**Post-gastrectomy hypoglycemia: a novel concept unveiled by a prospective study**

Takeshi Kubota1, Masayuki Yubakami1, Emi Ushigome2, Takuma Ohashi1, Katsutoshi Shoda1, Hirotaka Konishi1, Atsushi Shiozaki1, Hitoshi Fujiwara1, Kazuma Okamoto1, Michiaki Fukui2, Eigo Otsuji1

1 Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii‑cho, Kawaramachi‑Hirokoji, Kamigyo‑ku, Kyoto 602‑8566, Japan

2 Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, 465 Kajii‑cho, Kawaramachi‑Hirokoji, Kamigyo‑ku, Kyoto 602‑8566, Japan

**Correspondence to:**

Takeshi Kubota, M.D., Ph.D.

Division of Digestive Surgery, Department of Surgery,

Kyoto Prefectural University of Medicine

465 Kajii‑cho, Kawaramachi‑Hirokoji, Kamigyo‑ku, Kyoto 602‑8566, Japan

Phone: +81-75-251-5527

Fax: +81-75-251-5522

E-mail: tkubot@koto.kpu‑m.ac.jp

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**ABSTRACT**

**Objective**: Late dumping syndrome is a common post-gastrectomy complication characterized by reactive hypoglycemia. This study aimed to reveal the glycemic trend in patients who had undergone gastrectomy for gastric cancer and to clarify its changes over time in association with post-gastrectomy symptoms.

**Design:** We conducted a prospective study of patients who underwent curative gastrectomy for gastric cancer. The patients underwent continuous glucose monitoring (CGM) twice, at 1 and 12 months post-gastrectomy, and were assessed with the Post-gastrectomy Syndrome Assessment Scale 37-item questionnaire (PGSAS-37) at 1, 6, and 12 months post-gastrectomy.

**Results:** We studied 71 patients who underwent gastrectomy for gastric cancer between November 2017 and April 2020. Our results revealed that hypoglycemia (< 70mg/dL), especially nocturnal hypoglycemia (0 − 6 o’clock), occurred frequently even 12 months post-gastrectomy (mean, 42.5 to 27.6% [nocturnal hypoglycemia: 71.1 to 48.4%] in total gastrectomy, 16.3 to 18.7% [nocturnal hypoglycemia: 30.3 to 39.8%] in distal gastrectomy). Glycemic variability (expressed by standard deviation of glycemic trend) was exacerbated in both gastrectomy groups (mean, 28.9 to 45.3 mg/dL in total gastrectomy vs. 22.9 to 33.2 mg/dL in distal gastrectomy).On the other hand, PGSAS-37 score was unchanged, and living status and quality of life tended to improve. Hypoglycemia unawareness, which includes postprandial hypoglycemia without symptoms and nocturnal hypoglycemia, was evident even 12 months post-gastrectomy.

**Conclusion:** We would like to proposea novel concept, **‘**post-gastrectomy hypoglycemia,’ which includes late dumping syndrome with/without symptoms and nocturnal hypoglycemia. We hope this becomes recognized as an important issue pertaining to post-gastrectomy syndrome.

**Summary**:

What is already known about this subject?

What are the new findings?

How might it impact on clinical practice in the foreseeable future?

**INTRODUCTION**

Gastric cancer is the fifth most common type of cancer and the third most common cause of cancer-related death worldwide.[1] Surgical resection has been the only curative treatment and regional lymphadenectomy is recommended as a part of the procedure. However, because of surgical alteration in gastrointestinal anatomy, many patients who undergo gastrectomy suffer from postoperative sequelae. Dumping syndrome is the most common post-gastrectomy syndrome and has been well known to impair patient quality of life (QOL).[2] Tack et al. had reported that dumping syndrome occurs in up to 40% of patients who undergo gastrectomy.[3]

