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Intestinal Glycolysis Visualized by FDG PET/CT Correlates With Glucose Decrement After Gastrectomy

Diabetes 2017;66:385–391 | DOI: 10.2337/db16-1000

Gastrectomy method is known to influence glucose homeostasis. ¹⁸F-fluoro-2-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) images acquired after gastrectomy often reveals newly developed physiological small bowel uptake. We correlated newly developed small bowel FDG uptake and glucose homeostasis in postgastrectomy gastric cancer patients. We retrospectively analyzed 239 patients without diabetes who underwent staging and follow-up FDG PET/CT scanning before and after gastrectomy for gastric cancer. Postoperative small bowel glycolysis was quantified by recording intestinal total lesion glycolysis (TLG). TLG was assessed with regard to surgical method (Billroth I, Billroth II [BII], Roux-en-Y [RY]), fasting glucose decrement (≥ 10 mg/dL), and other clinical factors. Patients' weight, fasting glucose, cholesterol, TLG, and body fat levels significantly decreased after surgery. The 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 g) correlated with glucose decrement in RY patients. Newly developed small bowel glycolysis on postgastrectomy FDG PET/CT scanning is correlated with a glucose decrement. These findings suggest a potential role of FDG PET/CT scanning in the evaluation of small bowel glycolysis and glucose control.

The incidental finding that bariatric surgery ameliorates hyperglycemia has emerged as an important treatment consideration in obese patients with type 2 diabetes (T2D). Multiple randomized clinical studies (1–6) have shown a clear benefit of bariatric surgery over medical therapy in T2D management. Despite the clear clinical evidence of hyperglycemia improvement after bariatric surgery, the mechanisms underlying the resolution of T2D by bariatric surgery have not been fully elucidated.

The most widely radiotracer used for positron emission tomography (PET)/computed tomography (CT) is ¹⁸F-fluoro-2-deoxyglucose (FDG). During the imaging workup for the diagnosis of malignancies, FDG PET/CT scanning identifies malignant foci by targeting the high glycolytic rate of cancer cells. However, the 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 in whom intense FDG uptake develops in the bowel, despite there being no discernible lesions seen on contrast-enhanced CT scanning 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 a pathological uptake. However, no studies have evaluated the clinical significance of this phenomenon.

Recent studies (7–9) have suggested that the small bowel might have a pivotal role in regulating glucose homeostasis. Two recent animal studies (8,9) that focused

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Received 15 August 2016 and accepted 23 November 2016.

This article contains Supplementary Data online at <http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db16-1000/-/DC1>.

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on the biochemical role of the small bowel in glucose homeostasis after bariatric surgery have suggested that glucose may be excreted into the intestinal lumen via sodium–glucose cotransporter proteins, as well as increased glucose metabolism by the enteric cells themselves. On the basis of these findings, the evaluation of FDG bowel patterns after gastrectomy may be beneficial in elucidating the mechanisms of bariatric surgery in achieving glucose homeostasis, as it provides a noninvasive picture of changes in glucose metabolism of the 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.

RESEARCH DESIGN AND METHODS

Patient Selection and Imaging Analysis

Between December 2005 and May 2015, a total of 669 patients underwent FDG PET/CT scanning within 90 days before undergoing gastrectomy and had 1 underwent a follow-up FDG PET/CT scan after undergoing gastrectomy. All patients had baseline glucose levels checked on both days of PET/CT scanning. We excluded 430 patients who had preoperative glucose levels >126 mg/dL or had malignancies seen on postoperative FDG PET/CT scans. We excluded patients with diabetes because administration of oral antihyperglycemic agents, especially metformin, 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 scanning were also excluded. The final population was 239 patients. All patients had baseline glucose levels checked on both days of PET/CT scanning. All serum samples including glucose levels were acquired after fasting for >8 h. Of the 239 patients, 128 patients had decrease in serum glucose levels after surgery. The average reduction in serum glucose concentration was 10 mg/dL. Patients with diabetes were excluded because the administration of oral antihyperglycemic agents can be a confounding factor in determining the effect of surgery on bowel uptake of FDG. Weight and BMI measurements and samples for biochemical analysis were collected from all patients within 2 days of preoperative and postoperative FDG PET/CT scanning. Changes in fasting glucose levels were stratified into patients with a ≥ 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).

