J Gastric Cancer. 2021 Dec;21(4):325-334
https://doi.org/10.5230/jgc.2021.21.e31
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Postprandial Asymptomatic Glycemic Fluctuations after Gastrectomy for Gastric Cancer Using Continuous Glucose Monitoring Device

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Received: Aug 16, 2021
Revised: Sep 26, 2021
Accepted: Sep 26, 2021

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ABSTRACT

Purpose: Although dumping symptoms are thought to involve postprandial glycemic changes, postprandial glycemic variability without dumping symptoms remains poorly understood due to the lack of a method that allows the easy and continuous measurement of blood glucose levels.
Materials and Methods: Patients having undergone distal gastrectomy with Billroth-I (DG-BI) or Roux-en-Y reconstruction (DG-RY), total gastrectomy with RY (TG-RY) and pylorus preserving gastrectomy (PPG) for gastric cancer 3 months to 3 years prior, diagnosed as pathological stage I or II, were prospectively enrolled from March 2018 to January 2020. The interstitial tissue glycemic levels were measured every 15 min, up to 14 days by continuous glucose monitoring. Moreover, using a diary recording the diet and symptoms, asymptomatic glucose profiles without sugar supplementation within 3 h postprandially were compared among the four procedures.
Results: A total of 40 patients were enrolled, 10 patients for each of the four procedures. There were 47 glucose profiles with DG-BI, 46 profiles with DG-RY, 38 profiles with TG-RY, and 46 profiles with PPG. PPG showed the slowest increase with a subsequent gradual decrease in glucose fluctuations, without hyperglycemia or hypoglycemia, among the four procedures. In contrast, TG-RY and DG-RY showed spike-like glycemic variability, sharp rises during meals, and rapid drops. The glucose profiles of DG-BI were milder than those of RY.
Conclusions: The asymptomatic glycemic changes after meals differ among the types of surgical procedures for gastric cancer. Given the mild glycemic fluctuations in PPG and the glucose spikes in TG-RY and DG-RY, pylorus preservation and physiological reconstruction without changes in food pathways may optimize postprandial glucose profiles after gastrectomy.

Keywords: Gastric cancer; Gastrectomy; Blood glucose; Hyperglycemia; Hypoglycemia

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Despite the falling incidence, especially in the industrialized nations, gastric cancer remains among the most common malignancies worldwide and is the third most common cause of cancer-related deaths [1]. Gastrectomy with lymph node dissection is the mainstay of treatment for resectable gastric tumors, with the exception of early lesions that can be curatively removed by endoscopic resection [2].

Post gastrectomy, physiological differences in digestion and absorption are known to develop depending on the type of operation performed [3,4]. Moreover, postoperative changes in digestion and absorption due to altered gastrointestinal anatomy may provoke dumping symptoms, the most common of post-gastrectomy syndromes. Although the cause of dumping syndrome has not been fully elucidated, postprandial reactive hypoglycemia has been widely regarded as one of the mechanisms underlying the dumping symptoms [5,6]. Our previous research, using a continuous glucose monitoring (CGM) device enabling the continuous measurement of interstitial glucose levels closely related to blood glucose levels suggested that postprandial rapid glycemic changes are associated with both early and late dumping symptoms after standard gastrectomy for gastric cancer [7].

On the other hand, increased glycemic variability, including hypoglycemia, has long been recognized as a risk factor for mortality in patients with diabetes [8-10]. It was recently recommended that the glycemic levels be controlled by maintaining an appropriate therapeutic range using CGM [11]. Therefore, if the glycemic levels after gastrectomy fluctuate asymptomatically and differ among the types of surgical procedures, the surgeon may need to determine the most appropriate procedure by taking blood glycemic variability into consideration. However, possible differences in real-time postprandial glucose variability without dumping symptoms, among several surgical procedures for gastric cancer, remain unclear because no studies using CGM have examined this issue.

Therefore, to investigate whether real-time asymptomatic glucose changes after meals differ among procedures or reconstruction methods, we designed a prospective study using CGM to measure and compare the real-time glucose fluctuations in patients, who had undergone one of four widely used gastric cancer operations.

