

Immediate Changes of Glucose Metabolism After Gastrectomy for Early Gastric Cancer in Patients with Type 2 Diabetes

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Objectives: It is well known that type 2 diabetes (T2DM) is dramatically improved after bariatric surgery, although the mechanisms have not been clearly identified. The skill required for gastric surgery for gastric cancer is very similar to that needed in bariatric surgery. In this study, we evaluated the immediate improvement of T2DM after gastrectomy for gastric cancer.

Methods: A total of nine patients who were diagnosed with early gastric cancer (EGC) and already had T2DM underwent a 75 g oral glucose tolerance test (OGTT) before surgery and within two weeks after gastrectomy. Glucose, insulin, and c-peptide were measured before, and 30 and 60 minutes after ingesting 75 g of glucose. From these trials, we calculated the HOMA-IR, insulinogenic index, Matsuda index, and area under the curve (AUC).

Results: The mean age of participants was 57.23 ± 11.08 years and eight of them were men. HOMA-IR (4.2 vs. 2.3, $P = 0.012$) levels were decreased after surgery. There were no significant differences of insulinogenic index, fasting blood sugar before and after surgery. The Matsuda index (3.3 vs. 8.3, $P = 0.002$) was significantly increased and AUC (512.9 vs. 388.7 mg-hr/dL, $P > 0.001$) upon 75 g OGTT was significantly decreased after surgery.

Conclusions: Insulin sensitivity was immediately improved after gastrectomy for early gastric cancer in patients with T2DM.

Key Words: Early Gastric Cancer, Insulin Secretion, Insulin Sensitivity, Type 2 Diabetes

The surgical procedures for stomach cancer and obesity are very similar. Both include resection of stomach and bypass of part of the proximal intestine. Previous studies showed improvement of diabetes after gastrectomy for stomach cancer patients. One retrospective study reported T2DM was cured in 15.1% and was improved in 30.4% of individuals after stomach cancer surgery.¹ Another study showed

an improving effect for diabetes; 85% of patients that underwent Billroth-II (B-II) surgery showed improvement, and 88% of those receiving Roux-En-Y gastric bypass (RYGB) showed improvement.²

However, these results have an important bias. Almost all patients change their lifestyle after being diagnosed with cancer. They stop smoking and drinking alcohol, eat healthier food, and ex-

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ercise more. Further, almost all patients report weight loss after gastric cancer surgery, unlike other procedures. These differences can lead to the improvement of diabetes.

In cases of metabolic surgery, improvement of diabetes occurs by both weight-dependent and -independent mechanisms. The most powerful evidence of weight-independent mechanism is the improvement of hyperglycemia that occurs rapidly after surgery before patients observe weight loss.³ Moreover, glycemic improvement was noted even in the mild obesity group, and not only in the severe obesity group.⁴

Therefore, we hypothesized that immediate improvement of insulin sensitivity also occurs after stomach cancer surgery, but before being affected by lifestyle changes. In this study, we evaluated the immediate improvement of glucose metabolism after gastrectomy for gastric cancer. In addition, we investigated whether these improvements were due to changes in insulin sensitivity or β -cell function.

MATERIALS AND METHODS

Participants

Participants are patients who were diagnosed with early gastric cancer (EGC) and already had T2DM from April 2014 to March 2015 at the Kosin University Gospel hospital. All patients underwent routine surgery for gastric cancer. The present study approved by the institutional review board of the Kosin University Gospel Hospital, Republic of Korea (KUGH 2018-02-

005-001).

Anthropometric parameters and biochemical assessment

Anthropometric measurements and blood sampling were conducted prior to operation and 12-weeks after surgery. Height and weight were obtained, and body mass index (BMI) was calculated by dividing patient weight (kg) by height squared (m^2). Blood pressure was measured on the left arm with an automated blood pressure monitor. Blood sampling was done after more than eight hours fasting. Plasma glucose was measured by the hexokinase method, and total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and lipoprotein cholesterol (LDL-C) levels were measured via enzymatic procedures using AD2400 (Siemens, Germany). Triglyceride (TG) was measured by the GPO method using an AD2400 (Siemens, Germany). Insulin and C-peptide levels were analyzed with direct chemiluminescent method using an ADVIA Centaur XPT (Siemens, Germany).

