Asian Journal of Surgery (2020) 43, 297—303

Available online at www.sciencedirect.com

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journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Multicenter results of long-limb bypass reconstruction after gastrectomy in patients with gastric cancer and type II diabetes

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Received 9 February 2019; received in revised form 22 March 2019; accepted 26 March 2019
Available online 3 May 2019

KEYWORDS
Type II DM;
Gastric cancer;
Long limb Roux-en Y

Summary *Background/Objective:* The number of gastric cancer and type II diabetes mellitus is increasing in Korea. Metabolic surgery could be extended to gastric cancer patients with type II diabetes, especially those who are expected to achieve long-term survival. This study aimed to investigate change of diabetic status in patients undergoing long-limb Roux-en-Y bypass reconstruction compared with conventional Billroth II after curative gastrectomy. In total, 130 patients from five university hospital centers underwent long-limb Roux-en Y reconstruction after radical distal gastrectomy.
Methods: In the long-limb group, the length of biliopancreatic limbs was more than 80 cm, and the length of the Roux limb was more than 80 cm. The control group comprised 96 patients who underwent conventional Billroth II reconstruction after distal gastrectomy. Follow-up data at three, six, nine, and 12 months were compared between the two groups.
Results: Fasting blood sugar (FBS) and hemoglobin (Hb) A1c levels decreased more significantly in the long-limb Roux-en-Y group (FBS: 28.8 mg/dL; HbA1c: 0.72%). However, decreases in body mass index, albumin, and hemoglobin did not differ significantly between the two groups. Diabetes control significantly improved in the long-limb group. In multivariate analysis, long-limb bypass reconstruction was the significant factor for glycemic outcomes.

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https://doi.org/10.1016/j.asjsur.2019.03.018

Conclusion: Roux-en-Y bypass with increased length of limbs after gastrectomy shows a favorable glycemic control for gastric cancer patients with type II diabetes without nutritional deficit and anemia. To obtain future perspectives, large-scale prospective studies with long-term outcomes are needed.

1. Introduction

The number of patients with gastric cancer and type II diabetes mellitus (DM) is increasing, especially in Asian people, who develop type II DM at a younger age with a lesser degree of obesity, tend to experience complications and die earlier.[1,2] It has been demonstrated that metabolic surgery resolves type II DM in morbidly obese patients and it is possible that this treatment can be applied to non-morbidly obese patients.

The basic mechanisms of metabolic surgery are insulin sensitivity and beta cell secretory function improvements. Proximal small intestinal bypass and/or early arrival of chime are considered major contributing factors for metabolic effects, and this phenomenon might be applicable to gastric cancer patients.[3]

However, drug discontinuation rates of DM patients after gastric surgery with conventional reconstruction are relatively low.[4,5] Patients with type II DM and gastric cancer are frequently old, non-obese, and often have severely deteriorated pancreatic β-cell function and relatively low body weight. To enhance the metabolic effect, increased length of the Roux limb and/or biliopancreatic limb have been tried. But there are few relevant studies of gastric cancer patients with type II DM.

This study aimed to investigate change of diabetic status in patients undergoing long-limb bypass reconstruction after curative gastrectomy.

2. Materials and Methods

A total of 226 patients at five university hospital centers were retrospectively enrolled. The study group comprised 130 patients who underwent radical subtotal gastrectomy with long-limb Roux-en-Y bypass reconstruction. A control group of 96 patients underwent Billroth II reconstruction. One-year laboratory follow-up data were recorded for all patients, including fasting blood sugar (FBS) and hemoglobin (Hb) A1c levels. Outcomes for glycemic control, including antidiabetic medication and insulin treatment, were assessed. This retrospective study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB number AS17069).