MATERIALS AND METHODS

Patients

From March 2018 to January 2020, we prospectively enrolled patients who underwent gastrectomy for gastric cancer at the Cancer Institute Hospital, Tokyo, Japan. The inclusion criteria were as follows: 1) gastric adenocarcinoma diagnosed at pathological stage I or II; 2) surgical procedures with R0, such as distal gastrectomy with Billroth-I reconstruction (DG-BI), distal gastrectomy with Roux-en-Y reconstruction (DG-RY), total gastrectomy with Roux-en-Y reconstruction (TG-RY), and pylorus-preserving gastrectomy (PPG); 3) age, 20–75 years; 4) 3 months to 3 years after the operation; and 5) Eastern Cooperative Oncology Group Performance Status score 0 or 1. For reconstruction after DG, either BI or RY reconstruction was selected depending on the location of the tumor, which was decided by the primary surgeon. We estimated that 10 patients would need to be recruited for each surgical procedure to assure the feasibility of the study, based on a pilot study with no sample

https://doi.org/10.5230/jgc.2021.21.e31

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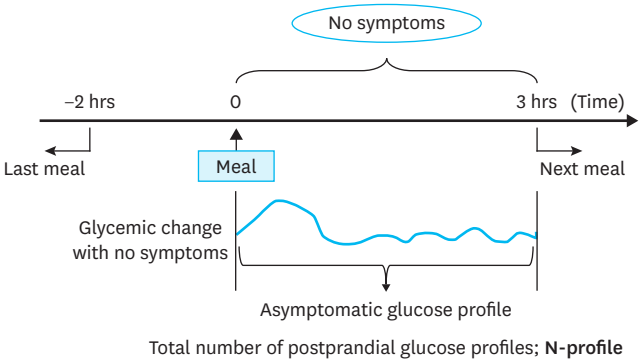
size premise. The exclusion criteria were the simultaneous resection of other organs (except cholecystectomy or splenectomy), diabetes under treatment, adjuvant chemotherapy, and dietary supplements, including enteral nutrition. The pathological stages were determined according to the 14th edition of the Japanese Classification of Gastric Carcinoma [12]. This study was approved by the Institutional Review Board of the Cancer Institute Hospital (No. 2017-1110). All the participants provided written informed consent.

Continuous glucose monitoring

The glucose concentrations were measured using FreeStyle Libre Pro (Abbot Diabetes Care Inc., Alameda, CA, USA), a CGM device. The sensor attached to the posterior surface of the patient's upper arm continuously measured and recorded the interstitial fluid glucose concentration in the subcutaneous tissue every 15 minutes for up to 14 days. The measurement results were automatically saved on the sensor and then transferred wirelessly to the reader. Subsequently, we analyzed the results using the FreeStyle Libre Pro Software via the reader.

Definition of asymptomatic glucose profiles after meals

Our strategy for defining the asymptomatic glucose profiles after meals is outlined in **Fig. 1**. The patients kept a diary for five patient-selected days within the 14-day period during which the sensor was attached. The diary entries were made every 15 minutes and listed the typical symptoms related to dumping, as previously reported [13,14], and the patient filled in the time of starting meals and the time of symptom occurrence. Considering that the patient dietary records after gastrectomy often document three or more meals, the snacks described by the patient as being about the same amount as an ordinary meal were regarded as meals and were recorded as such in the diary. The glycemic changes, which were not associated with symptoms that did not require sugar supplementation within three hours after starting a meal were defined as an asymptomatic glucose profile. To avoid the effects of the intake of other foods, we excluded cases in which another meal was consumed from two hours prior to three hours after the baseline meal. The asymptomatic glucose profiles consisted of up to one series per patient per day. Among the asymptomatic glucose profiles obtained on a single day, the earliest was included in the present study. The total number of asymptomatic glucose profiles was designated as the N-profile.



