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Intestinal glycolysis visualized by FDG PET/CT correlates with glucose decrement after gastrectomy

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Abbreviations: BI, Billroth I; BII, Billroth II; BMI, body mass index; CI, confidence interval; FDG, ^{18}F-fluorodeoxyglucose; OR, odds ratio; PET/CT, positron emission tomography/computed tomography; RY, Roux-en-Y; TLG, total lesion glycolysis

Abstract

Gastrectomy method is known to influence glucose homeostasis. ^{18}F-fluorodeoxyglucose (FDG) PET/CT acquired after gastrectomy often reveals newly developed physiologic small bowel uptake. We correlated newly developed small bowel FDG uptake and glucose homeostasis in post-gastrectomy gastric cancer patients. We retrospectively analyzed 239 non-diabetic patients who underwent staging and follow-up FDG PET/CT before and after gastrectomy for gastric cancer. Post-operative small bowel glycolysis was quantified by recording intestinal total lesion glycolysis (TLG). TLG was assessed with regard to surgical method (Billroth I, II [BI, BII], Roux-en-Y [RY]), fasting glucose decrement (≥10 mg/dL), and other clinical factors. Patients' weight, fasting glucose, cholesterol, TLG, and body fat significantly decreased after surgery. Glucose decrement was significantly associated with fasting glucose, surgical methods, total cholesterol, TLG, and total body fat on univariate analysis. Multivariate analysis showed that BII surgery (odds ratio: 6.51) and TLG (odds ratio: 3.17) were significantly correlated with glucose decrement. High small bowel glycolysis (TLG>42.0) correlated with glucose decrement in RY patients. Newly developed small bowel glycolysis on post-gastrectomy FDG PET/CT is correlated with glucose decrement. These findings suggest a potential role of FDG PET/CT in the evaluation of small bowel glycolysis and glucose control.

Introduction

The incidental finding that bariatric surgery ameliorates hyperglycemia has emerged as an important treatment consideration in obese patients with type 2 diabetes (T2DM). Multiple randomized clinical studies have shown a clear benefit of bariatric surgery over medical therapy in T2DM management.(1-6) Despite the clear clinical evidence of hyperglycemia improvement after bariatric surgery [12, 13], the mechanisms underlying the resolution of T2DM by bariatric surgery have not been fully elucidated.

The most widely used Positron Emission Tomography/Computed Tomography (PET/CT) radiotracer is ^{18}F-fluoro-2-deoxyglucose (FDG). During the imaging work-up for diagnosis of malignancies, FDG PET/CT identifies malignant foci by targeting the high glycolytic rate of cancer cells. However, FDG uptake pattern also reflects the distribution of physiological glucose metabolism and secretion. During the clinical follow-up of postoperative gastric cancer patients, we have noticed a significant number of patients who develop intense FDG uptake in the bowel, despite having no discernible lesions on contrast-enhanced CT or evidence of recurrence during follow-up studies. This observation suggests that newly developed FDG uptake in the bowel after gastrectomy may be physiological, rather than pathological uptake. However, no studies have evaluated the clinical significance of this phenomenon.

Recent studies have suggested that the small bowel might have a pivotal role on regulating glucose homeostasis.(7-9) Two recent animal studies that focused on the biochemical role of the small bowel on glucose homeostasis after bariatric surgery have suggested that glucose may be excreted into the intestinal lumen via sodium-glucose cotransporter (SGLT) proteins, as well as increased glucose metabolism by the enteric cells themselves.(8; 9) Based on these findings, evaluation of FDG bowel patterns after gastrectomy may be beneficial in elucidating the mechanisms of bariatric surgery on glucose

homeostasis, as it provides a non-invasive picture of changes in glucose metabolism of small bowel.

The purpose of this study was to evaluate changes in FDG uptake patterns in the small bowel in patients who underwent gastrectomy for gastric cancer, and to investigate the relationship between small bowel FDG uptake and serum glucose changes.

Materials and Methods

Patient selection and imaging analysis

Between December 2005 and May 2015, a total of 669 patients underwent FDG PET/CT within 90 days before gastrectomy and had one follow up FDG PET/CT after gastrectomy. All patients had baseline glucose levels checked on both days of PET/CT. We excluded 430 patients who had pre-operative glucose levels of higher than 126 mg/dL or had malignancies on postoperative FDG PET/CT. We excluded diabetic patients because oral anti-hyperglycemic agents, especially metformin administration, is known to cause increased bowel uptake, which can be a confounding factor in determining the effect of surgery on bowel uptake of FDG. Furthermore, patients who received neoadjuvant or adjuvant chemotherapy within 3 months prior to FDG PET/CT were also excluded. The final patient population was 239 patients. All patients had baseline glucose levels checked on both days of PET/CT. All serum samples including glucose levels were acquired after fasting for more than 8 hours. Out of the 239 patients, 128 patients had decrease in serum glucose levels after surgery. The average reduction in serum glucose was 10 mg/dL. Diabetic patients were excluded because administration of oral anti-hyperglycemic agents can be a confounding factor in determining the effect of surgery on bowel uptake of FDG. All patients' weight, body mass index (BMI), and samples for biochemical analysis were collected within 2 days of preoperative and postoperative FDG PET/CT. Changes in fasting glucose levels were stratified into patients with a $\geq$10 mg/dL decrease after surgery (Group 1; G1) or a <10 mg/dL decrease (Group 2; G2) after surgery. This study was conducted in accordance with the Declaration of Helsinki and was approved by our institutional review board (No. 4-2016-0342).