2.1. Surgical methods

Curative subtotal gastrectomy with D1+ or D2 lymphadenectomy was performed for all patients. In subtotal gastrectomy, about 70 percent of the distal stomach is resected, and intestinal continuity is maintained via gastrojejunal reconstruction. After gastric resection, Roux-en-Y gastrojejunostomy was performed for the long-limb group, and Billroth II was performed for the control group. For the long-limb group, biliopancreatic limb length was 80–100 cm, and Roux limb length was 80–100 cm, for a total bypass length of 160–200 cm. For the conventional group, Billroth II reconstruction was performed for intestinal continuity, with a 20–30 cm length of the afferent limb.

2.2. Analytical methods

Baseline clinical data collected to evaluate metabolic outcomes were age, sex, preoperative diabetes control method, diabetes duration (year), and body mass index (BMI). Outcome measurements for diabetes control were FBS and HbA1c levels, which were measured at three, six, and nine months and one year postoperatively. Nutritional profiles of BMI and HbA1c and albumin levels were also measured at three, six, and nine months and one year postoperatively.

Diabetes resolution and improvement were evaluated following American Diabetes Association criteria.[6] Complete remission was defined as FBS level $<$100 mg/dL and HbA1c level $<$6.0% for one year without use of antidiabetic medication. Partial remission was defined as FBS level 100–125 mg/dL and HbA1c level $<$6.5% for one year in the absence of antidiabetic medication. The improved group included patients with type II diabetes who showed partial or complete diabetes remission and those with reduced antidiabetic medication dosages or decreased HbA1c and FBS levels without increasing antidiabetic medication dosage. Additional preoperative clinical factors of age, sex, diabetes duration, FBS level, and BMI were compared and analyzed as diabetes control factors.

2.3. Statistical analysis

We provided descriptive statistics of patient characteristics in two groups and compared the baseline characteristics between groups using χ^2 test for categorical data and t-test for continuous data. Means and 95% confidence intervals of clinical indices of FBS, HbA1c, BMI, and albumin level were calculated preoperatively and at three, six, and nine months and one year postoperatively. The generalized estimating equation (GEE) model was used to estimate the surgical effect on the clinical indices, including FBS and HBA1c levels, over time after adjustment for age, sex, and diabetes duration at baseline.[7] Glycemic outcomes one year after surgery were compared between groups using

Fisher's exact test. The odds ratios for the glycemic outcomes were calculated in accordance with surgery type, age, sex, diabetes duration, and preoperative clinical indices in both univariate and multivariate models. All statistical analyses were conducted using SAS ver.9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was considered at p-values <0.05.

3. Results

3.1. Clinical data variations in metabolic outcomes by surgery type

Preoperative clinical data showed no significant differences in sex, age, diabetes duration, diabetes control, BMI, HbA1c level, or FBS level between the two groups (Table 1). Time and treatment effects for change in FBS and HbA1c from baseline using the GEE are described in Table 2. Change in FBS was 2.4 mg/dL lower in the long-limb surgery group than in the conventional surgery group over a one-month period. Likewise, decrease in HbA1c was 0.06% greater in the long-limb surgery group compared with that in the conventional surgery group at one month. Differences in FBS and HbA1c between the long-limb and conventional surgery groups were estimated at 28.8 mg/dL and 0.72% at 12 months, respectively (Table 2).

Three, six, and nine months and one year after surgery, the mean FBS and HbA1c levels in the long-limb group decreased more significantly than those in the conventional Billroth II group (Fig. 1a, b). However, nutritional profiles, such as HbA1c level, BMI reduction, and albumin level were not significantly different between the two groups (Fig. 2a, b, c).

3.2. Glycemic control outcomes by surgery type

Regarding diabetes remissions, there was only one partial and no complete remission in the conventional Billroth II group. However, in the long-limb group, four patients (3.1%) had partial remission, and 11 patients (8.5%) had complete remission. Diabetes control improvement was significantly different between the two groups as measured by glycemic control outcomes one year after surgery (Table 3). In multivariate analysis for glycemic outcomes during 12 months after surgery, long-limb bypass reconstruction was the only significant factor for diabetes control improvement (Table 4).