Total number of postprandial glucose profiles; **N-profile**

Fig. 1. How the asymptomatic glucose profiles after meals were defined. The patients kept a diary to record the times of starting meals and the onset of symptoms for five patient-selected days within the 14-day period during which the continuous glucose monitoring (CGM) device was attached. Asymptomatic glucose profiles after meals were defined as symptom-free glycemic changes within 3 hours after starting a meal. To avoid the effects of the intake of other foods, glucose profiles in which another meal was consumed from 2 hours prior to three hours after the baseline meal were excluded. Asymptomatic glucose profiles consisted of up to one series per patient per day, and the total number of profiles was designated as the N-profile.

https://doi.org/10.5230/jgc.2021.21.e31

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Statistical analysis

The patient characteristics and surgical and postoperative findings were collected from our database and information contained in the electronic medical records. Based on the measurement results obtained by CGM, we determined the mean, maximum, and minimum glucose levels, as well as the percentage of time in the target range. Hypoglycemia was defined as a glycemic level of < 70 mg/dL [15]. Furthermore, the asymptomatic glucose profiles were compared among the four operative procedures. All the missing values obtained by employing the CGM were adjusted by linear interpolation according to the single imputation method [16]. All continuous variables are presented as median values. Statistical analyses were conducted using the Mann-Whitney U test, Kruskal-Wallis test, and chi-squared test. Differences were considered statistically significant when the P-value was less than 0.05. All statistical analyses were performed using JMP Pro 13 (SAS Institute Japan Ltd., Tokyo, Japan) for Windows.

RESULTS

Patient characteristics

The patient background data are presented in **Table 1**. A total of 40 patients were prospectively enrolled and 10 patients were enrolled for each procedure. The DG-BI group had a significantly shorter period since surgery than the other three surgical groups (P=0.025). The surgical approach and pathological stage differed significantly among the four groups. There were no statistically significant differences in the HbA1c levels or nutritional status among the four groups.

Table 1. Background of the patients

Variables	DG-BI (n=10)	DG-RY (n=10)	TG-RY (n=10)	PPG (n=10)	P-value
Sex, No. (%)					0.493
Male	3 (30)	6 (60)	6 (60)	5 (50)	
Female	7 (70)	4 (40)	4 (40)	5 (50)	
Age (yr) [IQR]	60 [48–70]	63 [55–68]	62 [46–70]	54 [46–65]	0.798
Periods from operation (mon) [IQR]	7.1 [6.7–19.2]	23.5 [19.5–26.6]	20.3 [14.9–26.1]	20.9 [11.4–26.5]	0.025
Preoperative BMI (kg/m^2) [IQR]	20.3 [18.0–27.4]	21.7 [19.0–26.5]	23.6 [19.3–25.6]	20.3 [19.2–21.6]	0.363
Postoperative BMI* (kg/m^2) [IQR]	19.0 [16.1–23.1]	21.3 [18.4–23.5]	20.5 [19.4–23.1]	19.1 [17.9–20.6]	0.250
Reduction rates in BMI† (%) [IQR]	8.4 [5.2–14.6]	4.6 [0.9–9.8]	9.0 [1.6–16.3]	4.6 [–1.9–9.9]	0.274
Serum total protein (g/dL) [IQR]	7.1 [6.8–7.4]	7.0 [6.7–7.3]	6.8 [6.5–7.3]	7.0 [6.8–7.7]	0.555
Serum prealbumin (mg/dL) [IQR]	23.4 [18.6–28.7]	23.0 [21.8–29.3]	22.0 [18.4–26.5]	24.7 [20.3–28.2]	0.746
Serum albumin (g/dL) [IQR]	4.3 [4.2–4.6]	4.2 [4.0–4.5]	4.1 [4.1–4.3]	4.2 [4.1–4.3]	0.581
Serum hemoglobin (g/dL) [IQR]	12.9 [12.2–14.3]	13.6 [12.2–15.0]	12.1 [11.3–13.2]	13.0 [12.7–13.4]	0.214
Blood glucose level (mg/dL) [IQR]	96 [95–99]	96 [89–114]	93 [88–100]	97 [93–103]	0.828
HbA1c (%) [IQR]	5.7 [5.3–5.9]	5.7 [5.6–5.9]	5.6 [5.5–5.8]	5.5 [5.4–5.9]	0.782
Approach					0.001
Open	0 (0)	2 (20)	6 (60)	0 (0)	
Laparoscopy	10 (100)	8 (80)	4 (40)	10 (100)	
pStage, No. (%)					<0.001
I	10 (100)	9 (90)	3 (30)	9 (90)	
II	0 (0)	1 (10)	7 (70)	1 (10)	