Gastric cancer surgery

All patients underwent Billroth-II (B-II) or total gastrectomy with Roux-en Y (R-Y). All patients received radical oncologic resection. Radical oncologic gastric resection includes omentectomy, lymph node dissection with vagotomy, and resection margin, which should be negative. The subtotal gastrectomy was performed, with approximately 75% of the distal stomach consisting of resection B-II reconstruction of intestinal continuation. In the case of B-II reconstruction,

anastomosis was done at the site of 15 to 20 cm afferent limb. In the case of total gastrectomy, an R-Y esophagojejunostomy was performed with 40 cm of Roux limb and 20 cm of afferent limb.

Measurement of insulin sensitivity and β -cell function

All patients underwent a 75 g oral glucose tolerance test (OGTT) before and after gastrectomy. Post-surgical OGTT was done within one or two weeks after surgery. Glucose, insulin, and c-peptide were measured before, and then 30 and 120 minutes after 75 g glucose loading. OGTT was done after more than eight hours of overnight fasting. The area under the curve (AUC) of glucose was calculated before and after surgery. We performed a homeostasis model assessment of β -cell (HOMA- β)⁵ and insulinogenic index⁶ as an estimate of β -cell function. The HOMA-beta cell function (HOMA- β) was calculated by using the following formula: $(20 \times \text{fasting insulin } (\mu\text{IU/mL})) / (\text{fasting glucose (mg/dL)} - 3.5)$. The insulinogenic index was calculated by using the following formula: $(\text{insulin at 30 min} - \text{insulin at 0 min}) / (\text{glucose at 30 min} - \text{glucose at 0 min})$. Insulin sensitivity was estimated by homeostasis model assessment for insulin resistance (HOMA-IR)⁵ and Matsuda index.⁷ HOMA-IR was computed with the formula: $\text{fasting insulin } (\mu\text{IU/mL}) \times (\text{fasting glucose (mg/dL)} / 18) / 22.5$. The Matsuda index was calculated using the following formula: $10,000 / \text{square root of } [\text{fasting glucose} \times \text{fasting insulin}] \times [\text{mean glucose} \times \text{mean insulin during OGTT}]$.

Statistical analysis

Statistical analysis was carried out with SPSS 19.0 (Chicago, IL). A paired t-test was used to compare the changes of anthropometric measurements, blood pressure, serum lipid levels, and indices of β -cell function and insulin sensitivity at baseline after surgery. All data are presented as the mean and standard deviation (SD). A *P*-value < 0.05 was considered statistically significant.

RESULTS

The mean patient age was 57.23 ± 11.08 years old. From a total of 14 patients, eight were male. Patients who had DM for more than five years numbered eight. One patient used insulin, eight patients used oral hypoglycemic agents, and five patients took no medication.

The results of OGTT before and within two weeks after surgery are represented in Figure 1. Plasma glucose and insulin levels at 120 minutes after glucose loading were significantly decreased after surgery (177.6 vs. 258.1 mg/dL, *P* = 0.001, 24.6 vs. 78.1 $\mu\text{U/mL}$, *P* = 0.001, respectively). C-peptide level at 12 minutes was increased after surgery, but not at a significant level (7.6 vs. 6.2 ng/mL, *P* = 0.747).

Table 1 shows the immediate changes of insulin sensitivity and beta cell function after gastrectomy. Fasting blood sugar decreased from 136.2 to 119.2 after surgery, but this difference is not statistically significant. HOMA-IR significantly decreased after surgery. HOMA-beta and insulinogenic index increased after surgery. The

