THE INFLUENCE OF TOTAL OR SUB-TOTAL GASTRECTOMY ON GLUCOSE CONTROL IN DIABETIC AND NON-DIABETIC PATIENTS

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Abstract

Objective. Although bariatric surgery including gastrectomy has recently emerged as a useful treatment for type 2 DM with obesity, it is not clear whether gastrectomy itself can have beneficial effects on glucose metabolism. Therefore, in this study, we investigated changes in blood glucose in patients with and without diabetes who underwent gastrectomy.

Methods. From Jan 2010 to May 2014, 77 patients with diabetes and 77 patients without diabetes who underwent gastrectomy at Chonbuk National University Hospital, South Korea, were included. We compared fasting plasma glucose levels and HbA1c value before and after gastric surgery.

Results. After gastrectomy, 59 patients (38.3%) showed reduced fasting plasma glucose levels at the 1 year point, and 80 patients (51.9%) exhibited reduced fasting plasma glucose at 3 years, irrespective of their diabetes status. Among 77 patients with diabetes, decreased fasting plasma glucose was observed in 22 (28.6%) and 46 patients (59.7%) 1 and 3 years after gastrectomy, respectively. In patients who exhibited reduced fasting plasma glucose after gastrectomy, the degree of reduced glucose was as follows: 56.4 ± 48.5 vs 23.2 ± 16.1 mg/dL after 1 year, 58.3 ± 52.3 vs 18.4 ± 13.7 mg/dL after 3 years, in DM and non-DM patient respectively.

Conclusions. Although there was a significant drop in mean fasting glucose after gastrectomy, not all patients experienced a drop in fasting glucose. Gastrectomy did not show a consistent association with glucose reduction in patients with and without diabetes, and in about half of the patients, fasting plasma glucose levels increased after gastrectomy. Therefore, bariatric surgery including gastrectomy needs to be performed with care in diabetes, and glucose monitoring including oral glucose tolerance tests should be done for assessing or prediction of the glucose state after gastric surgery in non-DM patients.

Key words: bariatric surgery, gastrectomy, fasting plasma glucose, HbA1c.

INTRODUCTION

Type 2 diabetes and obesity are closely related and are common diseases that can result in serious health problems these days (1). The WHO estimated that more than 700 million people will be obese by 2015 and the number of people suffering from diabetes will reach more than 438 million in 2030 (2). Insulin resistance combined with obesity is one of the main components of the pathogenesis of type 2 diabetes and, therefore, weight reduction or obesity management is an important strategy in the therapeutic intervention for glucose control in type 2 diabetes (3). However, many patients suffering from obesity cannot achieve optimal glycated hemoglobin (HbA1c) levels due to failure of weight reduction with current therapies (4). Because of these limitations, bariatric surgery including diverse types of gastrectomy has emerged as a potentially useful treatment for type 2 diabetes with obesity. There have been several observational trials (5-7) and randomized, controlled trials (8-11) that reported improved glycemic control from bariatric surgery when compared to intensive medical therapy. These results could lead to withdrawal or reduction of oral hypoglycemic agents in addition to weight loss. Weight loss may have a synergistic effect on diabetes management, and may improve insulin sensitivity, reduce hyperinsulinemia, and improve pancreatic beta cell function related to an incretin effect (12, 13). Based on these concepts, bariatric surgery is an important therapeutic option for type 2 diabetic patients.

