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Feasibility and Safety of Super Energy-dense Oral Nutritional Supplementation in Postoperative Gastric Cancer Patients

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Abstract. *Background/Aim: Ensuring that postoperative gastric cancer patients receive sufficient oral nutritional supplementation (ONS) to prevent body weight loss (BWL) is a serious challenge. The present pilot study evaluated the feasibility and safety of small, frequent sip feeds (SIP) with super energy-dense ONS (SED ONS; 4 kcal/ml) in postoperative gastric cancer patients. Patients and Methods: Patients received 400 kcal/day of SED ONS in four, daily, 25 ml SIP for 12 weeks after gastrectomy. The primary outcome was the percentage of postoperative weight change. The expected mean weight change was 90% (10% standard deviation). A sample population of 14 patients, sufficient for a 95% confidence interval with a 10% margin of error, was enrolled. Results: The mean weight change for patients receiving SIP with SED ONS was 93.8%. The mean SED ONS intake was 348 kcal/day. Thirteen patients consumed more than 200 kcal/day of SED ONS. One patient with a mean intake of 114 kcal/day had undergone total gastrectomy followed by adjuvant chemotherapy. Conclusion: Small, frequent SIP with SED ONS was found to be feasible and safe in postoperative gastric cancer patients. A multicenter randomized controlled trial is warranted to determine whether SIP with SED ONS is effective in preventing BWL.*

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Key Words: Gastrectomy, body weight loss, oral nutritional treatment, gastric cancer.

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Gastrectomy remains indispensable for treating gastric cancer despite recent progress in other medical techniques. However, it impairs certain physiological functions, such as food storage and digestion. Patients with gastrectomy are usually unable to maintain an ideal weight, and some have long-term difficulties maintaining their postoperative nutritional status. As a result, many of these patients suffer from post-gastrectomy body weight loss (BWL), which has a negative impact on their prognosis and quality of life (1). Recently, the concept of oral nutritional supplementation (ONS), in which medically designed nutritional supplements are administered orally to supplement regular meals, has become increasingly popular (2, 3). Several studies have reported that post-gastrectomy ONS has some efficacy in preventing BWL (4-6). In contrast, other studies have reported that ONS cannot prevent post-gastrectomy BWL, and the topic remains controversial (7, 8). Many patients with a gastrectomy have difficulty ingesting adequate amounts of ONS because of the reduced capacity of their stomach.

Most studies to date have used ONS 1-1.5 kcal/ml. Terumeal uplead® (Terumo Corporation, Tokyo, Japan), a very high-concentration ONS (4 kcal/ml), was developed as a more calorie-dense alternative to the standard varieties of ONS. The present study hypothesized that administering this super energy-dense ONS (SED ONS) in four, daily doses at regular intervals to coincide with mealtimes and bedtime may increase adherence and be effective in preventing post-gastrectomy BWL. A recent study reported that SIP with SED ONS after gastrectomy did not lead to hypoglycemia but rather increased the total energy intake without reducing the size of the regular meal (9). The present, preliminary

Table I. *Nutritional information of super energy-dense oral nutritional supplement.*

Content	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

study aimed to evaluate the feasibility and safety of SIP with SED ONS in preventing BWL in a small number of post-gastrectomy patients when consumed in small, equal, and regular doses. Adherence to the SED ONS regimen, the effects of the supplementation on food intake, and postoperative quality of life were also examined.