DG-BI = distal gastrectomy with Billroth-I reconstruction; DG-RY = distal gastrectomy with Roux-en-Y reconstruction; TG-RY = total gastrectomy with Roux-en-Y reconstruction; PPG = pylorus-preserving gastrectomy; IQR = interquartile range; BMI = body mass index.
*At the beginning of the study; †From the operation to the beginning of the study.

https://doi.org/10.5230/jgc.2021.21.e31

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Table 2. Glucose concentrations and percentage of time in the target range

Variables	DG-BI (n=10)	DG-RY (n=10)	TG-RY (n=10)	PPG (n=10)	P-value
Mean glucose level (mg/dL) [IQR]	89 [80–104]	93 [87–103]	95 [88–102]	87 [83–95]	0.627
Maximum glucose level (mg/dL) [IQR]	192 [175–244]	241 [206–283]	259 [219–288]	175 [161–193]	<0.001
Minimum glucose level (mg/dL) [IQR]	44 [40–49]	41 [40–45]	40 [40–43]	46 [40–54]	0.162
Percentage of time in 70–140 mg/dL range, % [IQR]	75.6 [60.7–81.4]	69.7 [60.1–79.0]	62.0 [43.2–72.0]	87.9 [70.5–95.0]	0.033
Percentage of time above 140 mg/dL, % [IQR]	6.4 [1.4–16.7]	10.0 [5.9–14.4]	11.3 [9.0–18.0]	2.6 [1.2–3.9]	0.001
Percentage of time below 70 mg/dL, % [IQR]	14.8 [4.6–34.3]	19.7 [8.4–29.6]	24.1 [13.4–45.3]	10.1 [4.4–28.1]	0.324

DG-BI = distal gastrectomy with Billroth-I reconstruction; DG-RY = distal gastrectomy with Roux-en-Y reconstruction; TG-RY = total gastrectomy with Roux-en-Y reconstruction; PPG = pylorus-preserving gastrectomy; IQR = interquartile range.

Glucose concentration measured by CGM and percentage of time in the target range

Table 2 shows each of the glucose levels during the entire measurement period and the percentage of time in the target range of 70–140 mg/dL. The mean glucose levels did not differ significantly among the four gastrectomy groups. However, as to the maximum glucose value, the highest was 259 mg/dL in the TG-RY while the lowest, 175 mg/dL, was seen in the PPG. Thus, the highest and lowest values differed significantly among the four groups. Moreover, periods during which the glycemic levels were within the optimal range, i.e. ≥70 mg/dL and <140 mg/dL, were the longest in the PPG (87.9%) and shortest in the TG-RY (62.0%), with significant differences among the four groups. In contrast, the periods of hyperglycemia, with glucose levels ≥140 mg/dL, were the longest in the TG-RY (11.3%) and shortest in the PPG (2.6%), showing statistically significant differences among the four groups.

Asymptomatic glucose profiles after meals

Fig. 2 shows the asymptomatic glucose profiles after meals for the four types of gastrectomy. During the five days of diary recording, the N-profiles were 47, 46, 38, and 46 for the procedures of DG-BI, DG-RY, TG-RY, and PPG, respectively. The N-profiles of TG-RY were lower than those of the other surgical procedures because post-TG-RY patients generally had larger numbers of meals, and there were relatively few glucose profiles that met the definition for an asymptomatic glucose profile. PPG showed the slowest increase and a subsequent