PET/CT protocol and imaging analysis methods are described in the online supplemental materials.

Statistical analysis

The Kolmogorov-Smirnov test was performed to evaluate normality, and *P* values > 0.05 were assumed to fulfill the normality assumption. Receiver operating characteristic (ROC) analysis was performed to determine the postoperative intestinal glycolysis (TLG) cut-off value with the highest sensitivity for predicting patients with a ≥10 mg/dL decrement of fasting glucose (G1) after surgery. Patients with a <10 mg/dL decrement of fasting glucose were categorized as G2. This cut-off was used to group patients according to high or low intestinal glycolysis. The Wilcoxon signed-rank test was performed to compare changes in imaging and clinical indices before and after gastrectomy. The Mann-Whitney U test was performed to compare imaging and clinical factors with bowel uptake changes or fasting glucose changes. All bivariate factors were evaluated with either chi-squared test or Fisher's Exact Test, and linear-by-linear association for tri-variate factors. A multivariate logistic analysis was performed, including statistically significant or clinically significant factors for predicting G1 on Mann-Whitney U test. Finally, the chi-square test was performed to assess the prediction of fasting glucose decrement with TLG according to surgical method. Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc.), and *P* values < 0.05 were considered statistically significant. The data were expressed as median (95% confidence interval; CI) for continuous variables and number of patients for nominal variables.

Results

Patient characteristics before and after surgery

Of the 239 patients, 81 underwent Billroth I surgery (BI), 56 underwent Billroth II surgery (BII), and 102 underwent RY (16 subtotal gastrectomy, 86 total gastrectomy). All patients underwent gastrectomy because of stomach cancer (early gastric cancer in 66 patients, advanced gastric cancer in 173 patients). The median FDG PET/CT follow-up period after surgery was 12.4 months (range, 10.5–27.4 months). Table 1 shows clinical and imaging indices before and after surgery. After surgery, small bowel FDG uptake significantly increased in both intensity (SUVmax, from 2.9 preoperatively to 4.3 postoperatively) and amount (TLG, from 2.0 preoperatively to 39.8 postoperatively). There was no discernable pattern in FDG uptake in the small bowel, as it ranged from single foci to multifocal increased FDG uptake. Body weight, BMI, and fasting total cholesterol were also significantly reduced after surgery, and fat analysis indicated significant postoperative decreases in both abdominal visceral adipose tissue (AVAT) and abdominal subcutaneous adipose tissue (ASAT). Other clinical indices shown in Table 1 were not significantly different after surgery.

Clinical and metabolic changes in patients with ≥10 mg/dL decrement of fasting glucose after gastrectomy

Among 239 enrolled patients, 61 (25.5%) experienced ≥10 mg/dL decrement in fasting glucose (G1after surgery. Before surgery, G1 patients had significantly higher fasting glucose than G2 patients (Table 2). After surgery, G1 patients experienced a significant drop

in fasting glucose, and G2 patients experienced a mild increase in fasting glucose (fasting glucose: 87 [82–92] and 95 [89–105] mg/dL, P<0.001). This indicates that patients with higher basal fasting glucose were more likely to have significant drop of glucose levels after surgery.

BMI was also significantly higher in G1 compared to G2 patients before surgery, but in contrast to glucose, BMI became comparable between G1 and G2 after surgery (BMI: 21.6 (19.7–23.0) and 21.0 (19.1–22.6) kg/m^2, *P*=0.344). Similarly, G1 patients had significantly higher preoperative total abdominal fat, ASAT, and AVAT compared to G2 patients. Fat measurements also decreased significantly after surgery in the G1 group, leading to similar values between G1 and G2. Stratified according to surgical method, 11.1% (9/81), 41.1% (23/56), and 28.4% (29/102) of patients who underwent BI, BII, and RY, respectively, were assigned to the G1 group (Figure 1A). There were no preoperative or postoperative differences in age, serum total cholesterol, uric acid, total protein, and albumin level between the G1 and G2 groups. The differences in clinical characteristics between the G1 and G2 groups were more prominent in obese patients with BMI above 23 kg/m2, which is the cut-off for obesity in Asian populations (Supplemental Table 1). Before surgery, 31 of 61 G1 patients (50.8%) and 75 of 178 G2 patients (42.1%) were obese. Among patients with BMI above 23 kg/m2, patients classified as G1 had significantly higher fasting glucose, serum total cholesterol, total abdominal fat, ASAT, and AVAT before surgery than patients classified as G2. After surgery, these parameters decreased more substantially in group G1 than G2 and resulted in no statistical difference between the G1 and G2 groups after surgery (Supplemental Table 1). There was no difference in glycolytic bowel activity between the G1 and G2 groups before gastrectomy in both obese and non-obese patients. However, obese G1 patients demonstrated significantly increased glycolytic activity of the small bowel after

surgery compared with obese G2 patients (86.3 [22.1–353.1] vs. 39.8 [11.0–156.3], P=0.048). In non-obese patients, FDG PET/CT revealed significantly higher SUVmax together with decrement of fasting glucose in the G1 group after gastrectomy.