4. Discussion

Bariatric surgery was developed as a weight-loss operation for treatment of morbid obesity. However, bariatric surgery can not only reduce body mass, but also ameliorate obesity-related complications, suggesting that surgery is the most effective therapeutic option for diabetes patients with severe obesity.[8–10] Recent international guidelines recommend surgery for type II diabetes patients with class II or III obesity (BMI >35 kg/m^2) or class I obesity with poorly controlled hyperglycemia despite appropriate lifestyle and pharmacological therapy.[11]

The number of patients with gastric cancer and type II DM has increased, especially among Asians, who develop type II DM at a younger age with a lesser degree of obesity, tend to experience complications, and die earlier.[1,2] For this reason, development of reconstruction methods to help control diabetes after gastrectomy has significant implications for gastric cancer treatment.

It is well known that, after gastrectomy for gastric cancer with type II DM, glucose control improves. However,

Table 1 General characteristics of patients by surgery type.

	Conventional Billroth II	Long-limb Roux-en Y	Chi-X^2 p-value
	n (%)	n (%)	
Total (n)	96	130	
Sex			
Man	71 (74.0)	104 (80.0)	0.2828
Woman	25 (26.0)	26 (20.0)	
Diabetes duration			
Missing	11 (11.5)	10 (7.7)	0.6158
0–9 years	55 (57.3)	76 (58.5)	
≥10 years	30 (31.3)	44 (33.9)	
Preoperative diabetes medication			
no medication	4 (4.2)	3 (2.3)	0.7275
oral medication	87 (90.6)	120 (92.3)	
Insulin injection	5 (5.2)	7 (5.4)	
	mean (SD)	mean (SD)	T-test p-value
Age	62.8 (9.5)	63.3 (8.9)	0.6653
Preoperative HbA1c (kg/m^2)	7.2 (1.3)	7.3 (1.4)	0.8664
Preoperative FBS (mg/dL)	145.3 (46.8)	153.8 (61.8)	0.2437
Preoperative BMI (kg/m^2)	25.3 (4.1)	25.8 (3.7)	0.302

Table 2 Generalized estimating equation models for fasting blood glucose, HbA1c according to surgery type.

	Fasting blood sugar		HbA1c	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Observation time (month)	−0.965 (−2.272–0.341)	0.148	−0.031 (−0.056∼−0.005)	0.020
Surgery type				
Conventional Billroth II	Reference	—	Reference	—
Long-limb Roux-en Y	10.025 (−7.557–27.608)	0.264	0.100 (−0.264–0.465)	0.590
Observation time & treatment method				
Observation time & conventional	Reference	—	Reference	—
Observation time & Long-limb	−2.432 (−4.239∼−0.625)	0.008	−0.064 (−0.100∼−0.028)	0.001
Sex				
Women	Reference	—	Reference	—
Men	−0.106 (−12.110–11.897)	0.986	−0.134 (−0.461–0.193)	0.423
Age (year)	−0.261 (−0.799–0.277)	0.342	−0.012 (−0.026–0.002)	0.102
Diabetes duration				
0–9 yrs	Reference	—	Reference	—
≥10 yrs	8.147 (−4.083–20.376)	0.192	0.253 (−0.054–0.559)	0.106
Missing	−5.768 (−18.804–7.268)	0.386	−0.104 (−0.502–0.293)	0.607

drug discontinuation rates after gastric surgery are reportedly lower than those after bariatric surgery.[3,5,12–15] Such outcomes were dependent on preoperative diabetes duration and weight reduction.[12] Also, diabetes improvement was dependent on reconstruction method, and Billroth II and Roux-en-Y gastrojejunal bypass reconstruction produced better outcomes than Billroth I gastroduodenal reconstruction.[13,15] However, some reports stress that total gastrectomy, rather than the reconstruction method, can offer superior outcomes in diabetes improvement,[14] and glycemic outcome is reportedly significantly correlated with BMI reduction ratio but not surgery type.[5] As a result, the effect of reconstruction method on glycemic control in gastric cancer patients with type II DM remains controversial.