The PET/CT protocol and imaging analysis methods are described in the Supplementary Data.

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 analysis was performed to determine the postoperative intestinal glycolysis (total lesion glycolysis [TLG]) cutoff value with the highest sensitivity for predicting patients with a ≥ 10 mg/dL decrement in fasting glucose levels (G1) after surgery. Patients with a <10 mg/dL decrement of fasting glucose levels were categorized as being in G2. This cutoff 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 the χ^2 test or Fisher exact test and by linear-by-linear association for trivariate factors. A multivariate logistic analysis was performed, including statistically significant or clinically significant factors for predicting G1 on the Mann-Whitney U test. Finally, the χ^2 test was performed to assess the prediction of the fasting glucose decrement with TLG according to the surgical method. Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc.), and P values <0.05 were considered to be statistically significant. The data were expressed as the median (95% CI) for continuous variables and the 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 Roux-en-Y surgery (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 scan 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 (maximum standard uptake value [SUV_{max}] from 2.9 preoperatively to 4.3 postoperatively) and amount (TLG values from 2.0 g preoperatively to 39.8 g postoperatively). There was no discernable pattern in FDG uptake in the small bowel because it ranged from single foci to multifocal increased FDG uptake. Body weight, BMI, and fasting total cholesterol concentrations 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 a ≥ 10 mg/dL Decrement of Fasting Glucose After Gastrectomy

Among the 239 patients enrolled in the study, 61 (25.5%) experienced a ≥ 10 mg/dL decrement in fasting glucose

Table 1—Clinical characteristic of enrolled patients

	Before surgery	After surgery	<i>P</i> value*
Patients (<i>n</i>)	239		
Age (years)	57 (46–65)		
Sex, <i>n</i> (%)			
Female	89 (37.2)		
Male	150 (62.8)		
Weight (kg)	60 (55–69)	56 (50–63)	<0.001
BMI (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 scan (months)	12.4 (10.5–27.4)		
Pathological diagnosis, <i>n</i> (%)			
Early gastric cancer	66 (27.6)		
Advanced gastric cancer	173 (72.4)		
Surgical methods, <i>n</i> (%)			
BI	81 (33.9)		
BII	56 (23.4)		
RY	102 (42.7)		
Bowel FDG uptake			
SUVmax	2.9 (1.7–3.7)	4.3 (3.3–6)	<0.001
MTV (cm ³)	0.7 (0–8.2)	13.5 (2.9–36.6)	<0.001
TLG (g)	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 the median (IQR), unless otherwise indicated. *Wilcoxon signed rank test or χ^2 test for bivariate factors. Bold *P* values indicate statistically significant values (*P* < 0.05). MTV, metabolic volume.

(in G1 after surgery). Before surgery, G1 patients had significantly higher fasting glucose concentration than G2 patients (Table 2). After surgery, G1 patients experienced a significant drop in fasting glucose concentration, and G2 patients experienced a mild increase in fasting glucose concentration (fasting glucose 87 mg/dL [95% CI 82–92] and 95 mg/dL [95% CI 89–105], *P* < 0.001). This indicates that patients with higher basal fasting glucose concentrations were more likely to experience a significant drop in glucose levels after surgery.

BMI was also significantly higher in G1 compared with G2 patients before surgery, but in contrast to glucose, BMI became comparable between G1 and G2 after surgery (BMI: 21.6 kg/m² [interquartile range (IQR) 19.7–23.0] and 21.0 kg/m² [IQR 19.1–22.6], *P* = 0.344). Similarly, G1 patients had significantly higher preoperative levels of total abdominal fat, ASAT, and AVAT compared with 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 of 81 patients), 41.1% (23 of 56 patients), and 28.4% (29 of 102 patients) of patients, respectively, who

underwent BI, BII, and RY were assigned to the G1 group (Fig. 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 values >23 kg/m², which is the cutoff for obesity in Asian populations (Supplementary 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 values >23 kg/m², patients classified as being in G1 had significantly higher fasting glucose, serum total cholesterol, total abdominal fat, ASAT, and AVAT levels before surgery than patients classified as being in 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 (Supplementary Table 1). There was no difference in glycolytic bowel activity between the G1 and G2 groups before gastrectomy in both obese and nonobese patients. However, obese G1 patients demonstrated significantly increased glycolytic activity of the small bowel after surgery compared