Correlation of postoperative small bowel uptake and fasting glucose decrement

ROC analysis indicated that a postoperative TLG cut-off of 42 had the highest sensitivity to predict ≥10 mg/dL serum glucose reduction (sensitivity 65.6%, AUC=0.621, *P*=0.003). Patients were re-grouped according to high small bowel uptake (TLG > 42) or low small bowel uptake (TLG ≤ 42) (Supplemental Table 2). The majority of patients with high intestinal uptake (n=115) underwent RY (n=62, 53.9%), followed by BI (n=32, 27.8%) and BII (n=21, 18.3%) (Figure 1B). Patients with high small bowel uptake after gastrectomy experienced significant reductions of fasting glucose (-5.0 mg/dL vs. 1.5 mg/dL, *P*<0.001) and postoperative fasting glucose (91 mg/dL *vs.* 93.5 mg/dL, *P*=0.045) compared to those with low small bowel uptake. Furthermore, they demonstrated significantly greater decreases in body weight, BMI, serum total cholesterol, total body fat, and AVAT after surgery.

Glycolytic activity of the small bowel as an independent factor for fasting glucose decrement after gastrectomy

Multiple logistic analysis was performed to determine factors that could predict G1 status (≥10mg/dL decrement of fasting glucose) after surgery (Table 3). BII surgery was the strongest predictor for decreased fasting glucose (odds ratio [OR] = 6.51, 95% confidence

interval [CI]: 2.47–17.18, *P*<0.001), and RY was also positively associated with decreased fasting glucose (OR=1.98, 95% CI: 0.78–4.99, *P*=0.148), but did not reach statistical significance in multivariate analysis. Furthermore, glycolytic activity of the small bowel was a significant risk factor for decreased serum glucose (OR=3.17, 95% CI: 1.49–6.73, *P*=0.005). Age, sex, change in BMI, preoperative body fat, and preoperative total cholesterol were not significant predictors of postoperative glucose decrease.

The correlation between small bowel uptake and surgical methods was also analyzed. Compared to BII or BI patients, a significantly higher proportion of RY patients presented with small bowel uptake after gastrectomy (Supplemental Table 3, Figure 1B). Furthermore, the correlation between surgical method and development of fasting glucose decrement was only seen in RY patients with increased glycolytic activity (Figure 1C).

Finally, to better predict serum glucose decrement in clinical settings, we sub-analyzed the decrease of serum glucose levels and small bowel uptake according to surgical method and BMI (Supplemental Table 3). High small bowel uptake did not predict changes in fasting glucose in patients who underwent BI or BII, but significantly predicted glucose level decrement in patients who underwent RY.

Discussion

In this study, we identified a potential image-based semi-quantitative marker of small bowel glycolytic activity that correlates with serum glucose decrement. We analyzed the correlation between increased glycolytic activity in the small bowel and changes in fasting serum glucose after gastrectomy. The major findings of this study include: i) the gastrectomy method-dependent increment of glycolytic activity in the small bowel, especially in obese patients; ii) the independent correlation of increased intestinal glycolytic activity with decrement of fasting glucose after gastrectomy; and iii) the correlation between increased intestinal glycolytic activity and decrement of fasting glucose, which was significantly stronger in patients treated with RY.

A variety of gastrectomy procedures have been developed for bariatric surgeries, and the choice of gastrectomy method has been established to have a significant effect on glucose homeostasis and weight loss.(10) However, the major mechanisms underlying this effect have not been fully elucidated in humans. Some studies suggest that gut-related hormones are the main factor, and others propose that improved glucose homeostasis is a secondary phenomenon caused by body weight reduction.(11; 12) Still others have shown that bariatric surgery improved glucose homeostasis independently from changes in body weight after surgery.(13) Regardless, gastrectomy enhances the secretion of incretin, which is followed by an improvement in hyperglycemia. (14) The role of gastric bypass in diabetes control has been studied extensively using animal models, and one of the proposed mechanisms for improved hyperglycemia after gastrectomy is the foregut and hindgut hypothesis for incretin secretion. Altered gastroenterological physiology derived from both duodenal exclusion (foregut) and rapid exposure of undigested nutrients to the distal ileum (hindgut) may induce increased incretin secretion leading to improved hyperglycemia in animal models. (12; 15)

Other gut hormones including adiponectin, leptin, PYY3-36, oxyntomodulin, and ghrelin were also reported to be associated with improved glucose homeostasis after gastrectomy. (12)

We evaluated patients who underwent gastrectomy for stomach cancer, which is similar to bariatric surgery procedure used for obesity treatment. BI surgery can be considered functionally analogous to vertical sleeve gastrectomy, as both surgical methods results in food passing through the duodenum, despite the differences in stomach resection method. RY and B2 gastrectomy can be considered to be analogous to Roux-en-Y gastric bypass in that the duodenum is bypassed. The differences between RY and BII in cancer surgery are the amount of stomach resected, and the higher likelihood of retrograde migration of food into the afferent loop in BII. Also, our institution did not perform Braun anastomosis (entero-enterostomy between afferent and efferent loop) to reduce bile reflux into the stomach at this time. The major physiologic differences between RY and BII are bile reflux.