Roux-en-Y gastric bypass is the most common procedure for bariatric surgery to improve type II DM. The Roux-en-Y bypass includes the gastric upper pouch, the alimentary or "Roux" limb, the biliopancreatic limb or afferent limb, and common limb, although there is no consensus on the optimal length of limbs. Kim et al. suggested that increasing the lengths of the alimentary and biliopancreatic limbs enhances glucose control after gastrectomy for gastric cancer and type II DM.[16] Other reports support this suggestion,[17,18] although they suffer from limitations due to small numbers of patients or applicability of the results to the period immediately after surgery.

Regarding metabolic surgery, type II diabetes remission can occur after gastric cancer surgery, and the basic mechanism is entero-insular axis modification.[19–21] This procedure involves altered glucose metabolism owing to different gut hormones, such as incretins, especially glucagon-like peptide-1.[19,21,22]

Recently, the incidence of early gastric cancer has increased in Korea,[23] so there is increased possibility that patients with gastric cancer and type II DM will achieve long-term survival. Onco-metabolic surgery is based on the hypothesis that modifying the traditional surgery in patients with gastric cancer and type II DM will improve glucose control.

We therefore designed an onco-metabolic surgical concept for early gastric cancer patients with type II diabetes and performed Roux-en-Y anastomosis with longer intestinal limbs than the conventional reconstruction

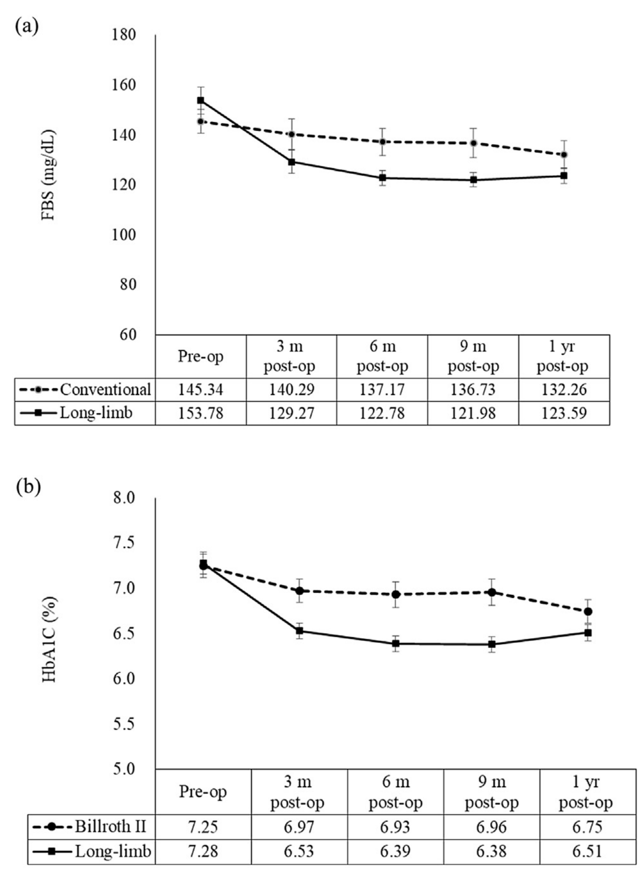

Figure 1 At the preoperative and postoperative 3, 6, 9 and 12 months levels of fasting blood sugar and Hemoglobin A1C (mean ± standard error). (a) Fasting blood sugar (mg/dL), (b) Hemoglobin A1C (%).