However, such surgical procedures are not always simple and safe, and may sometimes cause considerable morbidity and mortality, although the incidence of complications is low. Furthermore, little evidence is available on the long-term effects of bariatric surgery. The Swedish Obese Subjects (SOS)

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study (14), which has provided the best evidence thus far, was initiated more than 20 years ago and the surgical procedures used might not reflect current practice. Also, our understanding of the mechanisms of diabetes remission following bariatric surgery is still very limited (15). In addition, diabetes remission rates differed according to the type of surgery that patients received, which implies that the mechanism of diabetes remission is complex and encompasses a variety of anatomical, physiological, and molecular changes (16). Moreover, it is not clear whether gastrectomy has beneficial effects on glucose metabolism, even though animal studies suggest that bariatric surgery increases insulin secretion and improves enteroinsular responses, specifically of the main incretin hormones such as glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) (17-19). Above all, there is no study comparing the blood glucose-lowering effect in patients with and without diabetes after undergoing a gastrectomy. Therefore, if we understand the fasting blood glucose pattern with and without diabetes after gastrectomy, we will be able to speculate on the effect of gastrectomy on glucose metabolism. In this current study, we investigated changes in glucose and HbA1c levels according to subtotal or total gastrectomy in patients with type 2 diabetes and without diabetes.

METHODS

Study design

Patients from Jan 2010 to May 2014 were reviewed and a total of 77 diabetic patients who underwent total or subtotal gastrectomy to treat gastric cancer or GIST (gastrointestinal stromal tumor, n=4) were included. A retrospective and matched study was conducted, and data was gathered on age, sex, BMI, duration of diabetes mellitus, and size of the gastric

reservoir and type of anastomosis. Fasting plasma glucose and HbA1c levels were also assessed at baseline and at 1 and 3 years after the gastrectomy. Fasting plasma glucose was repeatedly measured in a consistent fashion during follow-up periods. Antecubital venous blood was withdrawn after a 10 hour overnight fast, collected in tubes containing EDTA and fluoride and centrifuged within 2 hours. Plasma glucose was assayed with a glucose-oxidase method (ADVIA 2400, Siemens, Germany). HbA1c data was not available for subjects without diabetes. We excluded patients who were expired, or did not have any data on their fasting plasma glucose levels at the regular follow-up periods. Also, non-DM group of 77 patients was matched on the basis of age, sex, and body mass index to those of DM patients before gastrectomy.

Statistical analysis

We used the independent-samples T test to compare the baseline characteristics between two groups and draw graphs. $p < 0.05$ was considered statistically significant. Continuous variables with a normal distribution were presented as mean $\pm$ SD. Repeated measures analysis with ANOVA was used to analyze and compare continuous laboratory parameters between patients with and without diabetes in different categories in respect with bariatric surgery indication (Body Mass Index) and different surgical technique. All statistical analyses were conducted with the use of PASW statistics software, version 18.0.0.

RESULTS

Baseline characteristics

Baseline characteristics of patients are summarized in Table 1. Diabetes (DM) and non-diabetes (non-DM) groups were generally well matched for age,

Table 1. Baseline characteristics of participants and fasting plasma glucose (FPG) values according to the time passage*

	DM (n=77)	Non-DM (n=77)
Age (years)	64.6 $\pm$ 8.7	64.5 $\pm$ 11.2
Female/Male	25/52	26/51
BMI† (Kg/m ²)	24.7 $\pm$ 3.5	24.8 $\pm$ 3.6
FPG (mg/dL)	170.8 $\pm$ 60.0	117.2 $\pm$ 20.7
HbA1c (%)	7.6 $\pm$ 1.3 %	-
Total cholesterol (mg/dL)	154.23 $\pm$ 2 mg/dL	158.29 $\pm$ 1 mg/dL
Triglycerides (mg/dL)	175 $\pm$ 31 mg/dL	168 $\pm$ 38 mg/dL
LDL cholesterol (mg/dL)	88 $\pm$ 19 mg/dL	90 $\pm$ 24 mg/dL
HDL cholesterol (mg/dL)	31 $\pm$ 21 mg/dL	35 $\pm$ 18 mg/dL

* The values are presented as means $\pm$ SD. There were no significant differences between two groups in baseline characteristics except fasting plasma glucose ($p < 0.01$).

