Surgery Today
https://doi.org/10.1007/s00595-022-02600-w

ORIGINAL ARTICLE

Impact of super energy-dense oral nutritional supplementation (SED ONS) on glycemic variability and food intake postoperatively in gastric cancer patients

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Received: 20 June 2022 / Accepted: 13 September 2022

Abstract

Purpose Adherence to oral nutritional supplements (ONS) to prevent weight loss after gastrectomy is problematic. The present study evaluated the impact of super energy-dense ONS (SED ONS; 4 kcal/mL) on glycemic change and energy intake after gastrectomy.

Methods Gastrectomy patients were placed on continuous glucose monitoring for a 3-day observation period after food intake had been stabilized postoperatively. In addition, they were given 0, 200, and 400 kcal/day of SED ONS on Days 1, 2, and 3, respectively. The primary outcome was the area under the curve < glucose 70 mg/dL (AUC < 70). The secondary outcomes were other indices of glucose fluctuation and the amount of food and SED ONS intake.

Results Seventeen patients were enrolled. The AUC < 70 did not differ significantly with or without SED ONS over the observation period. SED ONS did not cause postprandial hypoglycemia and prevented nocturnal hypoglycemia. The mean dietary intake did not change significantly during the observation period, and the total energy intake increased significantly according to the amount of SED ONS provided.

Conclusion SED ONS after gastrectomy increased the total energy intake without dietary reduction and it did not result in hypoglycemia.

Keywords Gastrectomy · Gastric cancer · Continuous glucose monitoring · Glycemic variability · Oral nutritional supplements

Introduction

According to the 2020 Global Cancer Statistics, gastric cancer is the fifth most diagnosed cancer in the world and the fourth-leading cause of cancer-related death [1]. Curative resection is the mainstay of treatment [2]. Body weight loss (BWL) is a serious postoperative complication because gastrectomy reduces the storage capacity of the stomach and impairs the initial digestion of food, resulting in a poor nutritional status. BWL compromises quality of life and affects the long-term prognosis of gastric cancer patients [3, 4]. Previously, we reported the findings of a randomized controlled trial (RCT) demonstrating the effectiveness of postoperative oral nutritional supplements (ONS) in preventing BWL [5]. Other studies have reported similar results of ONS administration after gastrectomy [6, 7], although some found that ONS did not prevent BWL after gastrectomy [8, 9]. Thus, the efficacy of postoperative ONS for gastric cancer patients

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Published online: 05 October 2022

remains controversial. Moreover, gastrectomy patients may have difficulty ingesting adequate amounts of ONS. Most previous studies, including ours, used standard concentrations of ONS (1–1.5 kcal/mL). However, a very high calorie ONS (4 kcal/mL), Terumeal uplead® (Terumo Corporation, Tokyo, Japan) has now been developed [10]. In the present study, we named this supplement "super energy-dense ONS" (SED ONS) and hypothesized that it might be an effective means of providing more energy to post-gastrectomy patients. Yet, it is necessary to ascertain whether SED ONS is safe and effective for these patients.

In glucose fluctuation after gastrectomy, known as dumping syndrome [11], meal-induced hyperglycemia leads to hypoglycemia resulting from excessive insulin secretion. Since hypoglycemia may increase mortality both directly and indirectly [12], it requires careful monitoring. SED ONS administration after a gastrectomy may result in more frequent, postprandial episodes of hyperglycemia followed by hypoglycemia, which may exacerbate glycemic fluctuations. Continuous glucose monitoring (CGM) may be used to measure the interstitial glucose concentration, which closely approximates the plasma glucose concentration, as an accurate and convenient tool for treating diabetes [13]. Recent studies have reported the use of a flash CGM system to assess patient's glycemic profiles after gastrectomy [14–16].

We conducted the present study to verify the influence of SED ONS on glycemic variability by CGM of patients after surgery for gastric cancer. We also measured energy intake from meals and SED ONS to address the concern that SED ONS may decrease appetite and reduce food intake in patients with reduced gastric capacity following gastrectomy.