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

	Decrement of fasting glucose		<i>P</i> value*
	G1	G2	
Patients (<i>n</i>)	61	178	
Age (years)	55 (47.5–62)	57 (45.8–66)	0.353
Sex			0.025
Female	30	59	
Male	31	119	
Preoperative weight (kg)	55 (49.5–63)	56 (50–64)	0.649
ΔWeight (kg)	–5 (–10.7 to –2)	–4 (–7 to –1)	0.069
Preoperative BMI (kg/m ²)	23.0 (22.0–25.6)	22.5 (20.5–24.4)	0.019
ΔBMI (kg/m ²)	–1.5 (–4.2 to –0.7)	–1.5 (–2.8 to –0.2)	0.049
Preoperative fasting glucose (mg/dL)	104 (99–109)	92 (85–97)	<0.001
ΔFasting glucose (mg/dL)	–15 (–21 to –13)	3 (–3 to 12)	<0.001
Preoperative 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
BI	9	72	
BII	23	33	
RY	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 (cm ³)			
Preoperative	1.6 (0–12.1)	0.6 (0–6.2)	0.092
Postoperative	23.5 (6.2–53.1)	10.8 (2.1–34.8)	0.005
TLG (g)			
Preoperative	4.2 (0–33.6)	1.5 (0–17.6)	0.104
Postoperative	71.8 (17.6–166.3)	32.2 (5.6–100.2)	0.005
Preoperative total body fat (cm ³)	24.57 (18.08–30.71)	20.86 (14.62–25.76)	0.003
ΔTotal body fat	–10.6 (–16.7 to –6)	–7.7 (–12.5 to –4.2)	0.003
Preoperative visceral body fat (cm ³)	15.32 (11.02–20.49)	12.35 (9.39–16.46)	0.007
ΔVisceral body fat	–4.7 (–7.2 to –2.9)	–3.1 (–5.5 to –1.5)	0.001
Preoperative subcutaneous body fat (cm ³)	8.36 (5.63–11.50)	7.13 (4.01–9.34)	0.035
ΔSubcutaneous body fat	–6.1 (–9.9 to –1.7)	–4.5 (–7.5 to –1.5)	0.064

Data are presented as median (IQR), unless otherwise indicated. Δ, preoperative variable – postoperative variable. *Wilcoxon signed rank test or χ^2 test for bivariate factors. Bold *P* values indicate statistically significant values (*P* < 0.05). MTV, metabolic volume.

with obese G2 patients (86.3 g [IQR 22.1–353.1] vs. 39.8 g [IQR 11.0–156.3], *P* = 0.048). In nonobese patients, FDG PET/CT scanning revealed significantly higher SUVmax values together with a decrement in fasting glucose levels in the G1 group after gastrectomy.

Correlation of Postoperative Small Bowel Uptake and Fasting Glucose Decrement

Receiver operating characteristic analysis indicated that a postoperative TLG cutoff of 42 g had the highest sensitivity to predict ≥ 10 mg/dL serum glucose reduction (sensitivity 65.6%, area under the curve 0.621, *P* = 0.003). Patients were regrouped according to high small bowel uptake (TLG >42 g) or low small bowel uptake (TLG ≤ 42 g) (Supplementary 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%) (Fig. 1B). Patients with high small bowel uptake after gastrectomy experienced significant reductions of fasting glucose (–5.0 vs. 1.5 mg/dL, *P* < 0.001) and postoperative fasting glucose (91 vs. 93.5 mg/dL, *P* = 0.045) compared with those patients 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 (≥ 10 mg/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% CI 2.47–17.18], *P* < 0.001),