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

DM = Diabetes Mellitus, Non-DM = Non-Diabetes Mellitus, BMI = Body Mass Index, FPG = Fasting Plasma Glucose.

Table 2. The changes of anti-diabetic medication after gastrectomy in DM patients

	Baseline	1 year	3 years
Number of oral hypoglycemic agents of DM group	1 (34) 2 (22) 3 (21)	0 (3) 1 (36) 2 (24) 3 (14)	0 (1) 1 (30) 2 (26) 3 (20)
Patient number of insulin combination	9	6	10
Patient number of medication increase		6	9
Patient number of medication decrease		10	7
Patient number of remission from DM	0	3	1
Number of new onset DM of non-DM group	0	6	9

Figure 1. (a) Change of mean fasting plasma glucose value after gastrectomy according to the time passage in DM and non-DM patients. In DM patients, FPG was reduced after 1 year after gastrectomy, however, this trend was reversed after 3 years of gastrectomy. In non-DM patients, FPG was increased according to the time passage. (b) In DM patients, HbA1c levels were not changed significantly after gastrectomy irrespective of time passage. The value was presented as mean $\pm$ SD. * $P < 0.05$, vs before gastrectomy.

sex, and BMI. There were no significant differences in the data between the two groups at baseline ($p > 0.05$) except for fasting plasma glucose levels ($p < 0.01$). In diabetic patients, treatment with glucose lowering agents were continued before operation and these managements have been restored at observation point after gastrectomy although there were changes partly in the dose of these agents as shown in Table 2.

Fasting plasma glucose levels

At the time of 1 year after gastrectomy, fasting plasma glucose (FPG) level was reduced significantly in DM group ($P < 0.05$), however, non-DM group showed a mild increased pattern on the contrary ($p = 0.098$) as shown in Fig. 1(a). The average value of FBG was increased at 3 years compared with 1 year after the gastrectomy in the DM group. Notably, persistent increased levels of average FPG were observed in the

Figure 2. The number of patients that showed increase or decrease in glucose value at 1 year and 3 years after gastrectomy in (a) DM and (b) non-DM patients. In DM group, the number of patients showing increased FPG value was higher significantly than the number of patients that FPG decreased after gastrectomy at 1 year point, but this trend was reversed at 3 years point after gastrectomy although significant difference was not present. In non-DM patients, the number of patients was not different significantly irrespective of time passage after gastrectomy. The value was presented as mean $\pm$ SD.

non-DM group. The number of patients showing reduced FPG was 22 and 37 in DM and non-DM, respectively as shown Figs 2 and 3. The reduced degree of FPG was 56.4 ± 52.3 mg/dL in DM group and 23.2 ± 13.7 mg/dL in non-DM group as shown in Fig. 4 (a). The number of patients showing increased FPG was 55 in DM and 40 in non-DM patients and the average increased value was 51.2 ± 48.5 mg/dL and 32.1 ± 16.0 mg/dL in DM and non-DM group, respectively as shown in Figs 2, 3, and Fig. 4(a). After 3 years of gastrectomy, the average FPG of both DM and non-DM groups were increased compared to 1 year point after gastrectomy as shown in Fig. 1(a). The number of patients that showed decreased FPG was 46 in DM and 34 in non-DM group and the average decreased value was 58.3 ± 42.1 mg/dL in DM and 18.4 ± 15.3 mg/dL in non-DM group. The number of patients that were observed as increased state in FPG was 31 in DM group and the average value of increase

Figure 3. The percentile comparison of the patient number according to increased or decreased glucose value at 1 year and 3 years point after gastrectomy in (a) DM and (b) non-DM patients. The value was presented as mean $\pm$ SD.

was 56.3 ± 38.2 mg/dL. In non-DM group, 43 patients showed increased average of FPG of 42.1 ± 15.3 mg/dL as shown in Figs 2, 3 and Fig. 4(a).

