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# Jelly-type carbohydrate supplement in healthy subjects suppresses the catabolism of adipose tissue and muscle protein and improves their satisfactions☆

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SUMMARY

*Background & aims:* Many studies have reported the effects of preoperative clear fluid carbohydrate supplements; however, few studies have reported the effects of preoperative jelly-type carbohydrate supplements. This study aimed to assess the effect of a jelly-type oral nutritional supplement (ONS) on metabolism, redox balance by using various surrogate markers and to evaluate its excretion from the stomach.

*Methods:* This study was conducted according to a crossover design. Participants underwent a control experiment whereby they fasted after dinner and only ingested water until the experiment. The remaining participants underwent an ONS experiment whereby they ingested 400 g of ONS before bed and another 400 g at 7:00 am. Blood samples were collected at 9:00 am. After a break of at least 24 h, participants underwent the alternate experiment.

*Results:* Thirty minutes after intake of jelly, the gastric antrum appeared flat (the same result as that at baseline) on ultrasonography. The ONS group showed significantly lower serum free fatty acid levels (100 μEq/L, $p = 0.027$, vs. 327 μEq/L, $n = 6$), total ketone bodies levels, 3-MH/creatinine levels, and oxidative stress surrogate

☆ This study was approved by the Human Research Ethics Committee of the University of Tokushima and registered in a clinical trials database (UMIN000024024).

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markers. Serum insulin levels were significantly higher and participant's satisfaction was improved in the ONS group.
*Conclusions:* We have the limitations of our methodologies as surrogate markers, compared with direct measurement of lipolysis, proteolysis and redox balance regulation. But Jelly-type ONS suppresses the catabolism of adipose tissue and muscle protein, decreases oxidative stress and improves patient satisfaction in healthy participants, without any increased risk of aspiration.



## 1. Introduction

The Enhanced Recovery After Surgery (ERAS) program is a multimodal perioperative care pathway aimed at improving patient prognosis. Preoperative carbohydrate loading is included in the ERAS protocol [1]. Carbohydrate intake has been shown to enhance patient comfort prior to surgery and reduce postoperative discomfort, while preventing muscle wasting and loss of nitrogen and protein [2–4].

The ERAS protocol recommends an orally administered 12.6% carbohydrate supplement before surgery [1]. Previous studies have demonstrated that administration of liquid carbohydrate supplements before surgery can improve insulin resistance [5] and clinical outcomes [6]. There are a few studies regarding the preoperative ingestion of jelly as a clear liquid [7,8]. In these studies, jelly was included in the clear liquids and was ingested 2 h before surgery with no additional risk of aspiration of gastric contents in normal healthy children [7]. However, it is unclear whether there is any nutritional improvement from this ingestion. In the present study, we created a jelly-type oral nutritional supplement (ONS) with a carbohydrate concentration of 12.6%. There may be various factors which influence post-surgical conditions. First of all we explored whether the intake of this supplement could improve the starvation status, oxidative stress surrogate markers, and patient satisfaction in healthy participants who did not undergo a surgery.

## 2. Materials and methods

Written informed consent was obtained from all participants included in this study. This study protocol was approved by the Human Research Ethics Committee at the Tokushima University and was registered in a clinical trials database.

Six healthy male participants were included in the study. Obese [body mass index (BMI) > 30 kg/m$^2$], emaciated [ BMI < 17 kg/m$^2$], smokers, diabetics, and patients on prescription medication were excluded. The study was conducted with a crossover design.

The participants underwent two experiments with more than 24-h rest in between each experiment. In experiment 1 (control group), the participants fasted after dinner on the day before the experiment and only ingested water. On the day of the experiment, the participants drank water until 7:00 am and a blood sample was collected at 9:00 am (Fig. 1).

In experiment 2 (ONS group), the participants fasted after dinner on the day before the experiment and ingested 400 g of a jelly-type oral nutritional supplement with a carbohydrate concentration of 12.6% before they went to bed. Participants then ingested 400 g of the jelly at 7:00 am on the morning of the experiment and blood sample was collected after 2 h (Fig. 1). The order in which participants underwent two experiments was decided randomly. The jelly-type supplement (12.6% carbohydrate) was made by adding glucose to an OS-1 jelly (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan). An OS-1 jelly was goods on the market, but it wasn't equal to Preop (Nutricia, Zoetermeer, The Netherlands) in the concentration of carbohydrate. So we mixed glucose as additional carbohydrate

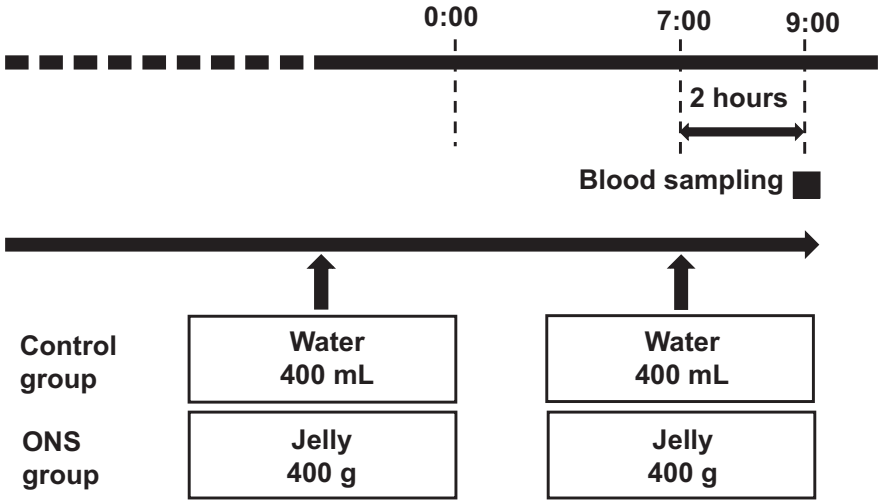


**Fig. 1. Study protocol**. In the control group, participants fast after dinner and only ingest water on the day before the experiment. In the ONS (oral nutritional supplement) group, the participants fast after dinner on the day before the experiment and ingest 400 g of a jelly-type ONS before bed. Additionally, they ingest 400 g of ONS at 7:00 am on the morning of the experiment. At 9:00 am, blood sample is collected in both groups.

into a OS-1 jelly. The jelly that we made contained 12.6 g/100 mL of carbohydrate, 115 mg/100 mL of sodium, no fat, and no protein (see Fig. 2).