Elucidation of the mechanism involved in small bowel uptake and decreased fasting glucose after gastrectomy is beyond the scope of this study. However, a possible mechanism has been proposed in animal studies. Two recent murine studies evaluating the mechanisms by which bariatric surgery contributes to the resolution of diabetes have suggested that glucose may be excreted into the intestinal lumen via sodium/glucose cotransporter (SGLT), as well as observing increased glucose metabolism by the enteric cells themselves. (8; 9) Our study may provide supporting clinical evidence to this theory.

The present study has several limitations. First, we could not perform mechanistic experiments to test the relationships between increased FDG uptake in the small bowel and decrement of fasting glucose after gastrectomy. However, to our knowledge, this study is the first to demonstrate quantitative measurements of postoperative FDG uptake in the small bowel and changes to glucose homeostasis status in the clinical setting. The novel evidence

of this clinical study supports the metabolic role of the small bowel. Second, we evaluated non-diabetic patients. However, in light of the abnormal FDG uptake caused by anti-hyperglycemic agents, the results of this study could provide evidence free from underlying medical biases. Finally, due to the retrospective nature of this study, investigation of the possible metabolic parameters was not possible. Further studies evaluating the appearance of bowel uptake after gastrectomy in diabetes patients are needed to validate these initial results.

In conclusion, this study evaluated the clinical significance of increased glycolytic activity of the small bowel with fasting glucose decrement after gastrectomy. Even in patients with neither diabetes nor severe obesity, postoperative changes in fasting glucose correlated with increased glycolytic activity of the small bowel, and this relationship was more significant in patients who underwent RY. Together with several previously reported biomarkers, glycolytic activity independently correlated with improvement of fasting glucose. Further studies evaluating the underlying mechanism of this effect might support consideration of the small bowel as a novel therapeutic target for diabetes.

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Author Contributions: CRK, MJY, AC contributed to study concept and design; NL, AC contributed in imaging analysis; AC, CRK, IGK, JWH, EJL and MJY interpreted data and manuscript drafting, WJH and SHN provided critical revision

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Duality of interest

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Table 1. Clinical characteristic of enrolled patients

	Before surgery	After surgery	P Value*
Number of patients	239		
Age (years)	57 (46~65)		
Sex (F/M)	89 :150 (37.2% : 62.8%)		
Weight (Kg)	60 (55~69)	56 (50~63)	**<0.001**
Body mass index (kg/m^2)	22.7 (20.8~24.7)	21.2 (19.3~22.7)	**<0.001**
Fasting glucose (mg/dL)	94 (88~103)	92 (87~100)	0.589
Total Cholesterol (mg/dL)	177 (154~204)	171 (153~192)	**0.022**
Uric Acid (mg/dL)	4.6 (3.7~5.6)	4.6 (3.8~5.5)	0.798
Total protein (mg/dL)	6.9 (6.5~7.3)	6.9 (6.6~7.2)	0.339
Albumin (mg/dL)	4.3 (4~4.6)	4.3 (4.1~4.5)	0.806
Follow up duration of PET/CT	12.4 (10.5~27.4)		
Pathologic diagnosis			
Early gastric cancer	66 (27.6%)		
Advanced gastric cancer	173 (72.4%)		
Surgical methods			
Billroth I	81 (33.9%)		
Billroth II	56 (23.4%)		
Roux-en-Y	102 (42.7%)		
Bowel FDG uptake			
SUVmax	2.9 (1.7~3.7)	4.3 (3.3~6)	**<0.001**
MTV	0.7 (0~8.2)	13.5 (2.9~36.6)	**<0.001**
TLG	2 (0~24.4)	39.8 (7.7~111.4)	**<0.001**
Body Fat (cm^3)			
Total body fat	21.5 (15.7~27.3)	12.9 (6.5~18)	**<0.001**
Visceral body fat	7.5 (4.4~10)	3.3 (2.1~5.6)	**<0.001**
Subcutaneous body fat	13 (9.7~17.4)	8.7 (4.4~12.4)	**<0.001**

Data are presented as median (interquartile range).

*Wilcoxon signed rank test or chi-squared test for bivariate factors.