HbA1c levels

Average HbA1c was 7.6 ± 1.3 % in the DM group and this value showed a decreased trend after 1 year compared to baseline level, however, there was no significant difference. And, an increased level was insignificantly observed after 3 years, similar to the change seen in FPG levels, as shown in Fig. 1. The number of patients that showed improved glycemic control was not significantly different compared to the number of patients whose glycemic control worsened regardless of time passage after gastrectomy (54.1% vs 45.9% after 1 year, 47.3% vs 52.7% after 3 years, $p > 0.05$). The degree of HbA1c change in each group of DM patients according to the increase or decrease was $+0.5 \pm 0.2$, -1.2 ± 0.5 , $+0.8 \pm 0.3$, and -1.1 ± 0.4 (%) at 1 year and 3 years after gastrectomy, respectively. Interestingly, 9 patients among non-DM patients (11.7%) were diagnosed as type 2 diabetes, however, the remission number of DM was only 3 patients in DM group after 3 years of gastrectomy as shown in Table 2.

Indication of bariatric surgery

The number of patients who were $\text{BMI} \geq 27.5$ kg/m² was 16. Average glucose level was 176.1 ± 62.2 mg/dL in the surgical indication group and 166.9 ± 58.0 mg/dL in the $\text{BMI} < 27.5$ kg/m² group. At the time of 1 year after gastrectomy, FPG level was 136.1 ± 61.9 mg/dL. Average FPG level was 140.0 ± 41.5 mg/dL,

Figure 4. The degree of increased or decreased value of (a) fasting plasma glucose and (b) HbA1c in DM and non-DM patients at 1 year and 3 years point after gastrectomy. In DM group, there were no significant differences in the degree of FPG change irrespective of decrease or increase at each 1 year and 3 years point after gastrectomy. However, the degree of decreases in the HbA1c value was larger than the degree of increases at each point. In non-DM patients, the degree of increased change was higher than that of decrease in FPG value on the contrary. The value was presented as mean $\pm$ SD. * $P < 0.05$, vs before gastrectomy. ** $P < 0.05$, vs after 1 year of gastrectomy.

after 3 years of operation, FPG level showed 157.9 ± 54.0 mg/dL and 157.6 ± 55.7 mg/dL in the $\text{BMI} \geq 27.5$ kg/m² and $\text{BMI} < 27.5$ kg/m² group, respectively. There were no significant differences between these groups, and glucose pattern was not different. Average HbA1c level was $7.4 \pm 1.5\%$ and $7.5 \pm 1.2\%$ in the $\text{BMI} \geq 27.5$ kg/m² and $\text{BMI} < 27.5$ kg/m², respectively. Decreased glucose level was observed after 1 year in the surgical indication group ($6.5 \pm 0.8\%$ vs $7.5 \pm 1.3\%$) compared to non-indication group. This trend was maintained after 3 years similar to 1 year level ($6.7 \pm 0.8\%$ and $7.6 \pm 1.1\%$) (Fig. 5).

Type of anastomosis

In 77 diabetic patients of gastrectomy, the number of subtotal gastrectomy with B-I (Billroth 1) anastomosis was 61 patients. B-II (Billroth-2) anastomosis was performed in 4 patients and other 4 patients were operated with E-G (Esophago-Gastric) anastomosis. 4 patients' records showed REY G-J (Roux-en-Y gastro-jejunostomy) and the last 4 patients were operated with wedge resection because of GIST. Average gastric reservoir were 2.73/5 (total gastric volume is 5) in the B-I anastomosis, 2.5/5 in the B-II, 2/5 in the REY G-J, and 3.75/5 in the E-G, respectively. Group of patients performed REY G-J technique showed persistent decreased level of average glucose

Figure 5. Change of mean fasting plasma glucose (a) and HbA1c values (b) after gastrectomy according to the time passage in BMI ≥ 27.5 kg/m² and BMI < 27.5 kg/m² patients. There were no statistically differences between two groups in the FPG level. Decreased level was significantly observed after 1 year in the surgical indication group. However, this value showed increased trend after 3 year. There were statistically significant differences between two groups according to the pre-operative BMI level. The value was presented as mean $\pm$ SD. * $P < 0.05$, vs before gastrectomy. ** $P < 0.05$, vs after 1 year of gastrectomy.