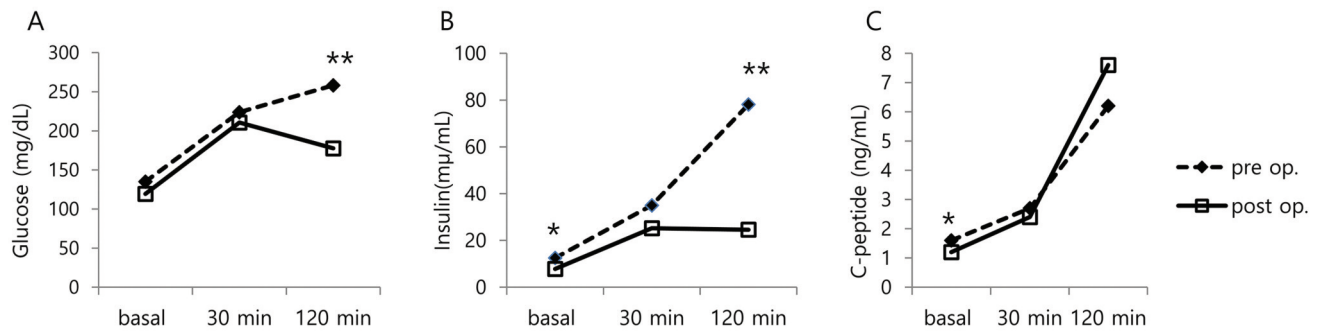


Fig. 1. The results of OGTT before and after surgery within two weeks: **A:** plasma glucose, **B:** insulin, **C:** C-peptide, significantly different between the values of pre-operation and post-operation by paired t-test (* $P < 0.05$, ** $P < 0.01$).

Table 1. Immediate changes of insulin sensitivity and beta cell function after gastrectomy

	Pre-op.	Post-op. (within 2 wks)	P-value
Fasting glucose	136.2 ± 4.2	119.2 ± 4.9	0.880
HOMA-B	72.1 ± 54.9	143.3 ± 304.5	0.400
Insulinogenic index	0.2 ± 0.2	0.2 ± 0.3	0.908
HOMA-IR	4.2 ± 2.6	2.3 ± 1.6	0.012
Matsuda index	3.3 ± 2.5	8.3 ± 5.1	0.002
AUC _{glucose}	512.9 ± 132.4	388.7 ± 78.5	0.000

AUC: Area under curve

Matsuda index significantly increased, while AUC significantly decreased after surgery.

Figure 2. exhibits individual changes of beta cell function and insulin sensitivity before and within two weeks after surgery. HOMA-β and insulinogenic index changed in various directions after surgery. On the other hand, HOMA-IR and Matsuda index showed consistency between pre- to post-operation levels.

Although eight of nine patients reduced or stopped their anti-diabetic drugs after surgery, the mean HbA1c was reduced from 7.24% to 6.5% at three months after surgery. The changes of anthropometric measurements, blood pressure, and serum lipid levels before and three months after

surgery are presented in Table 2. Weight and BMI values were significantly decreased after surgery.

DISCUSSION

Asian patients with stomach cancer have a normal body weight. In previous studies with stomach cancer patients, mean BMI values were 22-24 kg/m² in Korea.^{1,8} In this study, the preoperative mean BMI was 28.4 ± 6.4 kg/m², which is higher than previous studies; this is because this study included only EGC patients, and two patients had extremely high BMI. After gastric surgery, almost all patients showed weight loss.⁹ The participants of this study also demonstrated