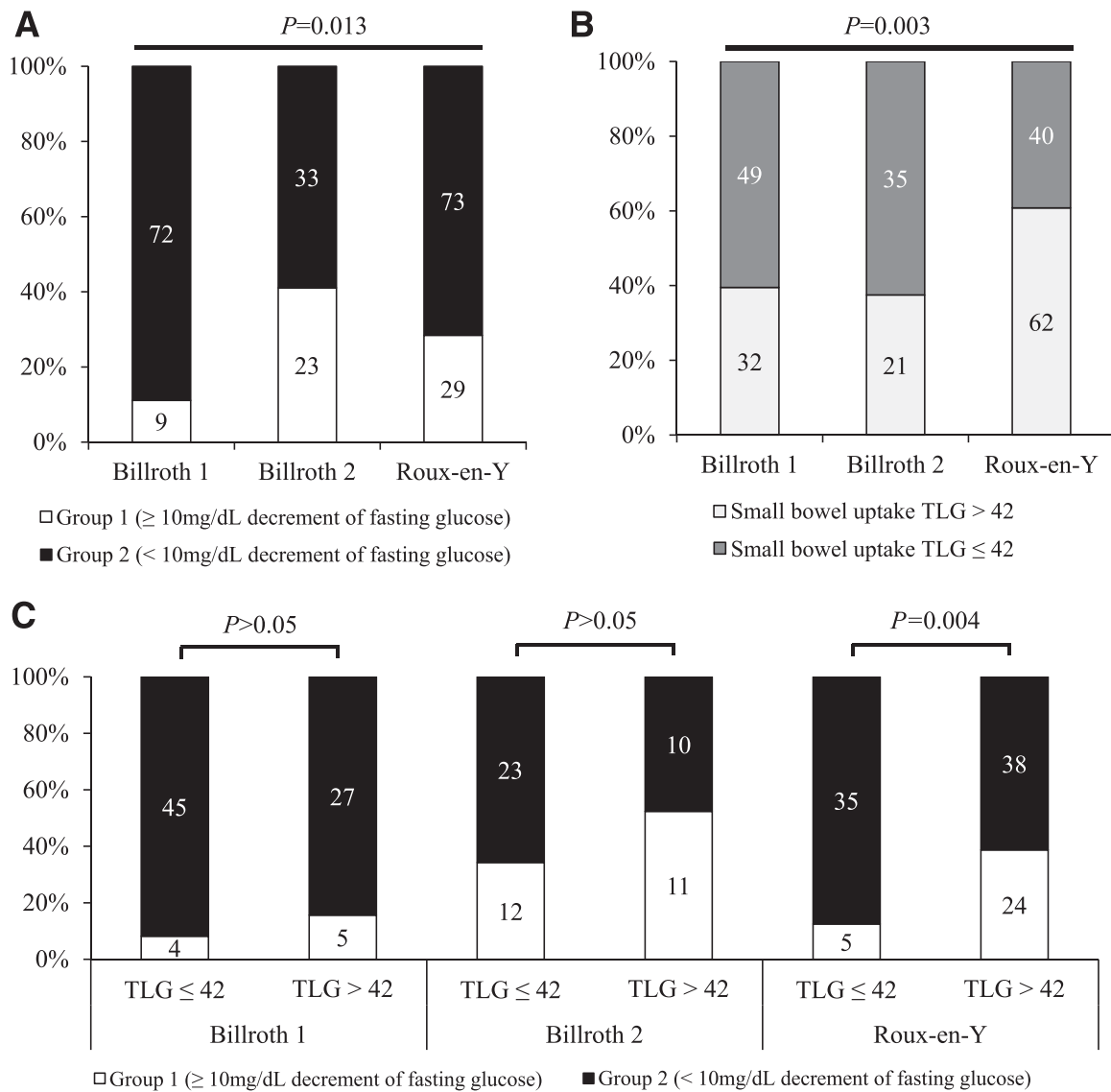


Figure 1—Changes in fasting glucose according to surgical methods and postoperative TLG uptake. Differences according to surgical method in glucose decrement (≥ 10 and < 10 mg/dL) (A) and TLG (≤ 42 and > 42 g) (B). C: Difference in glucose decrement in relationship to surgical method and TLG. Statistical methods were linear-by-linear association in A and B and Fisher exact test in C.