Dumping syndrome comprises a constellation of early and late symptoms that may occur jointly or separately.[4] Early dumping symptoms occur within the first hour after a meal, as the intake of the hyperosmotic food causes fluid to rapidly shift from the plasma compartment to the intestinal lumen, which results in hypotension and a sympathetic nervous system response. Early dumping syndrome is characterized by gastrointestinal symptoms (abdominal pain, bloating, borborygmi, nausea, and diarrhea) and vasomotor symptoms (fatigue, a desire to lie down after meals, flushing, palpitations, perspiration, tachycardia, hypotension, and, rarely, syncope). In contrast, late dumping syndrome usually occurs 1–3 h after a meal and is the result of an incretin‐driven hyperinsulinemic response to carbohydrate ingestion. It is characterized by hypoglycemia‐related symptoms related to neuroglycopenia (fatigue, weakness, confusion, hunger, and syncope) and autonomic/adrenergic reactivity (perspiration, palpitations, tremor, and irritability).

In actual clinical practice, dumping syndrome may not always be clearly separated into early and late symptoms because the symptoms’ onsets overlap. If a patient is symptomatic, blood glucose concentration is measured; if hypoglycemia is present, a glucose injection or diet therapy (oral glucose administration) is administered. In contrast, if a patient is asymptomatic, blood glucose is not routinely measured (at most three times a day, before meals, for patients with diabetes) prior to discharge from the hospital, and may not be measured at all after discharge.

We had previously measured the trend of subcutaneous glucose concentration by continuous glucose monitoring (CGM) in patients who were of 1-month post-gastrectomy status, which had revealed that patients who had undergone gastrectomy had larger glycemic variability and longer period of nocturnal hypoglycemia than we had expected; this was especially noted in patients who had undergone total gastrectomy.[5] However, we believe that various symptoms of dumping syndrome improve over time (6–12 months after surgery). In fact, poor post-operative nutritional status, observed as decrease in hemoglobin, albumin, and body weight, starts to stablilize 3–6 months after gastrectomy and then recovers.[6] Therefore, we hypothesized that glycemic variability and hypoglycemia may also improve with time.

In this study, we compared glycemic trends with changes in symptoms of dumping syndrome from 1–12 months post-gastrectomy. To our knowledge, there have been no reported studies that had investigated changes in individuals’ dumping syndrome symptoms and glycemic trends over time post-gastrectomy.

**MATERIALS AND METHODS**

**Ethical standards**

This study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. All patients provided written informed consent to undergo gastrectomy and to use their clinical data for research purposes. This study was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine (ERB-C-975–2).

**Patients**

Between November 2017 and April 2020, a total of 172 patients with gastric cancer underwent curative distal gastrectomy (DG) or total gastrectomy (TG) at our hospital. After excluding 51 patients who had diabetes, had undergone combined resection of other organs (excluding cholecystectomy), had undergone gastrectomy by laparotomy with thoracotomy, had jejunostomy placement, or had other organ malignancies, a total of 121 patients were enrolled for the first assessment of blood glucose levels. Diabetes was defined as under treatment, or a random blood glucose concentration ≥ 200 mg/dL and HbA1c ≥ 6.5%[7]. After exluding another 50 patients who had undergone adjuvant chemotherapy, had recurrence, had missing data, or had an American Society of Anesthesiologists physical status classification (ASA-PS) ≥ 2, a total of 71 patients were enrolled for the second assessment of blood glucose levels. A flow diagram of the patient selection process is presented as Figure 1.

Body mass index, blood glucose, and HbA1c were evaluated at the first visit before surgery. The clinical and pathological stages of the malignancies were determined on the basis of the 14th edition of the Japanese Classification of Gastric Carcinoma.[8]

**Continuous glucose monitoring**

A CGM device (FreeStyle Libre® Flash Glucose Monitoring System, Abbott Diabetes Care Inc., Alameda, CA, USA), which was used to document the post-gastrectomy glycemic profiles, provided records of individuals’ interstitial glucose concentrations, trends, and patterns. Interstitial glucose concentrations were continuously measured by a small sensor filament inserted just under the skin. Glucose concentrations were recorded every 15 min for up to 14 days and the data were displayed when scanned. A Flash CGM sensor was placed subcutaneously in each patient’s left upper arm immediately prior to discharge from the hospital. CGM was performed twice – at 1 and 12 months post-gastrectomy. The data were downloaded and analyzed using standard measures of amplitude and timing, including the average, standard deviation (SD), and percentage of time within the target range (glucose concentration < 70 mg/dL [time below range, TBR], 70 − 180 mg/dL [time in rage, TIR], > 180 mg/dL [time above range, TAR]).