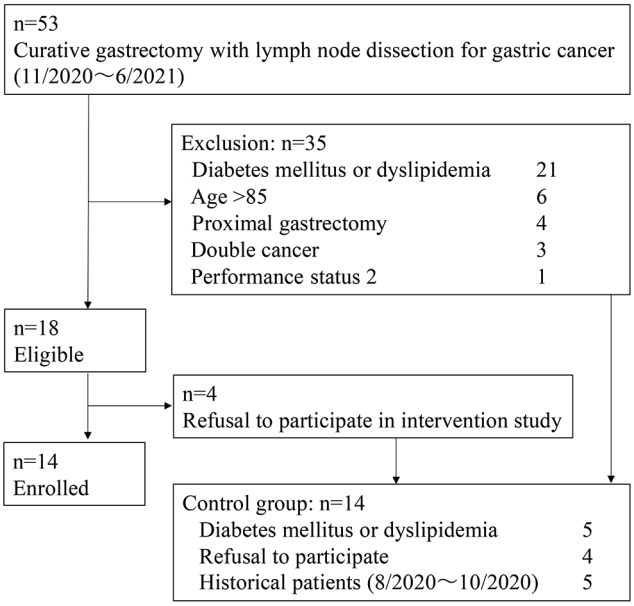

Figure 1. *Flowchart of the patients in the present study.*

Patients and Methods

Study design. The present, preliminary study was conducted at Tokyo Metropolitan Tama Medical Center from November 2020 to June 2021. Written informed consent was obtained from the patients before enrollment. Data collection and analysis were performed in accordance with the ethical standards of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. This study was approved by the ethics committee of Tokyo Metropolitan Tama Medical Center (No.2-59) and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR 000041494).

Study protocol. Patients who had received a curative resection for gastric cancer at our hospital were enrolled if they met the following inclusion criteria: 1. Age 20 to 84 years; 2. Eastern Cooperative Oncology Group Performance Status 0 or 1; 3. Ability to ingest food; 4. Scheduled conventional curative gastrectomy for gastric cancer. The exclusion criteria were as follows: 1. Current diabetes mellitus or dyslipidemia; 2. Function-preserving gastrectomy (pylorus-preserving gastrectomy, proximal gastrectomy, *etc.*); 3. Active double or multiple cancer; 4. Allergy to milk or gelatin components.

The safety of SED ONS, which has a high energy and lipid content, has not been verified in patients with diabetes or dyslipidemia. Therefore, patients with these conditions were excluded. Patients who underwent function-preserving gastrectomy were excluded because they had less weight loss than patients with distal gastrectomy or total gastrectomy.

The amount of food provided postoperatively to patients was gradually increased. The subjects were asked to taste the SED ONS and decide whether they wished to participate in this study a few days before discharge. Patients who volunteered to participate were instructed in how to take the SED ONS and educated about eating appropriately after their gastrectomy. The patients were prescribed SED ONS 400 kcal/day (100 ml/day) for 12 weeks after discharge and instructed to consume the same amount (100 kcal/25 ml) four times daily, immediately after each meal and at least one hour before bedtime and to record their intake precisely on a provided form. The amount consumed was measured using a measuring cup. Terumeal uplead® (Terumo Corporation) was used as the SED ONS. Table I lists the ingredients of the product. The patients visited the hospital with their record of SED ONS intake at weeks 4, 8, and 12 after discharge. The primary outcome was the postoperative percentage of weight change at week 12 after discharge. The secondary outcomes included ONS intake, dietary intake, quality of life (QOL), postoperative percentage of body composition change, hematological parameters, and the incidence of Common Terminology Criteria for Adverse Event (CTCAEV5.0) Grade 2-4 postoperative adjuvant chemotherapy. A registered dietitian calculated the estimated daily dietary intake using a food frequency questionnaire (FFQg version 5, Kenpakusha, Tokyo, Japan) preoperatively and at postoperative weeks 4, 8, and 12 after discharge (10). Body composition (fat and skeletal muscle) was assessed using InBody S10 (InBody Japan Inc., Tokyo, Japan) preoperatively and at week 12 after discharge. QOL was assessed using the Post-gastrectomy Syndrome Assessment Scale-37 (PGSAS-37) at week 12 after discharge (11). Body weight and hematological and biochemical parameters (albumin, prealbumin, total cholesterol, and lymphocyte count) were assessed preoperatively and at weeks 4, 8, and 12 after discharge. The clinical and pathological stages of gastric cancer were assessed using the Japanese Classification of Gastric Carcinoma, 15th edition (12).