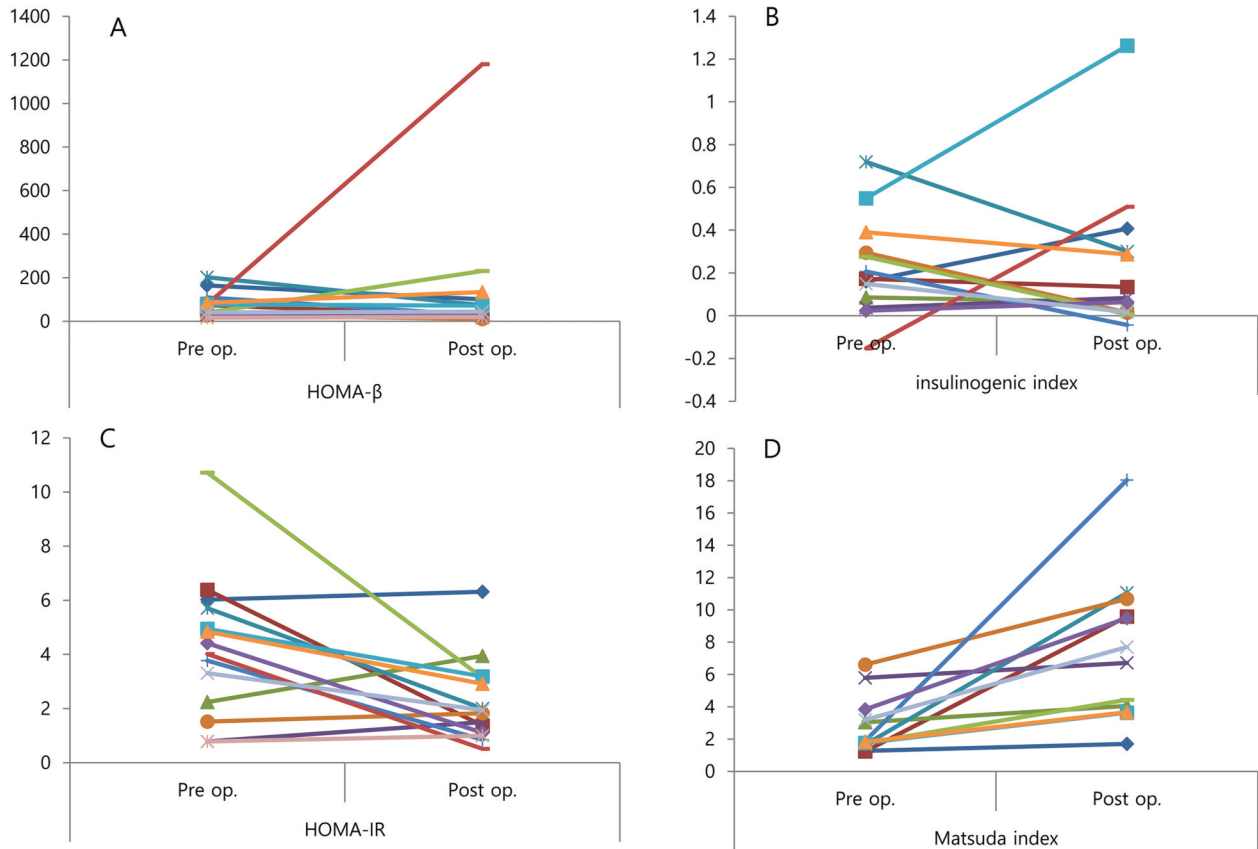


Fig. 2. Individual changes of indices of beta cell function and insulin sensitivity before and after surgery within two weeks: A: HOMA-β, B: insulinogenic index, C: HOMA-IR, D: Matsuda index.

weight loss and their mean BMI decreased to $24.5 \pm 14.4 \text{ kg/m}^2$ three months after surgery. The improved diabetes symptoms in previous studies may be due to weight loss. We performed the oral glucose tolerance test within two weeks after surgery and before significant weight loss was observed. Further, we investigated the mechanism of improving blood glucose regardless of weight reduction.

After surgery, glucose level was significantly decreased at 120 minutes after OGTT. Insulin level was also significantly decreased after fasting and at the OGTT 120 minute time point. C-peptide was only significantly decreased upon fasting (Fig. 1). $\text{AUC}_{\text{glucose}}$ was also significantly

reduced (from 512.9 ± 132.4 to 388.7 ± 78.5) after surgery. These results suggest that blood glucose level is improved immediately after surgery.