The SD was evaluated as an index of glycemic variability. The data from the first 10 hours (until the data had become stable) after placement of the CGM sensor was deleted.

**Post-gastrectomy syndrome**

The Post-gastrectomy Syndrome Assessment Scale 37-item questionnaire (PGSAS-37), developed by the Japan Post-gastrectomy Syndrome Working Party, was used to evaluate post-gastrectomy syndrome, including dumping syndrome.[9] The main outcomes on the PGSAS-37 were recorded on 5-point scales for seven symptoms (esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping), five measures of independent living status (body weight loss, ingested amount of food per meal, necessity for additional food, quality of ingestion, and ability for working), and four measures of QOL (dissatisfaction with daily life, dissatisfaction with symptoms, dissatisfaction with meals, and dissatisfaction with work). Dumping symptom score was calculated as the mean value for early dumping abdominal symptoms, early dumping general symptoms, and late dumping symptoms. The total symptom score was calculated as the mean score for the seven symptoms. High scores for the ingested amount of food per meal and the quality of ingestion reflected positive outcomes, whereas low scores for necessity for additional food, ability to work, and dissatisfaction with daily life reflected negative outcomes. All participants received the questionnarie and were instructed to complete it for the period between discharge and 1 month after the procedure, and then to return it to the department. The same questionnaire was performed again at the 6- and 12-month follow-up visits.

**Statistical analysis**

All statistical analyses were performed using JMP software, version 13 (SAS Institute, Cary, NC, USA). Continuous variables were analyzed using the Student’s t-test or the Wilcoxon signed-rank test, and were expressed as the mean ± SD for patient demographics and characteristics, and as the mean ± standard error (SE) for the results of the CGM and PGSAS-37 questionnaire. Categorical variables were analyzed using Pearson’s χ2 test were expressed as frequencies. Correlation between glucose measures of the CGM and the PGSAS-37 scores was evaluated using Spearman’s correlation test. The statistical tests were two-sided and *P* < 0.05 was considered statistically significant.

**RESULTS**

**Patient demographics and characteristics**

Of the 71 patients who were enrolled, 65 underwent DG and 6 underwent TG. Because patients who had undergone adjuvant chemotherapy or had recurrence were excluded, the proportions of patients with early stage and of those who underwent laparoscopic or robotic approach were relatively high. There were no significant differences in gender, preoperative BMI, random blood glucose, and HbA1c between the patients in the DG and TG groups. Due to our policy of avoiding TG in the elderly because of their poor QOL, the age of patients with TG tended to be low. Not surprisingly, patients in the TG group had more advanced cancer and underwent a more open approach. Complications which might have affected postoperative glycemic trend were minimum. Patient demographics and characteristics are presented in Table 1.

**Table 1.** Patient demographics and characteristics.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total (*n* = 71) | DG (*n* = 65) | TG (*n* = 6) | *P* value\*\* |
| Age (years) | 65.9 ± 11.2 | 66.4 ± 10.2 | 60.0 ± 18.8 | 0.1786 |
| Gender, male/female | 35/36 | 32/33 | 3/3 | 0.9712 |
| BMI | 22.4 ± 3.2 | 22.4 ± 3.2 | 22.7 ±2.4 | 0.9065 |
| Casual blood glucose level (mg/dL) | 109.3 ± 27.0 | 109.4 ±28.2 | 108.0 ± 6.8 | 0.8151 |
| HbA1c (%) | 5.7 ± 0.5 | 5.8 ± 0.5 | 5.6 ± 0.4 | 0.4636 |
| Approach, open/laparoscopic or robotic | 18/53 | 17/48 | 2/4 | 0.7097 |
| Pathological T factor, T1/2/3/4\* | 47/6/12/6 | 43/5/11/6 | 4/1/1/0 | 0.6184 |
| Pathological N factor, N0/1/2/3\* | 53/12/4/2 | 47/12/4/2 | 4/1/1/0 | 0.2455 |
| Pathological stage, I/II/III/IV\* | 50/12/9 | 45/12/8/0 | 5/0/1/0 | 0.5303 |
| Complication, ≥ CD grade 2 (%) | 9 (12.7) | 9 (13.8) | 0 (0) | 0.1881 |
| Hospital stays (days) | 13.3 ± 12.3 | 13.4 ± 1.5 | 12.0 ± 5.0 | 0.7871 |

BMI, body mass index; DG, distal gastrectomy; TG, total gastrectomy, CD, Clavien-Dindo classification.