Sample size and statistical analysis. As the present, single-arm study evaluated the feasibility and safety of SIP with SED ONS 400 kcal administered in four, equal, daily doses for possible advancement to a randomized controlled trial, we estimated the required sample size based on the desired precision. Previous studies (8, 13, 14) have reported that only about 50% of patients are able to consume more than 200 kcal of ONS/day postoperatively. It was previously reported (4) that the change in body weight at week 12 after

Table II. *Patient characteristics*.

	SED ONS	Non- SED ONS	*p*-Value
Number	14	14	
Age, years	68.5 (9.5)	67.7 (10.4)	0.84*
Male sex, n	10	6	0.25**
Weight, kg	59.9 (7.4)	55.7 (8.0)	0.16*
Body mass index, kg/m^2	23.1 (3.0)	22.0 (2.6)	0.32*
Procedure, n (DG/TG)	11/3	11/3	0.68**
Pathological stage, n (I/II/III/IV)	9/2/3/0	9/2/3/0	1.0**
Postoperative adjuvant chemotherapy, n	4	5	0.50**

Continuous variables are expressed as the mean (standard deviation). *p-Values were calculated using Student's t-test. **p-Values were calculated using the chi-square test and Fisher's exact test. SED ONS: Super energy-dense oral nutritional supplementation; Non-SED ONS: without SED ONS; DG: distal gastrectomy; TG: total gastrectomy.

discharge was 94.1% (SD 5.1) in patients with distal gastrectomy and 85.6% (SD 5.2) in those with total gastrectomy. Based on the findings of this and other reports (5-7), the weight change target was set at 90% in the present study. A sample size of 10 was necessary for a 95% confidence interval (CI) for weight change with a 10% margin of error, 10% standard deviation, alpha 0.05, and power 0.9. Fourteen patients were finally enrolled to provide for possible dropouts.

Patients with almost all the items of interest, matching clinical stage and treatment procedure were selected from a pool of patients who had received a distal gastrectomy or total gastrectomy at our hospital. The selected patients included six who did not meet the criteria for SED ONS administration because they had diabetes mellitus or dyslipidemia. Informed consent was obtained from these patients in the form of an opt-out clause on the institutional website. Four patients who refused to participate in the intervention arm agreed to participate as controls. The chi-square test or Fisher's exact test was used to compare discrete variables. Student's t-test was used to assess differences between groups in terms of patient demographics, percentage of change in body composition change, hematological and biochemical parameters, and QOL at week 12 after discharge. p-Value <0.05 was considered to indicate statistical significance. All statistical analyses were conducted using IBM (Armonk, NY, USA) SPSS Statistics version 27.

Compliance with ethical standards. The present study was performed in accordance with the ethical standards of the Declaration of Helsinki, approved by the ethics committee of Tokyo Metropolitan Tama Medical Center (No.2-59), and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR 000041494).

Results

Patient characteristics. Figure 1 shows a flowchart of the patients in the present study. Fifty-three patients received a curative gastrectomy with lymph node dissection for gastric cancer during the study period. Of these, 35 did not meet the inclusion criteria. Finally, 14 patients who agreed to participate were enrolled in the SED ONS group and remained until the end of the study. The SED ONS group was then compared with the same number of patients in a control group consisting of those who did not receive SED ONS. The latter were consecutively selected from a pool of patients who underwent surgery between August 2020 and July 2021 and had almost all items of interest. Table II summarizes the patient characteristics. None of the indices differed significantly between the groups.

Table III. *Body weight change in postoperative gastric cancer patients receiving super energy-dense oral nutritional supplementation*.

n	Pre (kg)	12w (kg)	Change (%)	95%CI (%)	*p*-Value
14	59.9 (7.4)	56.3 (8.2)	93.8 (4.8)	91.0-96.5	<0.001

Data are expressed as the mean (standard deviation). p-Values were calculated the one-sample t-test. Pre: Before surgery; 12w: 12 weeks after discharge; CI: confidence interval.