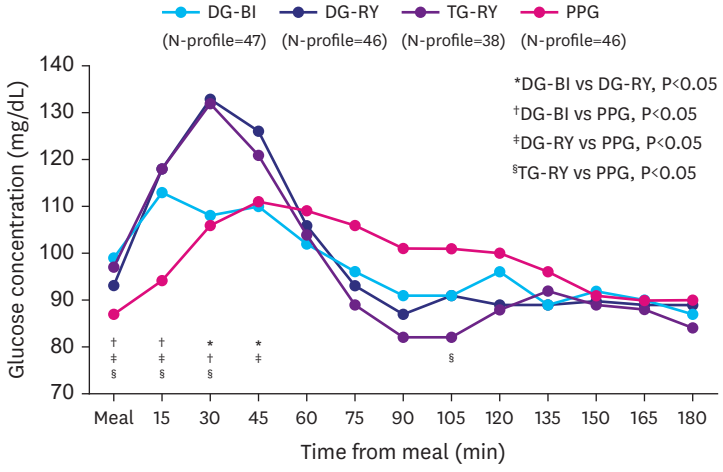

Fig. 2. Asymptomatic glucose profiles after meals of the four types of gastrectomy. The median glucose levels, measured by continuous glucose monitoring, every 15 minutes from the start of a meal to 180 minutes thereafter, are presented for each procedure. The total number of asymptomatic glucose profiles (N-profiles) was 47, 46, 38, and 46 in DG-BI, DG-RY, TG-RY, and PPG, respectively.
DG-BI = distal gastrectomy with Billroth-I reconstruction; DG-RY = distal gastrectomy with Roux-en-Y reconstruction; TG-RY = total gastrectomy with Roux-en-Y reconstruction; PPG = pylorus preserving gastrectomy.

https://doi.org/10.5230/jgc.2021.21.e31

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gradual decrease in glucose fluctuations, with neither hyperglycemia nor hypoglycemia, as compared to the other three procedures. In DG-BI, DG-RY, and TG-RY, the glycemic levels were observed to rise rapidly after starting a meal, with the glucose concentration in DG-BI peaking at 15 minutes after eating, and there were remarkable glycemic elevations in DG-RY and TG-RY exceeding 130 mg/dL at 30 minutes postprandially. The glycemic levels subsequently decreased until approximately 90 minutes after eating in the patients who underwent the three procedures other than PPG. In particular, a sharp glycemic drop was observed in DG-RY and TG-RY, with the lowest glycemic levels observed being 81 mg/dL in TG-RY at 105 minutes postprandially.

DISCUSSION

We prospectively investigated the postprandial glycemic fluctuations without dumping symptoms in patients who had undergone gastric cancer surgery. To the best of our knowledge, this is the first investigation of real-time asymptomatic glucose changes after several types of gastrectomy using CGM. The following findings were obtained: First, postprandial elevation and the subsequent drop in the glucose levels were most gradual in the PPG group, with no appearance of hyperglycemia or hypoglycemia. Second, the postprandial glucose levels in the TG-RY and DG-RY groups showed a rapid increase immediately after eating, followed by a marked decrease, resulting in lower glycemic levels in the TG-RY group. Third, the DG-BI group also showed a sharp rise after meals and a subsequent decline in postprandial glucose levels; however, the glycemic fluctuation range was smaller than that observed in the TG-RY and DG-RY groups.

PPG, a function-preserving gastrectomy, enables the maintenance of a sufficient remnant stomach volume and preservation of the pyloric function [17]. The most gradual and mildest increase and subsequent decline in the postprandial glucose values in PPG are attributable to sufficient storage capacity that may have been maintained after PPG as compared to the other procedures, resulting in the prevention of a rapid influx of food into the duodenum and small intestine. This theory might be supported by reports suggesting gastric emptying after ingestion of a meal to be slower after PPG than after DG-BI [18,19].

Postprandial asymptomatic glucose profiles in TG-RY and DG-RY showed spike-like glycemic fluctuations, rising immediately after the start of meals and subsequently dropping. As one of the mechanisms underlying these glycemic spikes, there might be a faster flow of food into the jejunum, resulting in a more rapid absorption of carbohydrates and subsequent glucose elevation, due to the lack of storage capacity caused by the absence of part or all of the stomach and loss of pyloric function. Moreover, postprandial hyperglycemia might further stimulate the secretion of incretins and gastrointestinal hormones, resulting in hyperinsulinemia followed by a rapid decrease in the glucose levels [20,21]. Disorders involving rapid digestion and subsequent fast absorption of food reflected in the rapid rise and subsequent drop in postprandial glucose levels might be a cause of the marked weight loss experienced by patients after RY reconstruction [22].