Continuous variables are presented as means with standard deviation.

\*Pathological T, N factors and stages of the malignancies were determined on the basis of the 14th edition of the Japanese Classification of Gastric Carcinoma.

\*\**P* value, DG vs. TG.

**Change over time in standard glucose measures post-gastrectomy**

Figure 2 show the changes in CGM glucose measurementsfrom 1–12 months after DG and TG. The average glucose level remained unchanged in the DG group and slightly improved in the TG group (92.9 ± 1.7 to 96.8 ± 1.7 mg/dL vs. 82.9 ± 5.4 to 97.8 ± 6.1 mg/dL, respectively). Glycemic variability (SD) of the TG group was significantly higher than that of the DG group, and increased in both groups from 1–12 months (28.9 ± 2.5 to 45.3 ± 5.9 mg/dL vs. 22.9 ± 0.8 to 33.2 ± 1.4 mg/dL, respectively). TIR and TBR of the TG group were significantly lower and higher, respectively, than those of the DG group at 1 month; however, both TIR and TBR of the TG group were almost similar to those of the DG group at 12 months. (TIR: 63.5 ± 8.8 to 74.7 ± 8.5% vs. 82.8 ± 2.1 to 77.4 ± 2.4%, rspectively; TBR: 42.5 ± 7.2 to 27.6 ± 8.7% vs. 16.3 ± 2.2 to 18.7 ± 2.5%, respectively). TIR and TBR of the DG group remained almost unchanged from 1–12 months. TAR was low at 1 month but was increased at 12 months in both the TG and DG groups (1.5 ± 0.8 to 8.5 ± 2.0% vs, 0.9 ± 0.3 to 3.8 ± 0.6%, respectively).

The right panel of Figure 2 shows the change in nocturnal (0 − 6 o’clock) glucose parameters from 1–12 months after gastrectomy. The nocturnal average glucose level was overall low, and remained almost unchanged in the DG group (77.5 ± 1.5 to 75.1 ± 1.7 mg/dL), whereas that of the TG group slightly improved to almost reach that of the DG group (63.5 ± 3.0 to 74.7 ± 6.0 mg/dL). Nocturnal TBR was extremely high in the TG group at 1 month. Considering that nocturnal TBR was about 12.0% in patients with local resection of the stomach as a control,[5] it was improving after 12 months but was still high (71.1 ± 12.2 to 48.4 ± 17.8%). The nocturnal TBR of the DG group increased slightly to almost reach that of the TG group by 12 months (30.3 ± 3.9 to 39.8 ± 5.1%).

**Change over time in post-gastrectomy syndrome**

The results from the PGSAS-37 questionnaire at 1, 6, and 12 months after gastrectomy are presented in Figure 3. In the DG group, almost all symptoms showed no change or improved. In the TG group, abdominal pain improved as well as DG. However, meal-related distress, dumping symptom, and indigestion in the TG group tended to be worse at 12 months, with higher scores than those in the DG group (meal-related distress [mean]: 3.2 vs. 1.9, *P* = 0.0399; dumping symptom: 3.2 vs. 1.6, *P* = 0.0226; indigestion: 2.9 vs. 2.2, *P* = 0.3395). Diarrhea in the TG group remained higher than that in the DG group throughout the study period (2.6 to 3.2 to 2.8 vs. 1.8 to 2.3 to 2.0, respectively). The PGSAS-37 total symptom score in both groups did not change after 12 months (Fig. 3-1).