Body weight change in patients using SED ONS. Table III shows the postoperative body weight change in gastric cancer patients receiving SED ONS. The primary outcome of the mean percentage of body weight change at week 12 after discharge in the patients receiving SED ONS was 93.8% (standard deviation: 4.8%), which had a 95%CI of 91.0-96.5%, showing a significantly better body weight change than the established threshold.

Comparison of weight change in patients with and without SED ONS. Figure 2A shows the mean body weight change in patients with and without SED ONS. The mean percentage of change at weeks 4, 8, and 12 after discharge in the patients receiving SED ONS was 95.7, 94.9, and 93.8%, whereas in the patients without ONS it was 93.5, 93.2, and 91.9%, respectively. Figure 2B shows the body weight change in each patient receiving SED ONS. All but one of the 14 patients maintained at least 90% of their preoperative weight at week 12 after discharge. Figure 2C shows the body weight change in each patient not receiving SED ONS. At week 12 after discharge, three of the 14 patients weighed <90%, and one patient weighed <80%, of their preoperative body weight.

Figure 3 shows the body weight change in each patient with and without adjuvant chemotherapy. In the patients receiving SED ONS but not adjuvant chemotherapy, those with distal gastrectomy maintained at least 90% of their preoperative weight at week 12 after discharge (Figure 3A). All but one of the nine patients receiving neither SED ONS nor adjuvant chemotherapy maintained at least 90% of their