Figure 6. Change of mean fasting plasma glucose (a) and HbA1c values (b) after gastrectomy according to the time passage in the type of anastomosis. REY G-J technique showed persistent decreased level of average glucose, and patients of E-G anastomosis showed the lowest average FPG levels among all groups. However, all types of subtotal gastrectomy showed trends of increased or not changed FPG levels over 3 years except wedge resection for GIST.

and group of patients of E-G anastomosis showed the lowest average FPG level. However, all types of subtotal gastrectomy showed glucose levels of increased state or did not show any changes over 3 years except wedge resection for GIST. Average HbA1c levels were also decreased over 3 years in the wedge resection group. However, other techniques of operation did not show any change or increase in the HbA1c level over 3 years (Fig. 6).

DISCUSSION

The International Diabetes Federation (20) and the American Diabetes Association (3) have recommended bariatric surgery as an appropriate therapeutic approach for type 2 diabetic patients with reasonable surgical risk who are unable to achieve or sustain health goals. However, the long-term efficacy of surgery is still unclear. Brethauer *et al.* reported that

the efficacy and durability of bariatric surgery affects the recurrence and remission of type 2 DM (6). Recurrence after initial remission was observed in 19% of patients over 6 years, particularly in those with prolonged disease duration. Another study reported that diabetes can recur in about 20-30% of patients who initially achieve remission over 5 years after bariatric surgery (6, 21), and fewer than 20% of those with initial remission remain in remission after 20 years (22). Recently, bariatric surgery studies have shown markedly improved outcomes in glycemic control in patients with severe obesity and type 2 DM when compared with medical therapy (11). In this study, more patients achieved target glycemic goals with 3 years of intensive medical therapy plus bariatric surgery than did those with medical therapy alone, although the patients with medical therapy were not intensified according to published guidelines (23). However, low-density lipoprotein cholesterol and blood pressure were not significantly reduced, and the incidence of nephropathy was increased in the surgical groups. This result can be explained by a long-term increase in urinary oxalate excretion in gastric bypass surgery (24) or fat malabsorption and subsequent reductions in the intraluminal free calcium concentration (25). Therefore, bariatric surgery may be an option, but the outcomes may not be superior to intensive medical therapy.

Ultimately, bariatric surgery seems to be an effective procedure for controlling plasma glucose and can lead to substantial weight loss in patients with diabetes. However, so far, few studies have compared glucose control in patients with and without diabetes after gastric surgery including bariatric surgery irrespective of obesity. The main aim of our study was to assess the indirect glucose-lowering effects related to gastric surgery. In this study, there was a persistent increase in the average fasting plasma glucose value and also decrease in the proportion of patients who declined fasting blood glucose levels after 3 years in the non-diabetic group. Furthermore, nine patients without diabetes were prescribed oral hypoglycemic agents because new diabetes occurred after gastrectomy, even though some of patients had risk factors of chronic disease before surgery. In recent years, there have been several studies suggesting the expansion of indications for bariatric surgery (26, 27), even though BMI is below 27.5 kg/m² (28). However, according to our data, a patient with BMI < 35kg/m² and type 2 DM cannot expect a sustained glucose lowering effect after gastric surgery although this operation was not performed for bariatric surgery.