Methods

Study design

This preliminary, prospective, monocentric, interventional study was conducted at Tokyo Metropolitan Tama Medical Center. Written informed consent was obtained from all the patients before enrollment. The interventions consisted of CGM placement and ONS administration during hospitalization after gastrectomy for gastric cancer. The inclusion and exclusion criteria were as follows:

Inclusion criteria

1. Age 20 years old or older
2. Ability to ingest food orally
3. Scheduled conventional curative gastrectomy for gastric cancer

Exclusion criteria

1. Current treatment for diabetes or HbA1C≧6.5%
2. Scheduled function-preserving gastrectomy, such as pylorus-preserving gastrectomy, or proximal gastrectomy
3. Allergy to milk or gelatin components
4. Visual impairment with no care giver

Study protocol

Curative gastrectomy for gastric cancer was performed at the study center. The surgeons chose the surgical approach and reconstructive method according to their experience. For distal gastrectomy (DG) they performed Billroth I (DG-BI) or Roux-en-Y reconstruction (DG-RY) and for total gastrectomy (TG), they performed Roux-en-Y reconstruction. The clinical and pathological stages of the malignancies were based on the Japanese Classification of Gastric Carcinoma, 15th edition [2]. Patients received standard postoperative management and the quantity of meals provided began at 600 kcal/day, which was increased gradually. When the meals provided 1300 kcal/day, the patients were enrolled in the study, regardless of the amount of food consumed, and received iPro2 (Medtronic, USA), a CGM device that provides a record of the individual's interstitial glucose concentrations every 5 min, 288 times a day. A CGM sensor with a thin needle was placed on the patient's lower abdomen. Hypoglycemia and hyperglycemia were defined as a glycemic level of < 70 and > 180 mg/dL, respectively, according to the international consensus [13]. Data were downloaded and analyzed using standard measures of amplitude and timing, including the mean, median, standard deviation (SD), maximum, minimum, and percentage of time within the target range (glucose concentration < 70 mg/dL, 70 – 180 mg/dL or > 180 mg/dL).

Figure 1 shows the time course of the present study. Day 1 was defined as the day when observation was begun with CGM, which was carried out for 3 days, starting at 0:00 on Day 1 and ending at 24:00 on Day 3. Meals were provided five times a day as follows: breakfast at 7:30, a snack at 10:00, lunch at 12:00, a snack at 15:00, and dinner at 19:00. Breakfast, lunch, and dinner each contained 330 kcal and each snack contained 155 kcal. The meal schedule was part of the standard postoperative management. The patients were served only meals on Day 1, 200 kcal of SED ONS in addition to meals on Day 2, and 400 kcal of SED ONS in addition to meals on Day 3. The patients did not receive parenteral nutrition during the study period and were discharged the day after the observation period ended.

Terumeal uplead® (Terumo Corporation, Tokyo, Japan) was used as the SED ONS. Table 1 lists the ingredients of the product. SED ONS was consumed in equal doses

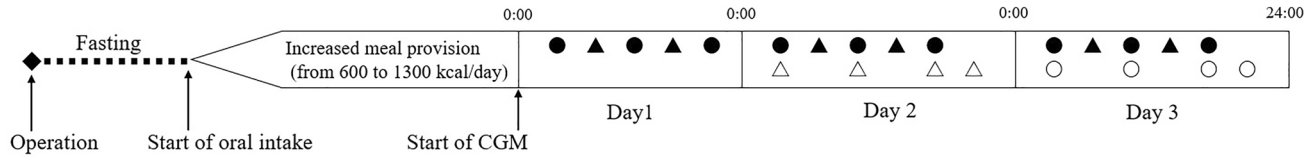

Fig. 1 Time course of the study. Black circle: Meal (330 kcal). Black triangle: Snack (155 kcal). White triangle: Super energy-dense oral nutritional supplements (50 kcal). White circle: Super energy-dense oral nutritional supplements (100 kcal). *CGM* continuous glucose monitoring

Table 1 Nutritional information on the oral nutritional supplement

Ingredients, etc	Per 100 mL
Energy	400 kcal
Protein	14.0 g
Fat	21.6 g
Carbohydrate	37.4 g
Water	43 g
Na	150 mg
Osmotic pressure	420 mOsm/L

four times daily, at the end of each meal and before bedtime. The quantity of food and SED ONS was calculated by measuring the amount of unconsumed food after each meal. The patients recorded any symptoms they experienced. Body mass index and HbA1c were measured preoperatively. The present study was preliminary, and the sample size was calculated by the number of patients able to be evaluated within the study period.

Outcomes

The primary outcome was defined as the area under the curve < glucose level 70 mg/dL (AUC < 70 mg/dL) on each day, a quantitative assessment of hypoglycemia as an area, based on several studies [17–19]. The international consensus report on CGM, published in 2019 [13], set out three key CGM measurements: time in range (TIR), time below range (TBR), and time above range (TAR), defined as the length of time spent with glucose 70–180 mg/dL, < 70 mg/dL, and > 180 mg/dL range, respectively. Therefore, the secondary outcomes for glycemic change were evaluated in terms of the TIR, TBR, and TAR. AUC > 180 mg/dL, the mean, maximum and minimum glucose level, the standard deviation (SD), and the mean amplitude of glycemic excursions (MAGE) were also evaluated. The other outcomes included dietary intake, SED ONS intake, and total caloric intake (meals and SED ONS). Symptoms occurring within 3 h after each meal were compared.