We also showed the improvement of glucose metabolism was not because improved β -cell function, but due to insulin resistance. In metabolic surgery, the most important change after surgery is dramatic improvement of diabetes symptoms. The main pathogenesis of type 2 diabetes is increasing insulin resistance and failure of insulin secretion from β -cells. Therefore, the improvement of diabetes means decreasing insulin resistance, increasing β -cell secretion, or both. Several studies revealed increased insulin

Table 2. Comparison between preoperative and postoperative (at 3 month after surgery)

	Pre-op.	Post-op. (after 3 mo.)	P-value
Age	57.23 ± 11.08		
Sex			
Male	8 (57.1%)		
Female	6 (42.9%)		
DM duration			
≤ 5 years	8 (57.1%)		
> 5 years	6 (42.9%)		
DM medication			
Insulin combination	1 (7.1%)	0 (0%)	
≥ 3 OHA	2 (14.3%)	2 (14.3%)	
2 OHA	5 (35.7%)	5 (35.7%)	
1 OHA	1 (7.1%)	1 (7.1%)	
No medication	5 (35.7%)	6 (42.8%)	
Height (cm)	162.9 ± 9.4		
Weight (kg)	72.8 ± 19.9	65.8 ± 16.3	0.002
BMI (kg/m ²)	28.4 ± 6.4	24.5 ± 14.4	0.012
Systolic BP (mmHg)	130.0 ± 24.0	113.9 ± 20.2	0.102
Diastolic BP (mmHg)	83.0 ± 6.7	62.4 ± 8.7	0.000
HbA1c (%)	7.0 ± 1.2	6.5 ± 0.7	0.278
Cholesterol total (mg/dL)	192.5 ± 61.3	178.6 ± 34.4	0.325
HDL-C (mg/dL)	47.8 ± 8.2	52.0 ± 12.9	0.327
LDL-C (mg/dL)	116.3 ± 62.3	97.2 ± 35.2	0.971
Triglyceride (mg/dL)	150.0 ± 122.0	130.3 ± 67.9	0.113
Free fatty acid (μEq/L)	642.6 ± 254.8	638.2 ± 306.5	0.909

secretion and β -cell function improvement after bariatric surgery.^{10,11} On the contrary, several studies proved the increasing β -cell function depends on the preoperative β -cell function.¹²⁻¹⁴ Our data also showed the representing factors of β -cell function did not improve (Table 1). HOMA-beta did not change individually after surgery, except in one patient (Fig. 2).

Improved insulin resistance has been demonstrated in many studies. In particular, some studies have shown that immediate improvement in insulin resistance is due to hepatic insulin resistance in the liver.¹⁵⁻¹⁷ In this study, the HOMA-IR

and Matsuda index were significantly improved immediately after surgery; almost every patient showed improved HOMA-IR and Matsuda index (Fig. 2).

These improvements may be caused by calorie restriction, not by operation. Patients should fast for several days before and after surgery. Lingvay et al. suggested rapid improvement in diabetes symptoms after gastric bypass surgery due to calorie restriction itself.¹⁸ Nevertheless, postoperative diabetes improvement is not explained by only fasting. The improvement effect is maintained after beginning to eat. In this study, the

improvement of blood glucose was maintained until three months after surgery.

A limitation of this study is the small number of patients evaluated. Prospective studies with a large number of patients may be needed. It also seems necessary to observe at long-term changes of insulin sensitivity. Patients may have had a healthier lifestyle or thorough blood sugar control after cancer diagnosis, as well as the effects of calorie restriction due to surgery. In this study, no investigation into changes in lifestyle after cancer diagnosis was conducted. These lifestyle changes can be expected to have a positive effect on insulin secretion and resistance. Another limitation is that we could not analyze differences by operation type. Nevertheless, this study is the first to analyze the immediate improvement of glucose metabolism after stomach cancer surgery. And the most reliable point of this study was the dynamic analysis of glucose metabolism by performing OGTT before and after surgery. So, this study could not just reveal changes in blood sugar level but could show the mechanism based on insulin resistance and beta cell function. In addition, only EGC patients were included, thus minimizing the impact of stomach cancer itself.

In conclusion, glucose metabolism was improved immediately after stomach cancer surgery in EGC patients. Insulin resistance was significantly improved, but β -cell function. The immediate change of glucose metabolism may be due to insulin resistance, even in early gastric cancer patients after gastrectomy. These results could be considered in the treatment of early gastric can-

cer patients with diabetes.

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