Regarding living status and QOL, the rate of body weight loss was significantly higher in the TG group than that in the DG group, which settled down from 6–12 months in both groups (-17.4 ± 3.0 vs. -8.1 ± 0.9%, *P* = 0.0046; -16.4 ± 3.4 vs. -8.0 ± 1.1%, *P* = 0.0024). Ingested amount of food per meal increased in both the DG and TG groups, and the necessity for additional food and quality of ingestion decreased accordingly. Dissatisfaction with daily life, symptoms, and meals were higher in the TG group than of those in the DG group during the entire study period, but both groups showed a decline in these measures by 12 months (dissatisfaction with daily life [mean]: 3.4 to 2.6 to 2.8 vs, 2.6 to 2.1 to 1.8; dissatisfaction with symptoms: 3.0 to 2.7 to 2.7 vs. 2.4 to 2.0 to 1.8; dissatisfaction with meals: 3.8 to 3.2 to 3.0 vs. 3.0 to 2.3 to 2.0; respectively) (Fig. 3-2).

**Correlation between the PGSAS-37 dumping symptom score and the CGM glucose measures**

Late dumping syndrome is defined as hypoglycemia secondary to excess insulin secretion following meal-induced hyperglycemia.[10] Therefore, it was assumed that the PGSAS-37 dumping symptom score might have had a positive correlation with glycemic variability (SD) and hypoglycemia (TBR). However, no significant correlations were found between these measures at 12 months post-gastrectomy (Fig. 4). However, individual daily glucose trends accurately captured hypoglycemia due to dumping syndrome (Supplemental Fig. 1A). This indicates, therefore, that the TBR and SD of the CGM are not reflected in the PGSAS-37 dumping symptom score.

**Hypoglycemia unawareness**

We also investigated the number of patients with hypoglycemia unawareness. Post-gastrectomy hypoglycemia unawareness was defined as follows: dumping symptom score ≤ 1, diurnal (6 − 24 o’clock) TBR > 20%, and nocturnal TBR > 50%. Our results showed that diurnal hypoglycemia unawareness and nocturnal hypoglycemia of both the DG and TG groups tended to improve, but occurred in 8.5% and 14.1% of the patients, respectively, even 12 months post-gastrectomy. Overall, the frequency of hypoglycemia unawareness was higher in the TG group than in the DG group during the study period. In particular, the high frequency of nocturnal hypoglycemia in both groups was prominent (Table 2).

**Table 2.** Hypoglycemia unawareness in patients with gastrectomy1 and 12 months after gastrectomy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Total (*n* = 71) | | DG (*n* = 65) | | TG (*n* = 6) | |
| 1M | 12M | 1M | 12M | 1M | 12M |
| Diurnal hypoglycemia unawareness\* (%) | 9 (12.7) | 6 (8.5) | 8 (12.3) | 7 (10.8) | 1 (16.7) | 1 (16.7) |
| Nocturnal hypoglycemia\*\* (%) | 22 (31.0) | 17 (14.1) | 16 (24.6) | 15 (23.1) | 6 (100.0) | 2 (33.3) |

DG, distal gastrectomy; TG, total gastrectomy.

\*Dumping symptom score ≤ 1.0 and diurnal TBR (time below range) > 20%, \*\*Nocturnal TBR > 50%

**DISCUSSION**

This prospective study evaluated the post-gastrectomy glycemic trends and its associated symptoms using CGM and the PGSAS-37 questionnaire, respectively, over a period of 12 months. Hypoglycemia occurred frequently, even at 12 months post-gastrectomy, and glycemic variability was rather exacerbated despite post-gastrectomy symptoms, living status and QOL were unchanged or improved. Furthermore, given the presence of patients who did not have hypoglycemic symptoms or nocturnal hypoglycemia, we recognized that hypoglycemia unawareness might have been an important issue after gastrectomy. Therefore, we proposed a novel concept, ‘post-gastrectomy hypoglycemia’, which includes late dumping syndrome with/without symptoms and nocturnal hypoglycemia. Many clinicians may be relieved by the apparent improvement of patients, but they need to be aware that this cannot be detected by the patient's complaints, random blood glucose levels, or HbA1c, and may be only grasped by CGM.