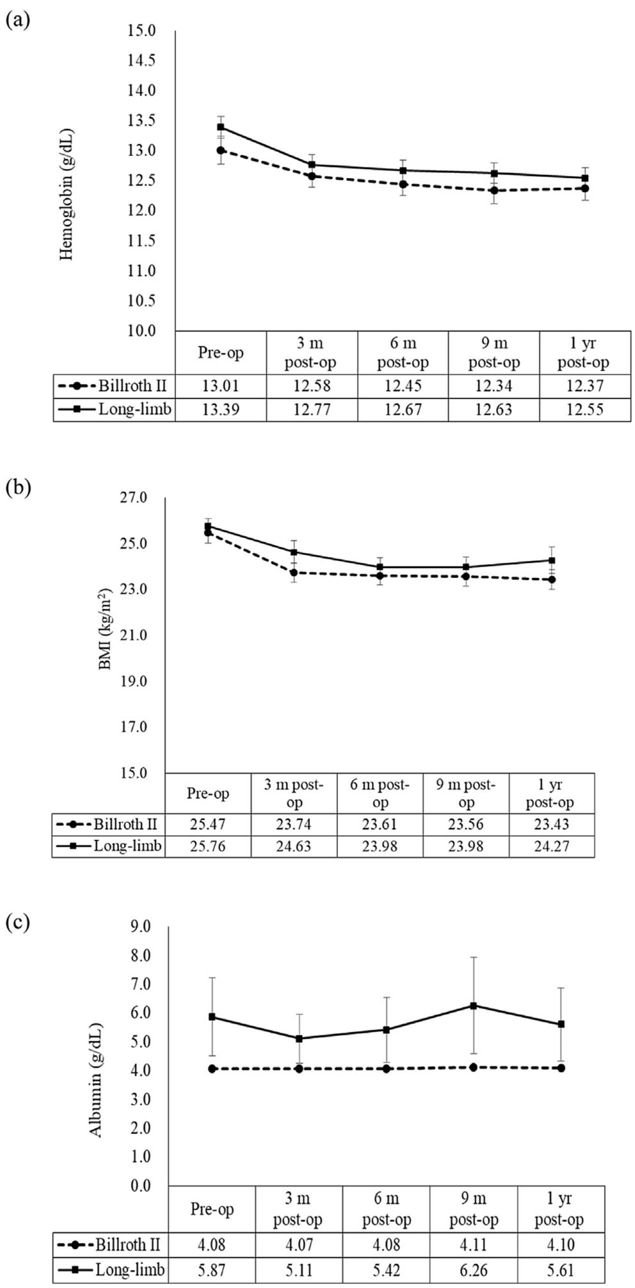

Figure 2 At the preoperative and postoperative 3, 6, 9 and 12 months levels of hemoglobin, BMI and albumin (mean ± standard error). (a) Hemoglobin (g/dL), (b) BMI (kg/m^2), (c) Albumin (g/dL).

method after distal subtotal gastrectomy. Glycemic control showed remarkably better outcomes in the long-limb group than the conventional group for up to one year after the operation.

One meta-analysis found that 78.1% of diabetic obese patients experienced complete resolution after bariatric surgery.[24] In another meta-analysis of non-obese diabetic patients (body mass index <30 kg/m^2) with type II DM, 61.8% of patients were off medication after bariatric surgery.[25] Also, Lanzarini et al. from Chile reported that 65.2% (15/23) of non-morbidly obese (BMI < 35 kg/m^2) diabetes patients with gastric cancer experienced remission and 30.4% (7/23) saw improvement after gastrectomy with Roux-en-Y reconstruction.[26] Our study, however, found a complete remission rate of only approximately 10%, and more than 42% of the patients showed no glycemic control change. There are several reasons for this difference in remission rate. The first possible explanation is that the mean age of our gastric cancer patients, about 60 years, is higher than that in the pure bariatric surgery group. Further, their diabetes duration was longer, and their pancreatic beta cell function could be poorly preserved. Second, we performed subtotal gastrectomy with fundus preservation, allowing our patients with gastric cancer to ingest enough food after a period. In contrast, fundus exclusion is the key procedure in pure bariatric surgery, including Roux-en-Y gastric bypass. Third, our patients with gastric cancer had relatively lower BMI and weight loss, possibly weakening the metabolic effect in our procedure compared to pure bariatric surgery. Finally, there were differences in the ethnic background of the patients.