Table 2 Patient characteristics

Patients, (*n*)	17
Age, years	67.3 [9.6]
Male (*n*)	6
Body mass index, kg/m^2	22.1 [2.5]
Preoperative HbA1c, %	5.6 [0.5]
Pathological stage (I/II/III/IV)	11/3/3/0
Approach (open/laparoscopic/robotic)	0/8/9
Procedure (DG-BI/ DG-RY/TG)	7/4/6
Time from surgery to start of CGM, days	11.5 [11.7]
Postoperative hospital stay, days	14.9 [11.8]

Continuous variables are expressed as means [standard deviation]

DG-BI distal gastrectomy with Billroth I reconstruction, *DG-RY* distal gastrectomy with Roux-en-Y reconstruction, *TG* total gastrectomy with Roux-en-Y reconstruction

Statistical analysis

Three-factor repeated measures ANOVA was used to compare AUC < 70 mg/dL, AUC > 180 mg/dL, the mean, maximum and minimum glucose levels, SD, MAGE, TIR, TBR, TAR, dietary intake, and the total caloric intake among Days 1, 2, and 3. For indices showing a significant difference, multiple comparisons were done using the Bonferroni correction. $P < 0.05$ was considered to indicate significance. All statistical analyses were conducted using IBM SPSS Statistics version 26.

Results

Patient characteristics

Between August, 2020 and October, 2021, 17 patients who underwent gastrectomy for gastric cancer were enrolled. Table 2 summarizes the patients' characteristics.

Glycemic profile

The CGM data were analyzed for 16 of the 17 patients, after the exclusion of one patient with DG-BI whose data could not be recorded because of technical difficulties. Table 3

Table 3 Area under the curve (AUC) < 70 mg/dL and AUC > 180 mg/dL each day

	Day 1	Day 2	Day 3	*P* value
AUC < 70 mg/dL (mg × min/dL)				
ALL (*N* = 16)	235.9 [594.5]	19.7 [71.1]	0	0.15
TG (*N* = 6)	590.4 [899.7]	5.0 [12.2]	0	0.17
DG-BI (*N* = 6)	38.8 [94.9]	47.5 [116.4]	0	0.36
DG-RY (*N* = 4)	0	0	0	–
AUC > 180 mg/dL (mg × min/dL)				
ALL	145.9 [448.1]	9.4 [37.5]	114.2 [441.0]	0.27
TG	287.9 [705.2]	25.0 [61.2]	297.5 [720.2]	0.36
DG-BI	0	0	7.1 [17.4]	0.36
DG-RY	151.9[303.8]	0	0	0.39

Data are expressed as means [standard deviation]

P values were calculated by three-factor repeated measures ANOVA

AUC area under the curve, *ALL* all patients, *TG* total gastrectomy, *DG-BI* distal gastrectomy with Billroth I reconstruction, *DG-RY* distal gastrectomy with Roux-en-Y reconstruction

shows the AUC < 70 mg/dL and the AUC > 180 mg/dL each day. The AUC < 70, being the primary outcome, did not differ significantly across the observation period. The glucose concentration in 10 of the 16 patients fluctuated between 70 and 180 mg/dL during the observation period. The six patients whose glucose concentration fell outside the range even briefly were classified by surgical procedure. A glycemic abnormality occurred in 33% (2/6) of the patients who underwent DG-BI, 25% (1/4) of those who underwent DG-RY, and 50% (3/6) of those who underwent TG. The influence of other background factors was not evident. Hypoglycemia (< 70 mg/dL) appeared in one patient who underwent DG-BI and three patients who underwent TG. Figure 2 shows a typical glycemic fluctuation at the onset of hypoglycemia. All hypoglycemia episodes occurred at night (0:00–6:00) on Day 1 or 2. No hypoglycemia was observed after breakfast on Day 2 when the SED ONS was begun. Hyperglycemia (> 180 mg/dL) appeared in one patient who underwent DG-BI, one patient who underwent DG-RY, and two patients who underwent TG. Three of these patients experienced hyperglycemia after ingesting SED ONS. Figure 3 shows a typical glycemic fluctuation at the onset of hyperglycemia. One patient who underwent DG-RY was hyperglycemic for 40 min before dinner on Day 1, but the reason for this was unclear. One patient who underwent TG was also hyperglycemic for 55 min after dinner on Day 1. AUC > 180 mg/dL was higher on Day 1 than on Day 2 or Day 3 because of these effects, but the difference was not significant. Hyperglycemia did not lead to hypoglycemia in these patients, who were asymptomatic and did not require treatment for abnormal glycemic changes. A comparison of the patients who underwent TG with those who underwent DG revealed that AUC < 70 and AUC > 180 were greater in the TG patients, but the difference was not significant.