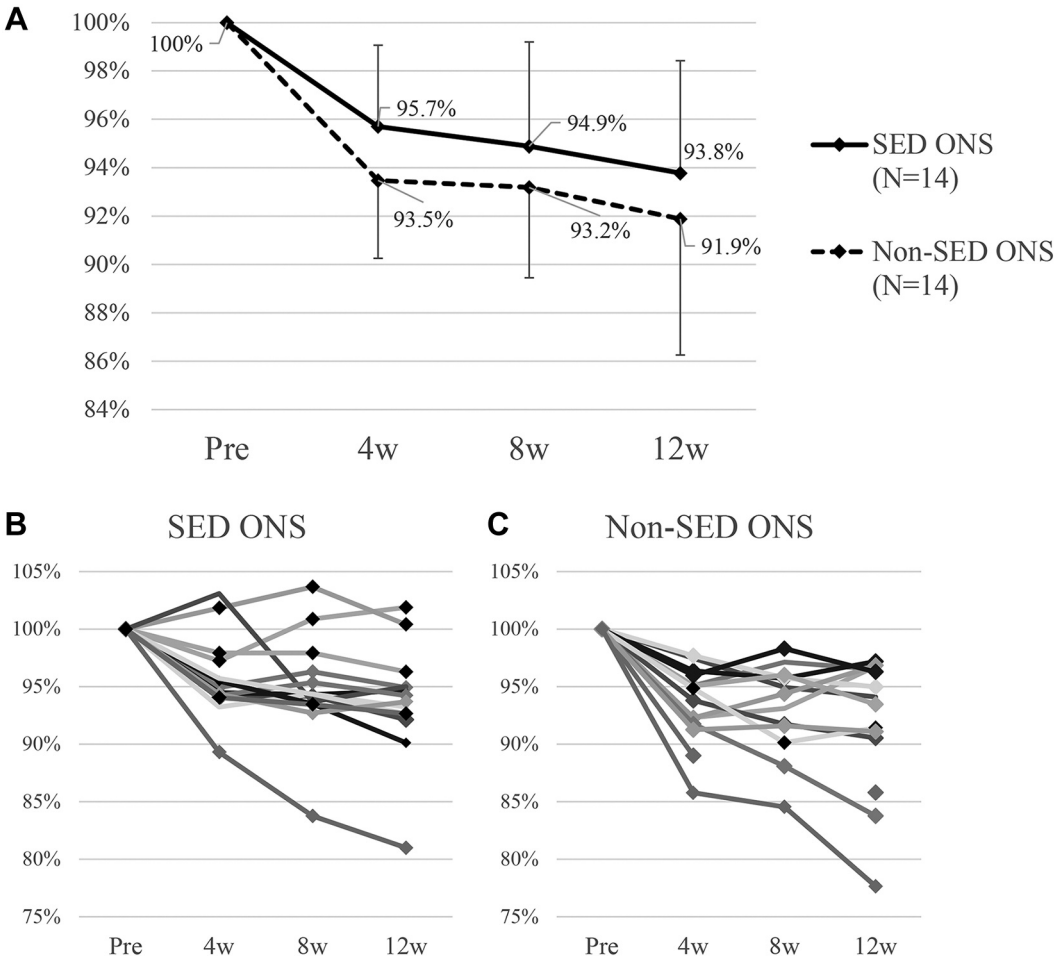

Figure 2. *Weight change in patients with and without super energy-dense oral nutritional supplementation (SED ONS). A) Mean weight change in patients with and without SED ONS. B) Weight change in each patient with SED ONS. C) Weight change in each patient without SED ONS. Error bars represent standard deviations. Non-SED ONS: Patients without oral nutritional supplementation.*

Table IV. *Patients with adverse effects of adjuvant chemotherapy.*

	Procedure	Chemotherapy	Adverse event: Grade	12w BW
SED ONS	TG	SOX	Anorexia: G2 Neutrophil count decrease: G3	81.0%
	DG	S-1 alone	Diarrhea: G2	95.0%
Non-SED ONS	TG	SOX	Neutrophil count decrease: G3	91.4%
	TG	SOX	Anorexia: G2	77.6%

SED ONS: Super energy-dense oral nutritional supplementation; Non-SED ONS: without SED ONS; 12wBW: weight change 12 weeks after discharge; DG: distal gastrectomy; TG: total gastrectomy; SOX: S-1 and oxaliplatin.

preoperative body weight at week 12 after discharge (Figure 3B). Figure 3C shows the body weight change in each patient receiving both SED ONS and adjuvant chemotherapy. One of the four weighed 81.0% of their preoperative body weight at week 12 after discharge. In the five patients not receiving SED ONS but receiving adjuvant chemotherapy, two weighed <85% of their preoperative body weight at week 12 after discharge (Figure 3D).

Grade 2-3 adverse events associated with postoperative adjuvant chemotherapy occurred in two of four (50%)