In addition, postprandial glucose spikes have recently been demonstrated in healthy subjects without conditions of impaired glucose tolerance, such as diabetes mellitus [23]. These spikes were also associated with the induction of endothelial dysfunction and oxidative stress, resulting in a risk of arteriosclerotic diseases, such as myocardial infarction [24-27].

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Considering that marked postprandial glucose spikes were more commonly observed in TG-RY and DG-RY than in the other two procedures, R-Y reconstruction, which is a non-physiological reconstructive procedure in that food does not pass through the duodenum, might adversely influence postprandial asymptomatic glucose fluctuations, while the other procedures have relatively little impact.

Additionally, TG-RY showed lower postprandial glycemic levels following glucose spikes, and the hypoglycemic period with glucose <70 mg/dL during CGM measurement was longer in the TG-RY group than in the other three procedure groups. Using CGM, Kubota et al. demonstrated nocturnal hypoglycemia after TG-RY in gastric cancer [28]. In addition, several hypoglycemic episodes after RY gastric bypass in obese patients have been reported to be asymptomatic [29]. Given that hypoglycemia is known to be associated with an increased risk of cardiovascular events and mortality [30-32], postprandial hypoglycemia might have a greater effect on the cardiovascular systems of post-TG-RY patients than in those who had undergone other forms of gastrectomy.

On the other hand, the results of comparisons between DG-BI and DG-RY, examining the amount of residue in the remnant stomach and the function of gastric emptying are controversial [33-35]. The difference in the postprandial asymptomatic glucose profiles between DG-BI and DG-RY might be affected by variability in the times that incretin hormones, secreted by so-called K-cells existing mainly in the duodenum and proximal jejunum, exert their actions, depending on the presence or absence of food passing through the duodenum and proximal jejunum [21]. In addition, a larger remnant stomach may have been maintained with DG-BI than with DG-RY, and the consequent greater volume capacity may have favored postprandial glycemic fluctuation.

In the present study, even in patients without symptoms and in those with a relatively long postoperative period of 3 months to 3 years after surgery, postprandial glucose profiles were found to be unstable with some of the surgical procedures performed. Although our previous study suggested that postprandial glycemic fluctuations with dumping symptoms were more unstable than those without symptoms [7], differences in the underlying glycemic fluctuations without symptoms might affect the frequency of dumping. This hypothesis is supported by a report describing dumping syndrome as most commonly experienced after TG-RY and least commonly after PPG, among the various gastrectomy procedures [36]. In addition, the measurement of glucose variability using CGM appears to be useful for detecting asymptomatic profiles, as well as adverse glucose profiles, such as glycemic spikes and hypoglycemia, for a certain period after the operation.

This study had several limitations. First, it was conducted at a single institution and had a small sample size, despite its prospective design. A multi-institution study with a sufficient sample size should be conducted to confirm the results obtained. Second, there were differences in the postoperative period among the four surgical procedures. Although these differences may have impacted the postprandial glucose profiles, these effects might be limited, considering that patients experienced quality of life recovery 1 to 3 months after gastrectomy and postoperative body weights stabilized at six months after surgery [37,38]. Third, the dietary details were not recorded in this study, even though caloric intake had a major effect on the postprandial glucose profiles. Postoperative dietary intake, which can be predicted to some extent from postoperative BMI changes, might be affected by the surgical procedure performed. Finally, the effect of differences in glycemic fluctuation among

https://doi.org/10.5230/jgc.2021.21.e31

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surgical procedures on postoperative body weight and nutritional indicators have not been investigated. The evaluation of the relationship between glucose profiles and postoperative nutritional status requires further study.

In conclusion, postprandial asymptomatic glycemic changes appear to differ depending on the surgical procedure performed to treat gastric cancer. In particular, PPG was characterized by the mildest glycemic fluctuations, while TG-RY and DG-RY showed glucose spikes, rising immediately after meals and subsequently dropping. The preservation of pyloric function and physiological reconstruction methods that do not alter food pathways may be advantageous in terms of postprandial glucose profiles after gastrectomy.

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