Table 4 shows the standard measures for glycemic data. In the other outcomes, repeated measures ANOVA showed a significant difference in the mean glucose level and the minimum glucose level among Days 1, 2, and 3. On a multiple comparisons test, the mean glucose level was significantly higher on Day 3 than on Day 1 ($P = 0.038$). Figure 4 shows the mean glycemic fluctuation in all the patients. The mean glycemic fluctuation on Day 3 (the green line) was above that on Day 1 (the grey line) for most of the time. The minimum glucose level was significantly higher on Day 3 than on Day 1 ($p = 0.042$). The maximum glucose level did not differ significantly over

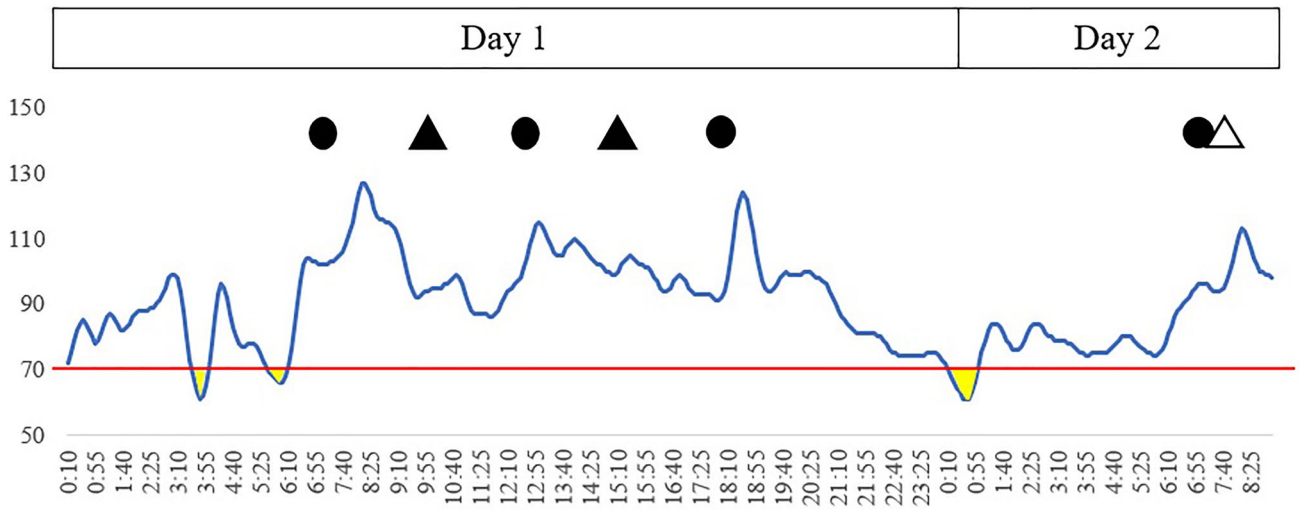

Fig. 2 Glycemic fluctuations in a representative patient with hypoglycemia. Black circle: Meal (330 kcal). Black triangle: Snack (155 kcal). White triangle: Super energy-dense oral nutritional supplements (50 kcal). Yellow area: Glucose concentration < 70 mg/dL