Table 2. Clinical characteristics of patients according to changes of postoperative fasting glucose

	Decrement of fasting glucose		P Value*
	Group 1	Group 2	
Number of patients	61	178	
Age	55 (47.5~62)	57 (45.8~66)	0.353
Gender (F/M)	30:31	59:119	**0.025**
Pre-op Weight (Kg)	55 (49.5~63)	56 (50~64)	0.649
Δ Weight (Kg)	-5 (-10.7~-2)	-4 (-7~-1)	0.069
Pre-op Body mass index (kg/m^2)	23.0 (22.0~25.6)	22.5 (20.5~24.4)	**0.019**
Δ Body mass index (kg/m2)	-1.5 (-4.2~-0.7)	-1.5 (-2.8~-0.2)	**0.049**
Pre-op Fasting glucose (mg/dL)	104 (99~109)	92 (85~97)	**<0.001**
Δ Fasting glucose (mg/dL)	-15 (-21~-13)	3 (-3~12)	**<0.001**
Pre-op Total Cholesterol (mg/dL)	185 (161.0~214.5)	174.5 (152.0~195.8)	**0.018**
Follow up duration of PET/CT	14.8 (11.1~24.9)	12.2 (10.1~29.2)	0.618
Surgical methods			**<0.001**
Billroth I	9	72	
Billroth II	23	33	
Roux-en-Y	29	73	
SUVmax			
Preoperative	3 (2.4~4)	2.9 (0~3.5)	**0.023**
Postoperative	4.6 (3.7~6.3)	4.2 (3.2~5.9)	**0.028**
MTV			
Pre-operative	1.6 (0~12.1)	0.6 (0~6.2)	0.092
Post-operative	23.5 (6.2~53.1)	10.8 (2.1~34.8)	**0.005**
TLG			
Pre-operative	4.2 (0~33.6)	1.5 (0~17.6)	0.104
Post-operative	71.8 (17.6~166.3)	32.2 (5.6~100.2)	**0.005**
Pre-op Total Body fat (cm^3)	24.57 (18.08~30.71)	20.86 (14.62~25.76)	**0.003**
Δ Total Body fat	-10.6 (-16.7~-6)	-7.7 (-12.5~-4.2)	**0.003**
Pre-op Visceral Body fat (cm^3)	15.32 (11.02~20.49)	12.35 (9.39~16.46)	**0.007**
Δ Visceral Body fat	-4.7 (-7.2~-2.9)	-3.1 (-5.5~-1.5)	**0.001**
Pre-op Subcutaneous Body fat (cm^3)	8.36 (5.63~11.50)	7.13 (4.01~9.34)	**0.035**
Δ Subcutaneous Body fat	-6.1 (-9.9~-1.7)	-4.5 (-7.5~-1.5)	0.064

Data are presented as median (interquartile range).

*Wilcoxon signed rank test or chi-squared test for bivariate factors.

Table 3. Multiple logistic analysis for decrement of fasting glucose after surgery

	Decrement of fasting glucose	
	Odds Ratio (95%Confidence interval)	*P* Value*
Age	0.98 (0.95~1.02)	0.310
Male Gender (vs Female)	0.73 (0.18~2.86)	0.647
Surgery Method		
Billroth II (vs Billroth I)	6.51 (2.47~17.18)	**<0.001**
Roux-en-Y (vs Billroth I)	1.98 (0.78~4.99)	0.148
Increased bowel uptake (>42)	3.17 (1.49~6.73)	**0.003**
Pre-op BMI	0.97 (0.7~1.34)	0.846
Δ BMI	0.66 (0.39~1.11)	0.119
Pre-op body weight	1 (0.9~1.1)	0.94
Δ body weight	1.15 (0.95~1.39)	0.148
Pre-op body fat	1.02 (0.93~1.11)	0.698
Δ Total body fat	0.93 (0.86~1.01)	0.071
Pre-op Total Cholesterol	1.01 (1~1.02)	0.088
Δ Total Cholesterol	1.01 (1~1.02)	0.133