With the advent of the CGM, the target treatment range for diabetes mellitus (DM) had been clearly set in 2019, and the mode of glycemic control began changing.[11] Treatment for hyperglycemia is the mainstream for patients with DM, but attention should also be paid to hypoglycemia and glycemic variability due to poor control. Many recent studies on patients with DM have reported that hypoglycemia is a risk factor for cardiovascular diseases,[12-14] such as cardiac ischemia and arrhythmia,[15, 16, 17], and dementia in the elderly.[18, 19] Glycemic variability has also been reported to be associated with coronary artery diseases.[20-22] Various adverse clinical outcomes due to hypoglycemia and glycemic variability have been reported even in non-diabetic patients. Nusca et al. had shown that glycemic variability is a potential risk factor for the development of cardiac complications in both diabetic and non-diabetic patients.[23] In our study, gastrectomy patients without DM who underwent gastrectomy had a high rate of hypoglycemia, which occurred frequently, even at 12 months post-gastrectomy. In addition, glycemic variability increased despite the type of gastrectomy. As gastric cancer patients are also elderly, patients who undergo gastrectomy may be at risk of developing cardiovascular diseases and/or dementia. The reason for this glycemic trend exacerbation may be predicted from the PGSAS-37 questionnaire. Post-grastrectomy, patients become accustomed to daily life and eating habits after with time; therefore, the ingested amount of food per meal is increased and the amount of additional food is decreased. We believe that this phenomena is due to postprandial hyperglycemia, which is followed by reactive hypoglycemia, which results in increased glycemic variability.

Another important issue is the presence of patients with hypoglycemia unawareness. Repeated and prolonged hypoglycemia may lead to hypoglycemia unawareness,[24] which obscures a patient’s notice and a physician’s suspicion of possible hypoglycemia. No significant correlation between the PGSAS-37 dumping symptom score with TBR or SD were found at 12 months post-gastrectomy. In consideration of the heterogeneity of dumping symptoms, it might not prove objectively that the PGSAS-37 dumping symptom score, including early and late dumping elements, and TBR were correlated. However, it is possible that a patient may not complain of dumping symptom, which may suggest the presence of hypoglycemia unawareness. Our results revealed that the PGSAS-37 symptom scores, except for TG, were unchanged or tended to improve 12 months post-gastrectomy despite the high frequency of hypoglycemia, which supports the hypothesis of asymptomatic patients having dumping syndrome. Furthermore, we observed that 8.5% of patients had diurnal hypoglycemia unawareness (PGSAS-37 dumping score ≤ 1 and diurnal TBR > 20%) and that 14.1% of patients had nocturnal hypoglycemia (nocturnal TBR > 50%). Night sweats, nightmares, bruxism, and tiredness and headache upon waking have been reported as symptoms of nocturnal hypoglycemia,[25, 26] but these are difficult to identify. Therefore, considering that nocturnal hypoglycemia is also asymptomatic, we believe that patients with hypoglycemia unawareness exist even 12 months post-gastrectomy. On the other hand, in patients who underwent TG, the dumping score probably became apparent because of increased food intake; however, overall, post-gastrectomy symptoms were unchanged or tended to improve, and living status and QOL improved as well. Therefore, it may be hard for clinicians to detect latent hypoglycemia and glycemic variability.