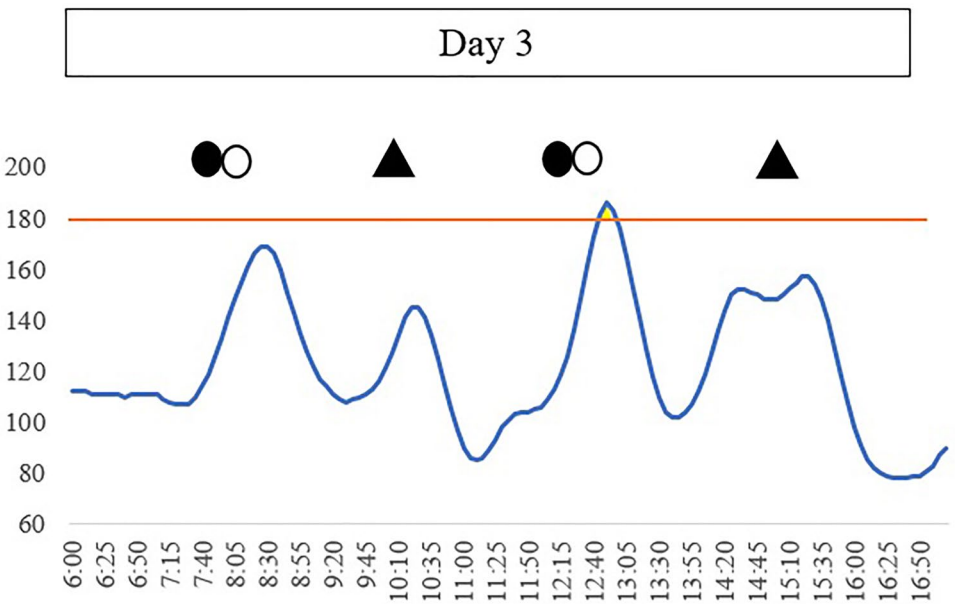

Fig. 3 Glycemic fluctuations in a representative patient with hyperglycemia after the administration of super energy-dense oral nutritional supplements. Black circle: Meal (330 kcal). White circle: Super energy-dense oral nutritional supplements (100 kcal). Black triangle: Snack (155 kcal). Yellow area: Glucose concentration > 180 mg/dL

Table 4 Standard measures of glycemic data

	Day 1	Day 2	Day 3	*P* value
Mean glucose level (mg/dL)	102.7 [7.1]*	104.8 [6.5]	109.7 [9.2]*	0.011
Minimum glucose level (mg/dL)	76.8 [12.3]**	80.2 [9.0]	85.9 [8.0]**	0.012
Maximum glucose level (mg/dL)	153.6 [29.1]	151.1 [17.2]	158.3 [21.1]	0.42
SD (mg/dL)	16.6 [5.7]	16.1 [4.9]	15.6 [5.1]	0.69
MAGE (mg/dL)	40.8 [9.7]	42.2 [15.9]	41.5 [14.7]	0.86
TIR (%)	97.1 [5.8]	99.3 [1.5]	99.4 [1.9]	0.086
TBR (%)	2.4 [5.5]	0.5 [1.4]	0	0.096
TAR (%)	0.5 [1.2]	0.2 [0.8]	0.6 [1.9]	0.36

$N = 16$

Data are expressed as means [standard deviation]

P values were calculated by three-factor repeated measures ANOVA

*Significant difference between two time points by multiple comparisons using the Bonferroni correction ($p = 0.038$)

**Significant difference between two time points by multiple comparisons using the Bonferroni correction ($p = 0.042$)

SD standard deviation of glucose, *MAGE* mean amplitude of glycemic excursions, *TIR* time in range, *TBR* time below range, *TAR* time above range

the 3 days. Glycemic variability, evaluated using the SD and MAGE, indicated no significant difference during the same period. The index of glycemic control using TIR showed a decreasing trend on Day 1, although the difference was not significant ($p = 0.086$). The TIR on Days 2 and 3 with SED ONS use was over 99%. The TBR showed an increasing trend on Day 1, although the difference was not significant ($p = 0.098$). The TBR on Day 3, when SED ONS 400 kcal/day was given, was 0%. In contrast, the TAR showed no significant difference during the observation period. Figure 5 shows the mean glycemic fluctuation by surgical procedure. Patients who underwent TG had more episodes of nocturnal hypoglycemia than those who underwent DG-BI or DG-RY, and the range of variability was apparently greater.

Amount of intake and symptoms after meals

Figure 6 shows the caloric intake. The mean dietary intake did not differ significantly during the observation period. SED ONS 200 kcal/day and 400 kcal/day was provided on Day 2 and Day 3, respectively. The mean SED ONS intake was 197.1 kcal/day and 382.4 kcal/day on Days 2 and 3, respectively. Three-factor repeated measures ANOVA showed a significant difference in the total caloric intake ($p < 0.01$), and multiple comparisons with the Bonferroni