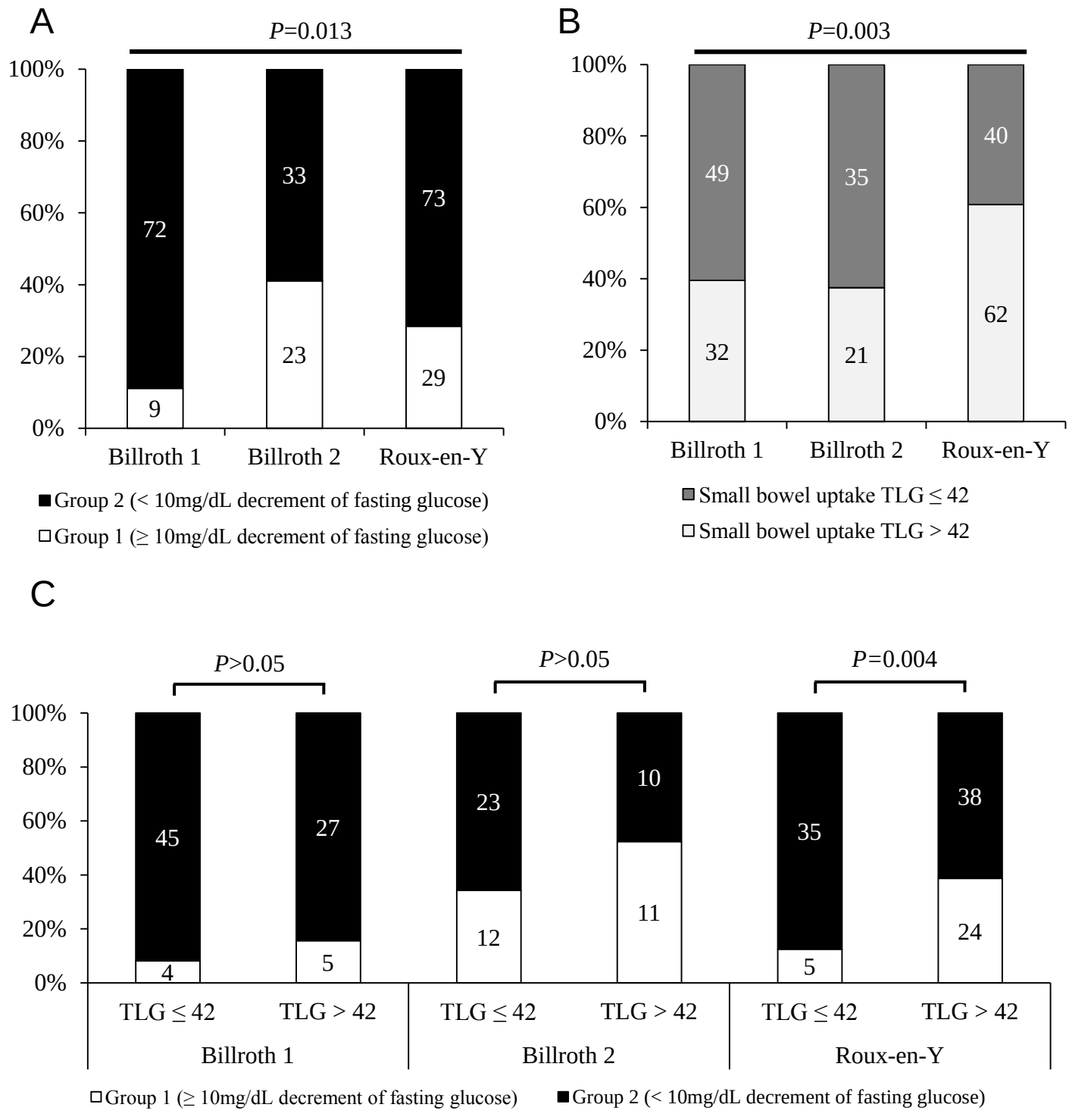
*multivariate logistic regression

Δ variable: preoperative variable – postoperative variable

Figure legends

Figure 1. Changes of fasting glucose according to surgical methods and postoperative TLG uptake. Differences according to surgical method in (a) glucose decrement (≥10mg/dL, <10mg/dL) and (b) TLG (≤42, >42). (c) Difference in glucose decrement in relationship to surgical method and TLG. Statistical method were linear-by-linear association in (a),(b) and Fisher's Exact Test for (c).

Figure 1. Changes of fasting glucose according to surgical methods and postoperative TLG uptake



PET/CT protocol and imaging analysis

All patients underwent routine FDG PET/CT scans with either Discovery STe or Discovery 600 PET/CT systems (GE Healthcare, Milwaukee, WI, USA). All patients fasted for at least 6 hours, and glucose levels in peripheral blood were confirmed to be ≤126 mg/dL in all patients before FDG injection. Approximately 5.5 MBq/kg of FDG was administered intravenously 1 hour before image acquisition. After the initial low-dose CT (30 mA, 130 kVp), standard PET imaging was performed from the neck to the proximal thigh with an acquisition time of 3 min/bed in three-dimensional mode. Images were then reconstructed using the ordered subset expectation maximization (2 iterations, 20 subsets).

Images were reviewed on a GE AW 4.0 workstation (GE Healthcare, Milwaukee, WI, USA) by two experienced nuclear medicine specialists (A.C., 12 years of experience; N.L, 6 years of experience) blinded to clinical information. Multiple volumes of interest were drawn on each metabolically active lesion (SUV threshold 2.5) in the small bowel. The metabolic volume (MTV, cm^3) was defined as total lesion volume of voxels above a threshold SUV of 2.5 within the volume of interest. For lesions with a SUV of less than 2.5, MTV was set as 0.0 cm^3. The mean SUV (SUVmean) of each lesion was recorded, and total lesion glycolysis (TLG) was obtained by multiplying SUVmean and MTV. Finally, global MTV and TLG were calculated by summing all corresponding values, recorded in Table 1. A representative image of TLG methodology is shown in Supplementary Figure 1. This process was performed for both baseline and postoperative FDG PET/CT data.

