However, calorie restriction and/or weight loss are not easy in non obese patients, and Asian people develop T2DM with a lesser degree of obesity.

The early recovery course and mismatched degree of T2DM improvement after gastric bypass compared with equivalent weight loss from other treatment modalities implicate weight-independent effects of bariatric surgery on glucose metabolism [6,19]. In addition, some reported

that non-morbidly obese patient with T2DM can be recovered after bariatric surgery [20-25]. These results suggested that surgery might induce remission even in non obese T2DM patients.

We had studied the long-term results of gastrectomy and conventional reconstruction in non obese T2DM patients with gastric cancer [13]. It was a very large scale study and the complete remission was only 27.3% even though in total gastrectomy and Roux-en Y esophagojejunostomy. There were some reports that demonstrate the effect of subtotal gastrectomy and Roux-en Y gastrojejunostomy on T2DM in non obese patients, but the remission rate was still not high [12]. Before we started this study, we tried some modifications of Roux limb length after gastrectomy and were not able to control glucose homeostasis without medications in gastric cancer and T2DM patients. In this study, we tested the safety and efficacy of Roux-en Y reconstruction with a 100-cm biliopancreatic limb and a 100-cm Roux limb after gastrectomy in T2DM gastric cancer patients. The main difference with previous reports was the longer length of biliopancreatic and Roux limbs.

Among 15 patients enrolled in this study, 9 patients received laparoscopic surgery with two anastomotic stricture or kinking. We assumed that this complication was related with technical failure in the learning period.

Rearrangement of the intestine and/or modification of the stomach might induce functional obstruction of the small bowel and metabolic problems such as vitamin and

trace element deficiencies [26]. Longer length of a Roux limb has been suggested to be effective in super obese patients without significant complications [27]. In this study, we found that there was no Roux stasis syndrome, anemia and hypoalbuminemia after surgery. Some patients complained of frequent diarrhea after eating fatty food, but normal diet was tolerable without malnutrition. In addition, most patients maintained their weight within normal range after surgery.

Mechanisms of antidiabetic effects after gastrointestinal surgery are not yet fully characterized. Except effects due to weight loss and calorie restriction, exclusion of the proximal small intestine from ingested nutrient, enhanced distal-intestinal nutrient delivery, impaired ghrelin secretion, modulations of intestinal nutrient sensing and regulation of insulin sensitivity, bile acid perturbations, changes in gut microbiota and other changes were proposed [19,28]. Our study showed that all of patients who received total gastrectomy and/or chemotherapy stop the anti-diabetic medication with normal glucose level and these might result from weight loss or calorie restriction. However, seven among ten patients who received subtotal gastrectomy without chemotherapy demonstrated normal glucose control after operation. In this study, bypassed segments of the small bowel were longer than conventional Roux-en Y reconstruction after gastrectomy. Also, nutrient stimulation of lower intestinal hormones (e.g., GLP-1) might be enhanced in the patients of this study. It was beyond the scope of this study to elucidate the mechanism by which T2DM was resolved. However, insulin secretion was significantly improved after surgery. We were afraid that the β cell function in non obese T2DM patients was decreased and such decrease might be irreversible. Fortunately, animal experiments demonstrated that T2DM in lean T2DM rats can be improved by rearrangement of the gastrointestinal tract without significant weight loss [29,30]. As mentioned above, these results are consistent with some human trials [20,21,24,25]. Now, we suggest that even when weight is maintained within the normal range, T2DM is still reversible in non obese patients. In this study, the improvement of insulin sensitivity was not clear. A long term follow-up study with increased enrolled patients is warranted to elucidate the

improvement of insulin sensitivity.

Taken together, we considered that long limb Roux-en Y reconstruction is feasible and has the potential to cure T2DM in gastric cancer patients. This was a pilot study and the duration of follow-up was short. To confirm the effectiveness of long limb Roux-en Y procedure, randomized controlled trial (RCT) is needed and our results will be helpful to design the RCT.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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