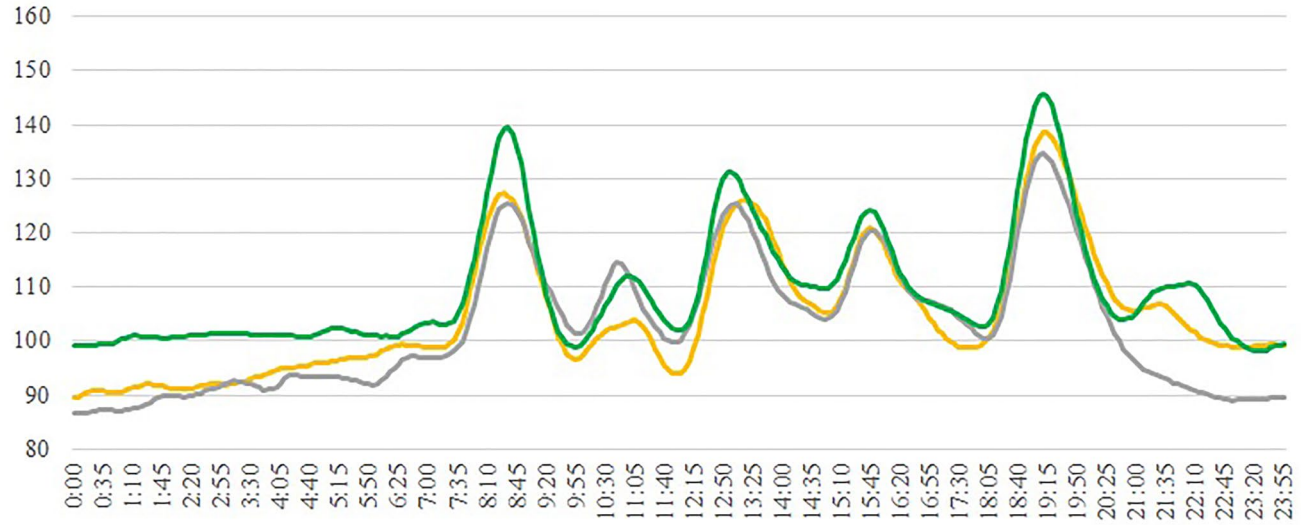

Fig. 4 Mean glycemic fluctuations. $N = 16$. Grey line: Day 1. Yellow line: Day 2. Green line: Day 3

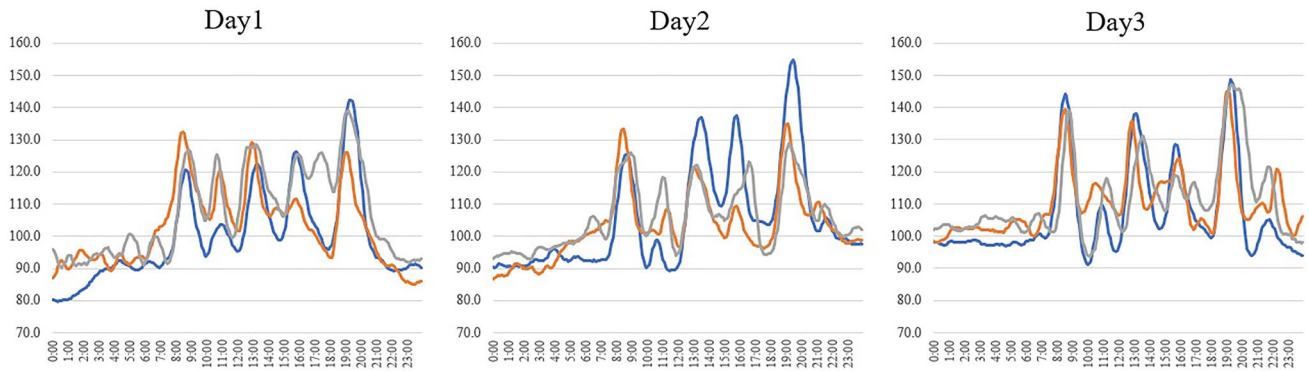

Fig. 5 Mean glycemic fluctuations by surgical procedure. Blue line: Total gastrectomy. Orange line: Distal gastrectomy with Billroth I reconstruction. Grey line: Distal gastrectomy with Roux-en-Y reconstruction