Abdominal fat analysis

Abdominal subcutaneous and visceral adipose tissue (ASAT and AVAT, respectively) were measured on the non-contrast enhanced CT scans acquired during PET/CT using a workstation (Volume Analysis, Advantage Workstation 4.0, GE Healthcare). Adipose tissue was defined as attenuation ranging from -50 to -200 HU, as reported in previous studies.(1; 2) Total abdominal fat volume (ASAT + AVAT) were measured on axial images at the umbilicus level using an ROI with this HU threshold to include the subcutaneous and visceral adipose tissue. On the same axial image, an additional ROI was drawn on the visceral fat portions using the same HU threshold to determine the AVAT. ASAT was calculated as total abdominal fat volume minus AVAT.

Supplementary Figure 1. Representative figure of total lesion glycolysis (TLG) methodology in a 50-year-old female patient who underwent Roux-en-Ygastrectomy for advanced gastric cancer. (a) Preoperative coronal and axial PET/CT fusion images shows no significant small bowel uptake. A volume of interest (VOI) was drawn on the small bowel using a SUV threshold of 2.5, resulting in a preoperative TLG of 0. (b) Postoperative FDG PET/CT showing newly developed small bowel activity. Right side bowel VOI showed total lesion glycolysis (TLG) of 406.6 and left side bowel VOI showed TLG of 72.7. Patient TLG was recorded as 479.3. Clinically, patient fasting glucose level decreased from 115mg/dL to 82mg/dL, and body weight reduced from 23.6 to 22.4 kg.

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Supplemental Table 1. Clinical characteristics of patients according to preoperative body mass index and changes of postoperative fasting glucose

	BMI<23 kg/m^2			BMI≥23 kg/m2		
	Decrement of fasting glucose		*P* Value	Decrement of fasting glucose		*P* Value
	Group 1	Group 2		Group 1	Group 2	
Number of patients	30	103		31	75	
Age	55 (46~60)	58 (44~69)	0.320	56 (50~63)	57 (48~64)	0.870
Gender (F/M)	18/12	42/61	0.063	12/19	17/58	0.092
Pre-op Weight (Kg)	56 (52~61)	56 (50~60)	0.747	68 (60~75)	69 (64~73)	0.967
Δ Weight (Kg)	-4 (-7~-2)	-3 (-6~0)	0.090	-9 (-12~-3)	-6 (-11~-2)	0.550
Pre-op Body mass index (kg/m^2)	22.0 (19.8~22.5)	20.8 (19.6~21.8)	0.054	25.6 (24.1~27)	24.7 (23.9~26.1)	0.067
Δ Body mass index (kg/m2)	-1.2 (-2.8~-0.6)	-1.1 (-2.1~0.2)	0.167	-3.2 (-4.7~-1.1)	-2.2 (-3.6~-0.8)	0.316
Pre-op Fasting glucose (mg/dL)	100 (93~108)	93 (85~97)	**<0.001**	105 (102~110)	91 (86~98)	**<0.001**
Δ Fasting glucose (mg/dL)	-15 (-20~-13)	1 (-4~12)	**<0.001**	-15 (-22~-13)	4 (-1~12)	**<0.001**
Pre-op Total Cholesterol (mg/dL)	179 (155~213)	171 (152~189)	0.260	191 (170~228)	177 (152~204)	**0.046**
Δ Total Cholesterol (mg/dL)	7 (-32~24)	-2 (-21~21)	0.730	-24 (-43~8)	-7 (-25~13)	0.309
Follow up duration of PET/CT	16.9 (9~24.8)	12.7 (9.9~35.5)	0.861	12.1 (11.7~29.8)	12.1 (10.1~24.4)	0.605
Surgical methods			**0.020**			**0.012**
Billroth I	6	44		3	28	
Billroth II	12	19		11	14	
Roux-en-Y	12	40		17	33	
SUVmax						
Preoperative	2.9 (2.1~4.3)	2.8 (0~3.5)	0.071	3.1 (2.8~3.6)	3.0 (2.2~3.8)	0.209
Postoperative	4.5 (3.7~6.0)	4.0 (3.1~5.1)	**0.029**	4.8 (3.7~7.3)	4.7 (3.3~6.7)	0.410
MTV						
Pre-operative	0.5 (0~10.8)	0 (0~8.1)	0.379	1.9 (0.3~13.3)	1.1 (0~5.3)	0.176
Postoperative	15.1 (5.5~30.0)	8.3 (1.6~30.8)	0.088	27.5 (7.2~116.0)	13.5 (3.6~48.0)	**0.040**
TLG						
Pre-operative	1.3 (0~31.1)	0.1 (0~22.7)	0.429	5.0 (0.8~38)	2.9 (0~14.9)	0.192
Postoperative	44.8 (16.2~92.5)	20.6 (4.5~94.9)	0.062	86.3 (22.1~353.1)	39.8 (11.0~156.3)	**0.048**
Pre-op Total Body fat (cm^3)	20.1 (13.6~25)	16.1 (11.6~22)	0.148	29.9 (23.5~33.8)	25.4 (21.3~29.2)	**0.007**
Δ Total Body fat (cm^3)	-7.6 (-13.8~-3.2)	-6.7 (-10.4~-2.1)	0.219	-11.8 (-17.7~-10)	-10.0 (-14.1~-5.6)	**0.008**
Pre-op Visceral Body fat (cm^3)	6 (3.8~8.5)	5 (3.5~7.6)	0.341	10.9 (8.1~14.1)	9.4 (7.3~11.9)	0.088
Δ Visceral Body fat (cm^3)	-3.3 (-4.9~-1.1)	-2 (-3.8~-0.9)	0.107	-6.7 (-8.1~-4.7)	-4.8 (-6.5~-2.8)	**0.003**
Pre-op Subcutaneous Body fat (cm^3)	12.6 (7.2~17.4)	10.4 (6.9~14.2)	0.154	18.5 (14.1~21.6)	15.1 (12.2~18.5)	0.056
Δ Subcutaneous Body fat (cm^3)	-4.8 (-7.3~-1.2)	-4.2 (-7.1~-0.7)	0.568	-6.8 (-10.4~-2.3)	-5.3 (-8~-2)	0.065