It is still unclear whether nocturnal hypoglycemia is a part of late dumping syndrome or is just an extension of postprandial reactive hypoglycemia. In the condition of hypoglycemia, counterregulation to maintain blood glucose concentration occurs by an autonomic nerve response followed by glycogenolysis and/or gluconeogenesis.[27, 28] We observed that some patients who had undergone TG – but were not included in this cohort – had recovered from reactive hypoglycemia on their own (Supplemental Fig. 1B). One of these patients had been faithfully treated by a dietitian and received oral nutritional supplementation immediately after surgery. However, in our cohort, the mean frequency of hypoglycemia was 40%, and 14% of patients had > 50% of nocturnal hypoglycemia 12 months post-gastrectomy (although it was improving). In patients with nocturnal hypoglycemia, counterregulation might not have worked. The mechanism of the effect of post-gastrectomy on the counterregulation to hypoglycemia is outlined in Figure 5. Repeated exposure to hypoglycemia may impair epinephrine secretion and its autonomic effects, leading to defective glucose counterregulation and hypoglycemia unawareness, which characterize hypoglycemia-associated autonomic failure.[24] Especially in the elderly, the threshold for autonomic symptom activation seems to be changed.[29] In this condition, glycogenolysis of glycogen stores in liver and gluconeogenesis from amino acids predominantly from muscle mass are impaired. From the perspective of symptoms and living status, the results of higher diarrhea and indigestion scores, especially in patients who have undergone TG, suggest that digestion and absorption of nutrients in the small intestine are insufficient despite increased food intake, leading to increased body weight loss. This suggests that patients are in the state of chronic undernutrition, which reduces glycogen stores in the liver (resulting in less glycogenolysis),[30] and facilitates muscle mass reduction (resulting in less gluconeogenesis).[31, 32] This was reflected in the results of our cohort, in whom hypoglycemia (TBR) and glycemic variability (SD) 12 months post-gastrectomy were correlated with body weight loss (Supplemental Fig. 2). In contrast, if epinephrine secretion is triggered by conterregulation at night, it may also cause cardiovascular events. We would like to, therefore, propose a new concept, ‘post-gastrectomy hypoglycemia,’ as one of the post-gastrectomy syndromes. Since nocturnal hypoglycemia is considered to be a mechanism different from late dumping syndrome, we have newly defined ‘post-gastrectomy hypoglycemia,’ which includes late dumping syndrome with/without dumping symptoms and nocturnal hypoglycemia. Therefore, patients with nocturnal hypoglycemia and patients with asymptomatic dumping syndrome are part of a hypoglycemia unawareness subgroup within patients with ‘post-gastrectomy hypoglycemia’ (Fig. 6). Recently, similar events have been reported post-bariatric surgery,[33-35] but in the concept we advocate; having malignancy, not having DM, purpose of surgery, age, body mass index, etc. are basically different from them.

Clinicians need to take action against post-gastrectomy hypoglycemia. Two main treatments, drug and diet therapies, are possible. Several case reports have suggested that alpha-glucosidase inhibitor (α-GI) administration is effective in treating late dumping syndrome.[36-39], because it suppresses the absorption of glucose in the small intestine, which reduces the likelihood of devloping hypoglycemia. It is believed that α-GIs reduce subsequent hypoglycemia by suppressing sudden postprandial hyperglycemia. At first glance, this seems to make sense, given the mechanism of late dumping syndrome. However, it is doubtful whether the suppression of postprandial hyperglycemia by hypoglycemic agents like α-GIs are effective for nocturnal hypoglycemia. Silvio et al. had reported in a 7-day CGM study, that acarbose (an α-GI) attenuated late dumping in a woman who had undergone gastrectomy for gastric cancer.[39] Based on the figure they had presented, acarbose surely attenuated hypoglycemia by decreasing sudden postprandial hyperglycemia. However, nocturnal hypoglycemia appeared slightly worse. In addition, α-GI carries a risk of causing abdominal fullness and ileus,[40, 41] so administration of α-GIs after abdominal surgeries should be done cautiously. On the other hand, somatostatin analogues are able to slow the rate of gastric emptying, slow small bowel transit, and inhibit the release of gastrointestinal hormones, insulin secretion, and postprandial vasodilation; these analogues are, therefore, potentially beneficial for both early and late dumping syndromes.[42, 43] The efficacy of somatostatin analogues for dumping syndrome has been reported by several randomized controlled trials.[44, 45] However, octreotide use may cause hypoglycemia as an adverse effect.[45] Hence, in theory, a worsening or different pattern of hypoglycemia with octreotide is possible. There have been few studies that monitor glucose levels with the CGM system, and the occurrence of hypoglycemia unawareness, including nocturnal hypoglycemia, cannot be denied. In addition, use of somatostatin analogues is impractical because it requires multiple injections daily. Therefore, a combination of drug and diet therapies is a more rational approach. In addition, CGM should be used to monitor late dumping syndrome and an oral hypoglycemic agent should be administered.