In patients with diabetes, the average fasting

plasma glucose value was increased again at 3 years compared to 1 year after gastrectomy and this was higher than non-diabetic groups. In addition, the proportion of decreased fasting plasma glucose was less than expected (28.6%) even though patients with diabetes had a continuous prescription of diabetes medication and insulin therapy. In other words, about 70 percent of patients with diabetes showed increased fasting plasma glucose levels after 1 year and 40 percent after 3 years. Also, as mentioned above, increased fasting plasma glucose was observed in more than half of the patients without diabetes after 1 year and that number increased after 3 years. The degree of increase in the glucose values of both groups was not significantly different according to diabetes presence and follow-up duration. In this study, gastrectomy did not show consistent results in glucose reduction in diabetic and non-diabetic groups. Moreover, in the group of patients with diabetes, 40 of the total patients maintained glucose lowering management after the operation. We also analyzed the patients in different categories in respect with the indication and anastomosis. Significant decreased HbA1c level was observed in the bariatric surgical indication group. However, long-term postoperative blood glucose lowering effect has not been proved because there were increased trends of FPG and HbA1c levels after 3 years.

There was a report that laparoscopic sleeve gastrectomy (LSG) was effective in the glucose control diabetes without bypassing any segment of the gut besides diverse metabolic surgery (29, 30). According to our result, REY G-J of surgical technique can be chosen for the best option in glucose control in diabetes. However, there was a limitation that the number of patients in each operation group was very small and this surgical technique was just for gastric cancer treatment not diabetes management. It may be required to need a larger trial with subgroups regarding the type of gastrectomy and type of anastomosis.

As is well known, diabetes can be diagnosed with three tests including HbA1c, fasting or random plasma glucose, and oral glucose tolerance tests. The one of common complications after gastrectomy is dumping syndrome, which is a condition where ingested food bypasses the stomach too rapidly and enters the small intestine largely undigested. In our study, change in mean fasting plasma glucose levels were different from diabetic and non-diabetic groups and post prandial glucose levels can be more important in gastrectomy patients due to dumping syndrome. Therefore, we suggest that the glucose loading test may be more helpful for diagnosing diabetes in

gastrectomy patients, especially in pitfall patients that show a discrepancy between HbA1c and fasting plasma glucose values.

There are several limitations in our study. First, the low number of reviewing patients was performed diverse type gastric surgery due to gastric malignancy or GIST irrespective of diabetes or obesity. Therefore, further research is needed to investigate the metabolic parameters in gastrectomy patients without other underlying diseases. Second, BMI is an important factor that affects the change in metabolic profiles. However, BMI data of patients in this study was influenced by underlying diseases and associated care for these diseases. Therefore, comparing BMI may be more helpful to show the gastrectomy effect after curing other underlying diseases. Third, basically, glucose levels may be influenced by many factors and the degree is more dynamic in diabetic patients than in non-diabetic patients. Therefore, it is difficult to conclude whether gastric surgery itself may decrease or increase glucose level in DM and non-DM subjects. Fourth, this present study included the gastric resection with no intention of restriction or malabsorption, and so our results cannot be connected to the principle of bariatric surgery. We just would like to suggest the necessity of reconsideration in the effect of gastrointestinal handling for glucose control in diabetes. Therefore, the meaning of this study is trial to show the glucose pattern after gastric surgery. Moreover, we would like to indicate the possibility of glucose control worsening, and furthermore, diabetes occurrence after gastric surgery should be monitored besides glucose lowering effect.

In conclusion, gastrectomy did not show consistent results in glucose reduction in patients with and without diabetes in our study. Moreover, over half of the analyzed patients showed an increase in fasting plasma glucose levels after gastrectomy, although gastrectomy in this study was performed due to gastric malignancy treatment. Moreover, to extend this concept, gastric operation for bariatric surgery should be performed with caution of possibility that may worsen glucose metabolism on the contrary although operation technique in the present study cannot be connected to the bariatric surgery. Therefore, management with an endocrinologist needs to be continued after bariatric surgery for early detection of diabetes occurrence. In addition, an oral glucose tolerance test may be needed to assess the glucose control state or to predict diabetes occurrence after gastrectomy.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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