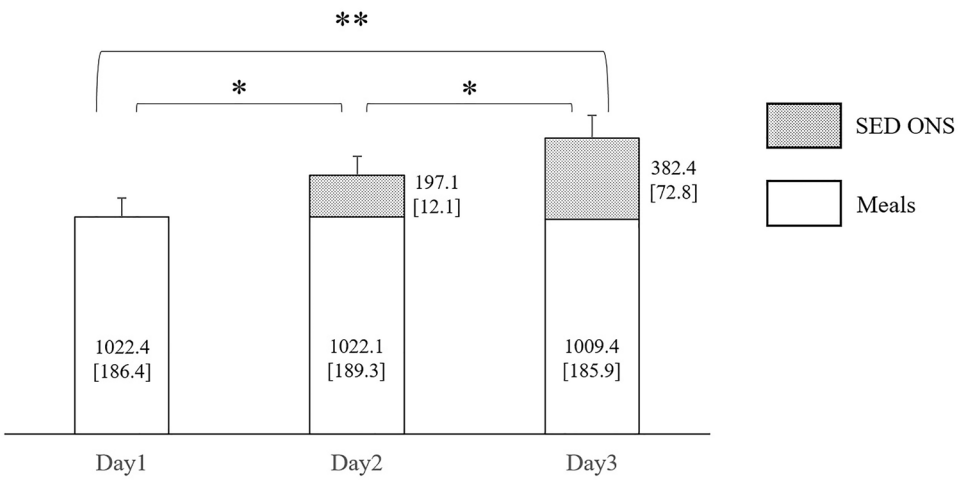

Fig. 6 Caloric intake. $N = 17$. Data are expressed as the mean kilocalories [standard deviation]. *P* values were calculated by multiple comparisons using the Bonferroni correction. Error bars represent the 95% confidence interval of the median of the total amount caloric intake.*$P = 0.01$; **$P < 0.01$. *SED ONS* super energy-dense oral nutritional supplements

correction also demonstrated a significant difference between all pairs (Days 1–2, Days 1–3, Days 2–3). Table 5 shows the symptoms occurring within 3 h after eating. The frequency of symptoms was similar for each day.

Discussion

To our knowledge, the present study is the first to investigate the impact of SED ONS on glycemic variability and food intake post-gastrectomy in gastric cancer patients. The study found the following: first, SED ONS given postoperatively did not induce postprandial hypoglycemia in gastrectomy patients; second, the mean and minimum glucose levels were significantly higher with SED ONS 400 kcal/day than without SED ONS. On the other hand, AUC > 180 mg/dL and the maximum glucose level did not differ significantly during the observation period. The glycemic concentration fluctuated in the range of 70–180 over 99% of the period of SED ONS use. Third, the mean dietary intake showed no significant difference and the total energy intake increased significantly depending on the amount of SED ONS provided.

The concept of ONS for medical purposes is gaining wide acceptance. Although many studies have described the impact of ONS on gastric cancer patients after gastrectomy, whether ONS can prevent postoperative BWL is uncertain. Patients with reduced gastric volume as a result of surgery find it difficult to ingest sufficient ONS. Several studies suggest that ONS > 200 kcal/day is required to stem BWL after gastrectomy [20, 21]. However, some post-gastrectomy patients find it difficult to consume ONS > 200 kcal/day [9]. Thus, it is necessary to devise ways to enable patients to consume enough ONS to prevent BWL after gastrectomy. The use of high-energy ONS is expected to improve post-gastrectomy patients' adherence to consuming ONS. Terumeal uplead® (4 kcal/mL), the most energy-dense ONS currently available, was used in the present study [10]. Only 50–100 mL/day of this product is needed to increase caloric intake by 200–400 kcal/day.

There is a risk of adverse events specific to post-gastrectomy patients receiving SED ONS. Gastrectomy impairs the storage capacity of the stomach, which normally results in a considerable amount of undigested food reaching the small intestine rapidly. Late dumping syndrome occurs when meal-induced hyperglycemia is followed by hypoglycemia caused by excessive insulin secretion [22]. In their study using CGM, Kubota et al. reported that the glucose values fell below 70 mg/dL 20.8 and 33.8% of the time after distal gastrectomy and total gastrectomy, respectively [14]. While SED ONS has the advantage of providing energy efficiently, the possibility of glycemic fluctuations caused by its high caloric density is a concern. However, in the present study, hypoglycemia only occurred without SED ONS administration and did not occur after the initiation of SED ONS. The duration of glucose concentration < 70 mg/dL was 0%, indicating that SED ONS is unlikely to cause hypoglycemia. Moreover, the minimum blood glucose level was significantly higher with SED ONS 400 kcal/day than without SED ONS, suggesting that SED ONS does not induce postprandial hypoglycemia, and that it also improves the minimum blood glucose level and prevents nocturnal hypoglycemia. The analysis by surgical procedure demonstrated that TG patients had greater glycemic variability, but the impact of SED ONS on glycemic variability was similar across the groups. Our previous prospective study also found that the mean energy intake of patients on discharge after DG and TG was 876 and 615 kcal, respectively [23], demonstrating that food intake after gastrectomy is very low and may trigger hypoglycemia. Kubota et al. reported longer periods of nocturnal hypoglycemia using CGM after a gastrectomy [14]. Numerous studies have found that hypoglycemia was associated with an increased risk of adverse clinical outcomes, such as cardiovascular disease, atherosclerosis, and dementia [24–27]. Postoperative SED ONS in gastric cancer patients improved nocturnal glucose levels in the present study and may have contributed to reducing these adverse effects.