This study had several limitations. First, this was a single-institute study and the sample size was small, especially in the TG group. In recent years, there has been a tendency to avoid TG due to its associated poor QOL, and it is a policy to perform proximal or subtotal gastrectomy or a jejunostomy with placement of a feeding tube if TG must be performed. Second, patient food intake was not standardized during glucose monitoring. All patients received dietary advice from a dietician before discharge and at follow-up visits, and provided details of their meal composition and timing through questionnaires. However, it was difficult to accurately evaluate their total energy, protein, fat, and carbohydrate intakes. Therefore, we evaluated the status of patient food intake in terms of ingested amount of food per meal, necessity for additional food, quality of ingestion, and dissatisfaction with meals in the PGSAS-37 questionnaire. Third, the onset of cardiovascular events and dementia after gastrectomy was unknown due to the short postoperative observation period. However, data obtained from our previous cases suggested that patients who had undergone TG had more deaths from other diseases than those in patients who had undergone DG (data not shown). We plan to follow-up these details in a prospective study of the current cohort.

In conclusion, our study revealed that hypoglycemia and glycemic variability persisted at a high frequency even 12 months post-gastrectomy. Furthermore, the presence of hypoglycemia unawareness was identified. Based on our results, we would like to proposea novel concept, **‘**post-gastrectomy hypoglycemia,’ which includes late dumping syndrome with/without symptoms and nocturnal hypoglycemia. We hope this becomes recognized as an important issue pertaining to post-gastrectomy syndrome.

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**Competing interests**

The authors declare that they have no conflicts of interest.

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**FIGURE LEGENDS**

**Figure 1.** Flow diagram of the patient selection process.

ASA-PS, American Society of Anesthesiologists physical status classification; CGM, continuous glucose monitoring; PGSAS-37, Post-gastrectomy Syndrome Assessment Scale 37-item questionnaire.

**Figure 2.** Changes in standard CGM glucose measures from 1–12 months post-gastrectomy.

CGM, continuous glucose monitoring; SD, standard deviation (index of glycemic variability); TAR, time above range (glucose concentration > 180 mg/dL); TBR, time below range (glucose concentration < 70 mg/dL); TIR, time in range (glucose concentration 70 − 180 mg/dL).

Error bar represents standard error. \**P* < 0.05.

**Figure 3-1.** Changes in the Post-gastrectomy Syndrome Assessment Scale 37-item questionnaire scores at 1, 6, and 12 months post-gastrectomy, in terms of symptom scores.

Error bar represents standard error. \**P* < 0.05.

**Figure 3-2** Change in the Post-gastrectomy Syndrome Assessment Scale 37-item questionnaire scores at 1, 6, and 12 months post-gastrectomy, in terms of living status and quality of life score.

Error bar represents standard error. \**P* < 0.05.

**Figure 4.** Correlation between dumping symptom score with (A) hypoglycemia (TBR) and (B) glycemic variability (SD) 12 months post-gastrectomy. The regression line and confidence ellipsoid (0.950) are shown in red and blue, respectively.

SD, standard deviation; TBR, time below range (glucose concentration < 70 mg/dL).

**Figure 5.** Mechanism of the effect of post-gastrectomy on the counterregulation of hypoglycemia.

The effect of chronic undernutrition due to gastrectomy is shown in blue. If patients develop hypoglycemia-associated autonomic failure (HAAF) due to repeated hypoglycemia, this system will fail, resulting in hypoglycemia without autonomic symptoms.

**Figure 6.** Schema representing post-gastrectomy syndrome.

Post-gastrectomy hypoglycemia is a part of glycemic variability, which includes late　dumping syndrome with/without symptoms and nocturnal hypoglycemia. Late dumping syndrome without symptoms and nocturnal hypoglycemia are recognized as hypoglycemia unawareness.

**Supplemental Figure 1. (**A)Glycemic trend of a representative case with hypoglycemia due to late dumping syndrome (black circles). (B)Glycemic trend of a representative case with recovery from postprandial hypoglycemia. Even if postprandial hypoglycemia happens due to late dumping, the patient may recover by counterregulation (red circle).

**Supplemental Figure 2.** Correlation of body weight loss with (A) hypoglycemia (TBR) and (B) glycemic variability (SD) 12 months post-gastrectomy.

The regression line and confidence ellipsoid (0.950) are shown in red and green, respectively.