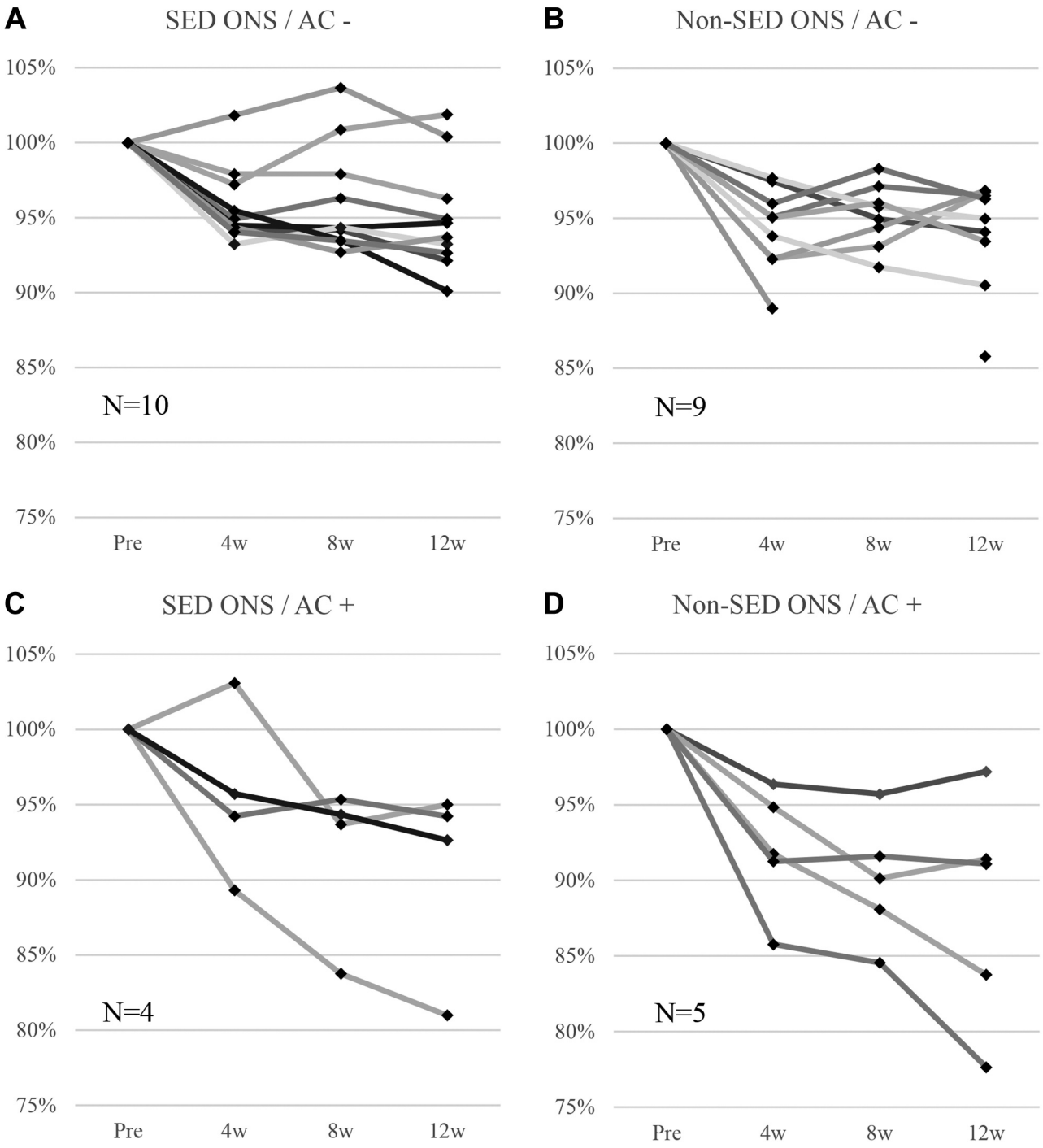

Figure 3. *Weight change in each patient with and without adjuvant chemotherapy. A) Patients with super energy-dense oral nutritional supplementation (SED ONS) and without adjuvant chemotherapy. B) Without SED ONS and without adjuvant chemotherapy. C) With SED ONS and adjuvant chemotherapy. D) Without SED ONS and with adjuvant chemotherapy. Non-SED ONS: Patients without oral nutritional supplementation; AC: without adjuvant chemotherapy; AC+: with adjuvant chemotherapy.*

patients receiving SED ONS and two of five (40%) patients not receiving SED ONS. Table IV shows the patients with adverse events related to adjuvant chemotherapy.

SED ONS adherence. The mean SED ONS intake was 348 kcal/day (95%CI=298-397). Figure 4 shows the SED ONS intake per patient. Thirteen patients (92.9%) consumed more