However, the present study showed promising onco-metabolic surgical results for patients with early gastric cancer and type II diabetes. To obtain future perspectives, a large-scale multicenter study with long-term outcomes is needed. Additionally, an appropriate proximal intestinal length for the bypass should be established.

The limitation of our study is that results from patients who underwent long-limb Roux-en-Y bypass reconstruction were compared with those who underwent conventional Billroth II bypass reconstruction. So, we could not tell whether the increased length of limbs made a difference or whether Roux-en-Y itself made a difference.

In summary, onco-metabolic surgery could produce a favorable prognosis for patients with type II diabetes and gastric cancer. Basic mechanism studies of pure metabolic effects for subjects with non-morbid obesity are needed to explore this possibility. We should also investigate and

Table 3 Glycemic outcomes at 12 months after surgery by surgery type.

	Conventional Billroth II n, mean (SD)	Long-limb Roux-en Y n, mean (SD)	Fisher's exact test *p*-value
Glycemic outcome[a]			
Unchanged	55 (57.3)	53 (40.8)	
Improvement	40 (41.7)	62 (47.7)	<0.001[2]
Partial remission	1 (1.0)	4 (3.1)	
Complete remission	0 (0.0)	11 (8.5)	

FBS, fasting blood sugar.
[a] Improvement was defined as reduction in the HbA1c and FBS levels not meeting the criteria for remission but showing a decrease in the antidiabetic medication requirements; partial remission was defined as sub-diabetic hyperglycemia (FBS level, 100–125 mg/dL; HbA1c level, 6–6.4%) in the absence of antidiabetic medications; complete remission was defined as normal measures of glucose metabolism (HbA1c level, <6%; FBS level, <100 mg/dL) in the absence of antidiabetic medications.

Table 4 Logistic regressions for the improvement of diabetes control after 1 year according to surgery type and pre-operation conditions.

	Univariate Model		Multivariate Model	
	OR	95% CI	OR	95% CI
Surgery type				
Conventional Billroth II	Reference	—	Reference	—
Long-limb Roux-en-Y	1.95	(1.14—3.33)	1.97	(1.14—3.42)
Sex				
Women	Reference	—	Reference	—
Men	1.18	(0.63—2.20)	0.84	(0.42—1.65)
Age (year)	0.99	(0.96—1.02)	1.00	(0.97—1.03)
Diabetes duration				
0—9 year	Reference	—	Reference	—
≥10 years	0.72	(0.41—1.27)	0.77	(0.41—1.43)
Missing	1.37	(0.53—3.54)	1.61	(0.60—4.35)
Preoperative FBS level	1.00	(0.99—1.00)	1.00	(0.99—1.01)
Preoperative HbA1c level	1.00	(0.82—1.22)	1.01	(0.80—1.29)
Preoperative BMI	1.09	(1.00—1.19)	1.09	(1.00—1.19)

OR, odds ratio; CI, confidence interval; BMI, body mass index; FBS, fasting blood sugar; HbA1c, Hemoglobin A1c.

develop more criteria to predict favorable metabolic outcomes for selective applications of this method.

Author contribution

Jong-Han Kim is the first author and provided the data and described this article.

Yeon-Ju Huh, Young Suk Park, Do Joong Park, Joo Ho Lee and Yoon Seok Heo are co-authors and provided the data for this article.

Susan Park and Jin-Won Kwon are co-authors and provided the statistical consultation.

Seung Ho Choi is the corresponding author and provided the data and final description.

Conflict of interest

No conflict of interest statement accompanies this report.

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