Data are presented as median (interquartile range). Wilcoxon signed rank test or chi-squared test for bivariate factors. Group 1includes patients with decreased fasting glucose above 10 mg/dL and Group 2 are the others.

Supplementary Table 2. Changes of metabolic parameters with newly developed FDG uptake in bowel

	Increased bowel uptake TLG≥42	No bowel uptake TLG<42	P Value*
Number of patients	115 (48.1%)	124 (51.9%)	
Age	56 (48~64)	57 (45~65)	0.885
Gender (F/M)	48:67	41:83	0.166
Follow-up duration † (months)	12.9 (11.7~35.6)	12.1 (8.8~24.3)	0.058
Pathologic diagnosis			0.611
Early gastric cancer	30 (45.5%)	36 (54.5%)	
Advanced gastric cancer	85 (49.1%)	88 (50.9%)	
Surgical methods			**0.003**
Billroth I	32 (39.5%)	49 (60.5%)	
Billroth II	21 (37.5%)	35 (62.5%)	
Roux-en-Y	62 (60.8%)	40 (39.2%)	
Pre-op Weight (Kg)	62 (56~71)	60 (54~66.1)	**0.028**
Δ weight	-5 (-9.3~-2)	-4 (-7~-1)	**0.021**
Pre-op Body mass index (kg/m^2)	23.3 (21.6~25.2)	22.1 (20.2~23.9)	**<0.001**
Δ BMI	-1.6 (-3.3~-0.4)	-1.2 (-2.6~-0.3)	**0.021**
Pre-op Fasting glucose (mg/dL)	96 (89~104)	93 (86~100)	**0.016**
Δ Fasting glucose	-5 (-13~5)	1.5 (-5.8~12)	**<0.001**
Pre-op Total Cholesterol (mg/dL)	180 (156~209)	174 (152~199.5)	0.175
Δ Total Cholesterol	-9 (-32~9)	-2 (-22~19)	**0.048**
Pre-op Bowel uptake			
SUVmax	3 (2.4~3.7)	2.8 (0~3.6)	**0.028**
MTV	1.6 (0~9)	0.2 (0~6.9)	**0.031**
TLG	4.2 (0~25.8)	0.5 (0~18.8)	**0.032**
Pre-op Total Body Fat (cm^3)	23.2 (16.7~28.8)	20.8 (13.9~25.5)	**0.034**
Δ Total body fat (cm^3)	-9.7 (-14.6~-5.1)	-7.7 (-12.5~-3.5)	**0.032**
Pre-op Visceral Body Fat (cm^3)	8.6 (4.9~10.3)	6.7 (4.1~9.4)	**0.036**
Δ Visceral body fat (cm^3)	-4.3 (-6.6~-2.1)	-2.9 (-5.3~-1.3)	**0.002**
Pre-op Subcutaneous Body Fat (cm^3)	14.1 (10.8~17.5)	12.2 (9~17.2)	0.091
Δ Subcutaneous body fat (cm^3)	-5.1 (-7.9~-1.9)	-4.4 (-7.8~-0.9)	0.229

*Wilcoxon signed rank test or chi-squared test for bivariate factors.

† Follow up duration: postoperative PET/CT - operation

Δ variable: preoperative variable – postoperative variable (minus values indicate decrease in values after surgery)

Supplementary Table 3. Additional benefit of bowel uptake in predicting decrement of fasting glucose after surgery

		Decrement of fasting glucose		*P* Value*
		Group 1	Group 2	
Billroth I				0.296
	No bowel uptake (TLG<42)	4	45	
	bowel uptake (TLG≥42)	5	27	
Billroth II				0.183
	No bowel uptake (TLG<42)	12	23	
	bowel uptake (TLG≥42)	11	10	
Roux-en-Y				**0.004**
	No bowel uptake (TLG<42)	5	35	
	bowel uptake (TLG≥42)	24	38	

*chi-squared or Fisher's Exact Test

Supplementary Figure 1. Representative figure of total lesion glycolysis methodology

(a) Preoperative (b) Postoperative