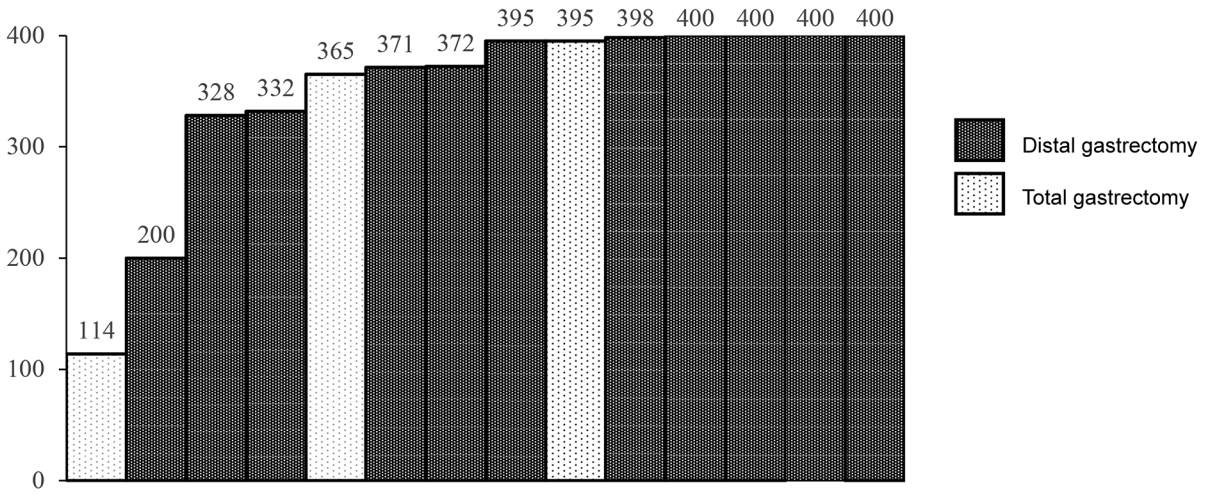

Figure 4. *Super energy-dense oral nutritional supplementation (SED ONS) intake per patient.*

Table V. *Changes in estimated daily caloric intake.*

	SED ONS			Non-SED ONS		
	n	Kcal	%	n	Kcal	%
Pre	14	1,955 (481)	100	11	1,796 (248)	100
4 w	14	1,571 (344)	84.0 (26.8)	10	1,430 (252)	77.6 (9.0)
8 w	14	1,540 (403)	84.0 (33.7)	9	1,430 (116)	80.6 (16.5)
12 w	14	1,688 (480)	89.9 (28.1)	11	1,628 (480)	89.3 (27.0)

Estimates of the daily dietary intake were made using the food frequency questionnaire (FFQ). Data do not include calories contained in SED ONS. Data are expressed as the mean (standard deviation). SED ONS: Super energy-dense oral nutritional supplementation; Non-SED ONS: without SED ONS; Pre: before surgery; 4w: 4 weeks after discharge; 8w: 8 weeks after discharge; 12w: 12 weeks after discharge.

than 200 kcal/day of SED ONS. The only patient whose SED ONS intake was <200 kcal/day on average was a post-total gastrectomy patient who was receiving adjuvant chemotherapy and had Grade 2 anorexia. The mean SED ONS intake of this patient at weeks 4, 8, and 12 after discharge was 212, 130, and 0 kcal/day, respectively. The patient weighed 81% of the preoperative body weight at week 12 after discharge.

Assessment of estimated dietary intake by FFQ. Table V shows changes in the estimated daily caloric intake of all the patients receiving SED ONS. However, some data for patients not receiving ONS were missing. Energy intake was defined as the number of calories obtained from meals and did not include calories from SED ONS. The mean energy intake at weeks 4, 8, and 12 post-discharge in patients receiving SED ONS was 84.0, 84.0, and 89.9% of their pre-operative intake, respectively. In patients not receiving SED ONS, the mean energy intake at weeks 4, 8, and 12 after discharge was 77.6, 80.6, and 89.3% of their pre-operative intake, respectively.

Other outcomes. Skeletal muscle, body fat mass, post-gastrectomy changes in serum albumin, prealbumin, total cholesterol, the total lymphocyte count, and QOL at week 12 after discharge did not differ significantly between the patients with and without SIP with SED ONS (data not shown).

Discussion

The present study found the following: first, postoperative body weight change after a gastrectomy in patients with small, frequent, SIP with SED ONS was 93.8% at week 12 after discharge, showing a statistically significant improvement over the preoperative, 90% figure. Second, the mean SED ONS intake was 348 kcal/day, and 13 patients (92.9%) had a SED ONS intake >200 kcal/day. Third, no adverse effects of supplementation on the daily dietary intake, hematological parameters or QOL were observed. On the other hand, one patient who received postoperative adjuvant chemotherapy after a total gastrectomy had lower SED ONS intake and severe BWL.