Hyperglycemia > 180 occurred mainly after meals, but sometimes before meals, showing no consistence with or without SED ONS. In the present study, to enhance the rigor of our safety assessment, SED ONS was administered immediately after a meal when it was most likely to increase the glycemic level. Nevertheless, the maximum glucose level and TAR did not differ significantly with or without SED ONS, suggesting that the risk of increasing the glycemic level with SED ONS use was low. However, in three patients, the glycemic level briefly rose above 180 mg/dL after consuming 100 kcal of SED ONS. In post-gastrectomy patients with impaired glucose tolerance, SED ONS use may pose a risk of problematic hyperglycemia. For this reason, diabetic patients were excluded from the present study cohort, but future studies are needed to evaluate the safety of SED ONS in diabetic patients. Previous studies of post-gastrectomy glycemic variability using a CGM demonstrated

Table 5 Patients who suffered symptoms within 3 h after eating

Day	1	2	3
Any symptoms, no (%)	7 (41.1)	5 (29.4)	5 (29.4)
Abdominal pain, no (%)	3 (17.6)	3 (17.6)	4 (23.5)
Esophageal reflux, no (%)	2 (11.8)	4 (23.5)	2 (11.8)
Diarrhea, no (%)	3 (17.6)	0	1 (5.9)
Cold sweat, no (%)	1 (5.9)	1 (5.9)	0
Dizziness, no (%)	1 (5.9)	0	1 (5.9)

$N = 17$

longer periods of hypoglycemia than in our study [14–16]. These studies used flash glucose monitoring (FGM), which is simple and convenient because it does not calibrate by blood glucose level [28] but is less accurate than the conventional CGM used in the present study [29, 30]. Therefore, it is likely that the present study was able to assess glycemic variability more accurately. Furthermore, in the present study the caloric density of meals reached 980 kcal, so the quantity of food intake may have been larger than in previous studies [23], raising the possibility that the comparatively higher caloric density contributed to preventing hypoglycemia. Terumeal uplead® also has a lower carbohydrate content than the standard ONS, possibly explaining its relatively smaller effect on glycemic variability. Further study is needed to compare Terumeal uplead® with the standard varieties of ONS.

Another important finding of this study was that SED ONS administration increased the total energy intake. Previous studies of ONS after gastrectomy were unable to record food intake accurately. In the present study, food intake was recorded accurately by dietitians during the patient's hospitalization. The average food intake remained unchanged with or without SED ONS during the observation period, and all patients received the same quantities of SED ONS, consumed mainly as small portions four times daily immediately after each meal and before sleeping. Therefore, SED ONS administration did not result in less food being consumed. Furthermore, SED ONS did not clearly increase the frequency of post-gastrectomy symptoms in the present study as the dosage used would be unlikely to exacerbate post-gastrectomy syndromes.

The present study had several limitations. First, it was a preliminary, monocentric study with no sample size premise. Because of the small number of patients, it may have failed to demonstrate hypoglycemia after SED ONS administration. Moreover, there may have been a bias affecting SED ONS intake and food consumption. Second, this study was conducted during a short hospital stay immediately after surgery. Postoperative weight changes were not measured because a 2-day intake of SED ONS would have had a negligible impact on body weight. Future studies are warranted to verify whether the same results can be achieved after discharge.

Conclusion

The findings of our study suggest that SED ONS after gastrectomy does not lead to hypoglycemia, and may even prevent hypoglycemia, but it would increase the total caloric intake without affecting food intake. SED ONS appears to be safe and feasible for gastric cancer patients post-gastrectomy. As our next step, a preliminarily study of a small number of patients is underway to test whether SED ONS intake over 12 weeks can reduce BWL after gastrectomy. If its efficacy and safety are confirmed, a large-scale RCT will be conducted.

Acknowledgements We thank Mr. James R. Valera for his assistance with editing this manuscript and Mr. Atsushi Nishida, Mr. Syudo Yamasaki, and Mr. Satoshi Usami for their assistance with the statistical analysis. We are especially grateful to Ms. Tokiko Matsukura, Ms. Keiko Yokota, and the other dietitians at our center for providing nutrition education and evaluating the patients' caloric intake.

Funding The present study was supported by a grant from the Clinical Research Fund of the Tokyo Metropolitan Government (Grant no. R02050302).

Declarations

Conflict of interest All authors have no conflict of interest to declare.

Ethical approval All data collection and analysis were performed in accordance with the ethical standards of the Declaration of Helsinki. This study was approved by the ethics committee of Tokyo Metropolitan Tama Medical Center (No.3–6) and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR 000041219).

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