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 with BII or BI patients, a significantly higher proportion of RY patients presented with small bowel uptake after gastrectomy (Supplementary Table 3 and Fig. 1B). Furthermore, the correlation between surgical method and the development

of a fasting glucose decrement was seen only in RY patients with increased glycolytic activity (Fig. 1C).

Finally, to better predict serum glucose decrement in clinical settings, we subanalyzed the decrease in serum glucose levels and small bowel uptake according to surgical method and BMI (Supplementary 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

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

	Decrement of fasting glucose	
	OR (95% CI)	P value*
Age	0.98 (0.95–1.02)	0.310
Male sex (vs. female)	0.73 (0.18–2.86)	0.647
Surgery method		
BII (vs. BI)	6.51 (2.47–17.18)	<0.001
RY (vs. BI)	1.98 (0.78–4.99)	0.148
Increased bowel uptake (>42 g)	3.17 (1.49–6.73)	0.003
Preoperative BMI	0.97 (0.7–1.34)	0.846
ΔBMI	0.66 (0.39–1.11)	0.119
Preoperative body weight	1 (0.9–1.1)	0.94
ΔBody weight	1.15 (0.95–1.39)	0.148
Preoperative body fat	1.02 (0.93–1.11)	0.698
ΔTotal body fat	0.93 (0.86–1.01)	0.071
Preoperative total cholesterol	1.01 (1–1.02)	0.088
ΔTotal cholesterol	1.01 (1–1.02)	0.133

Δ, preoperative variable – postoperative variable. *Multivariate logistic regression. Bold P values indicate statistically significant values (P < 0.05).

correlation between increased glycolytic activity in the small bowel and changes in fasting serum glucose after gastrectomy. The major findings of this study include the following: 1) the gastrectomy method-dependent increment of glycolytic activity in the small bowel, especially in obese patients; 2) the independent correlation of increased intestinal glycolytic activity with a decrement of fasting glucose after gastrectomy; and 3) the correlation between increased intestinal glycolytic activity and a decrement of fasting glucose, which was significantly stronger in patients treated with RY.

A variety of gastrectomy procedures has 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 (13) that bariatric surgery improved glucose homeostasis independently from changes in body weight after surgery. 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 the bariatric surgery procedure used for obesity treatment. BI surgery can be considered functionally analogous to vertical sleeve gastrectomy, as both surgical methods result in food passing through the duodenum, despite the differences in stomach resection method. RY and B2 gastrectomy can be considered to be analogous to RY 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 the afferent and efferent loops) to reduce bile reflux into the stomach at this time. The major physiological 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 (8,9) 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, as well as observing increased glucose metabolism by the enteric cells themselves. Our study may provide supporting clinical evidence for this theory.

The current study has several limitations. First, we could not perform mechanistic experiments to test the relationships between increased FDG uptake in the small bowel and the 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 patients without diabetes. However, in light of the abnormal FDG uptake caused by antihyperglycemic agents, the results of this study could provide evidence that is free from underlying medical biases. Finally, because of 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 patients with diabetes 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 levels. Further studies evaluating the underlying mechanism of this effect might support consideration of the small bowel as a novel therapeutic target for diabetes.

Funding. This study was supported by a faculty research grant of Yonsei University College of Medicine (grant 6-2015-0084).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.R.K. and M.Y. contributed to the study concept and design, interpreted the data, and contributed to the drafting of the manuscript. N.L. contributed to the imaging analysis. J.W.H., I.G.K., and E.J.L. interpreted the data and contributed to the drafting of the manuscript. W.J.H. and S.H.N. provided critical revision of the manuscript. A.C. contributed to the study concept and design, the imaging analysis, interpretation of the data, and the drafting of the manuscript. C.R.K. and A.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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