Post-gastrectomy syndrome hinders patients with decreased food intake from consuming sufficient ONS. Some studies have reported that ONS adherence affects post-gastrectomy BWL. Kobayashi *et al*. reported that ONS consumption significantly reduced BWL in post-gastrectomy patients who were able to tolerate an intake >200 kcal/day compared to those who were not (13). Miyazaki *et al*. reported that 50.4% of patients receiving ONS >200 kcal/day had significantly less BWL at postoperative year 1 than a control group (14). These studies indicated that ONS >200 kcal/day is required to stem BWL after a gastrectomy. However, several studies have demonstrated that some post-gastrectomy patients find it difficult to consume ONS >200 kcal/day. Kong *et al*. reported that only 26.2% of the patients in their study were able to consume ONS >250 kcal/day postoperatively during postoperative week 2 (8). Therefore, it is necessary to devise ways to enable patients to consume enough ONS to prevent BWL after a gastrectomy.

A systematic review of ONS compliance among the general patient population reported that adherence improved when high-energy ONS rather than normal ONS was used, and the total caloric intake consequently increased (15). The use of a high energy formulation may therefore improve ONS adherence in post-gastrectomy patients. The present study used Terumeal uplead® at a concentration of 4 kcal/ml as the SED ONS (9). Moreover, an RCT comparing adherence to two to four doses of ONS per day found that the intake increased significantly when the total amount was divided into four equal doses (16). In the present study, the ONS was administered in four, daily, 25 ml doses. The post-gastrectomy patients may have found it easier to adhere to the regimen because each dose consisted of only a few tablespoons of the supplement.

Ida *et al*. reported that an eicosapentaenoic acid-enriched oral diet failed to reduce post- gastrectomy BWL (7) and speculated that patients may have experienced a feeling of fullness resulting from the gastrectomy. The average food intake, recorded with FFQ, remained unchanged regardless of whether SED ONS was administered. SED ONS was consumed in small portions four times daily immediately after each meal and before sleeping. Therefore, the small, frequent, sip feeding method of administration might not have led to reduced food intake. Furthermore, quality of life assessment demonstrated that this method of administration was not associated with any increase in post-gastrectomy symptoms. The dosage used is therefore unlikely to exacerbate post-gastrectomy symptoms.

On the other hand, one patient in the SED ONS group weighed 81.0% of her preoperative body weight. This patient had undergone total gastrectomy followed by adjuvant chemotherapy (S-1 and oxaliplatin) and later experienced Grade 2 anorexia. In the non-ONS group, one patient with Grade 2 anorexia following a total gastrectomy with adjuvant chemotherapy (SOX) weighed 77.6% of the preoperative body weight. It is well known that total gastrectomy is associated with significantly greater weight loss than distal gastrectomy (17). Moreover, postoperative adjuvant chemotherapy with S-1 or SOX, required in patients with stage II/III gastric cancer, often results in the development of anorexia (18). It remains to be seen whether SED ONS will be effective in such cases of anorexia following a total gastrectomy with chemotherapy. Future studies should include gastrectomy and postoperative chemotherapy as allocation parameters.

The present, monocentric, preliminary study aimed to determine whether a large RCT testing the safety and feasibility of small, frequent, SIP with SED ONS in postoperative gastric cancer patients was justified. Therefore, the present study has some limitations. First, comparisons with the non-SED ONS group had value only as a reference because the patients were not allocated, and the sample sizes were not calculated. Second, the FFQ is an assessment method based on questions designed for the general patient population, and there is a lack of evidence to show that it can accurately assess post-gastrectomy patients.

In conclusion, the present pilot study found small, frequent SIP with SED ONS in postoperative gastric cancer patients was feasible and safe. A large, multicentric randomized controlled trial involving surgical procedures and chemotherapy as allocation factors is warranted to determine whether SED ONS is effective in preventing BWL.

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Conflicts of Interest

There are no potential conflicts of interest relevant to this article.

Authors' Contributions

Conception and design of the study: FH, MI, YoM, MH, KI, YaM; Data acquisition and analysis: RF, FH, RY, YI, YoM; Data interpretation: RF, RY, FH, YoM, MH; Manuscript: RF, RY, FH; Final approval of the version to be submitted: RF, RY, FH, MI, YoM, MH, YI, KI, YaM.

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