Jelly discharge was assessed by ultrasonography. Participants were scanned at baseline (fasting state), immediately after intake of the jelly, and 30 min after intake of the jelly. Ultrasonographic views of the antrum were obtained using an ALOKA prosound α7 system (HITACHI, Tokyo, Japan). As previously described, images were obtained with the stomach at rest and between peristaltic contractions. The antrum was examined in cross-section in the right lateral decubitus position [9].

Blood samples were centrifuged at 150 g at 4 °C for 15 min (Table Top cooling centrifuge 2800, Kubota, Tokyo, Japan). The plasma samples were stored at −20 °C until analysis. Serum free fatty acid, serum 3-methylhistidine, serum total ketone bodies, blood glucose, serum insulin, and serum creatinine levels were determined by a clinical laboratory testing company (SRL Inc, Tokyo, Japan). We used serum free fatty acid as lipolysis surrogate marker, serum 3-methylhistidine as muscular proteolysis surrogate marker, and serum ketone bodies as starving status surrogate marker.

Furthermore, to assess total serum oxidant levels, we used the d-ROMs (derivatives of reactive oxygen metabolites) test as oxidative stress surrogate markers, while antioxidant capacity surrogate markers were performed with the BAP (biological antioxidant potential) test. The analyses of d-ROMs and BAP levels were performed by a spectrophotometric method using the Free Carrrio Duo (Diacron, Grosseto, Italy) [10]. The d-ROMs test results are expressed in arbitrary units (U.CARR) [10]. In healthy subjects, the d-ROMs reference values are between 250 and 300 U.CARR and above 2200 μmol/L on the BAP test [11,12].

Patient satisfaction was determined subjectively on a 100-mm Visual Analogue Scale (VAS; 0, “not at all”; 100, “extreme”) after blood was collected. Six different variables were evaluated: anxiety, depression, hunger, malaise, nausea, and thirst.

## 3. Statistical analysis

The size of this study was decided to detect a difference in serum free fatty acid concentrations. A previous study reported that in patients who received preoperative oral carbohydrates with amino acids, the serum fatty acid concentration decreased by 40% before the induction of anesthesia [13]. Therefore, the required number of patients in each group was 6, with an alpha of 0.05 and a power of

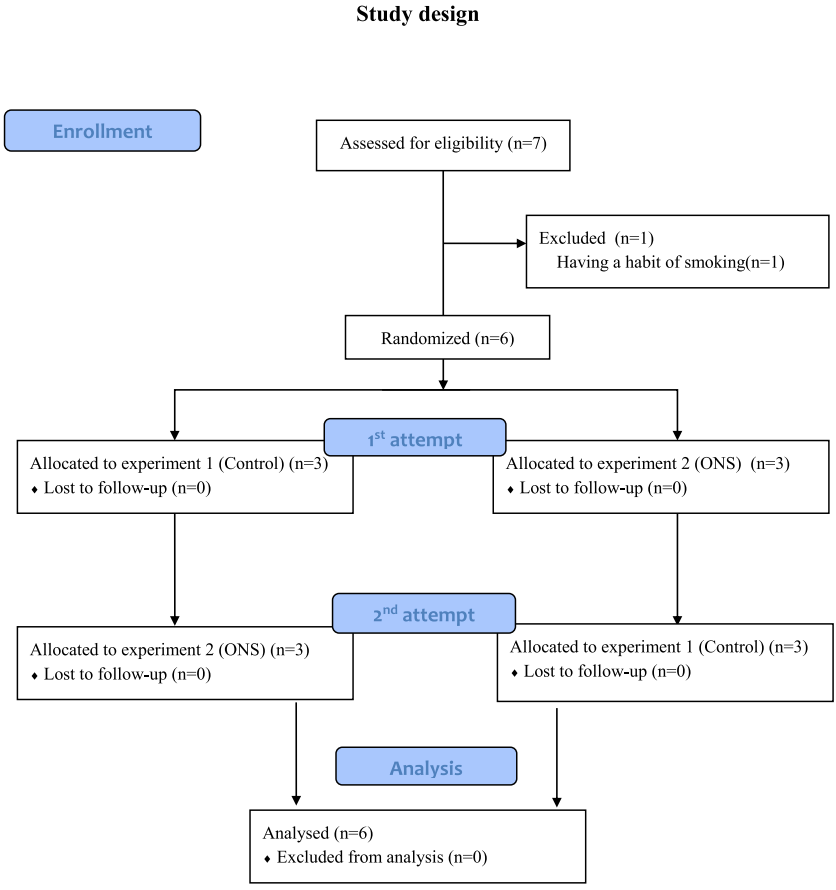


**Fig. 2. CONSORT flow chart showing the selection process for volunteers**. After obtaining informed consent, the order in which the participants underwent the 2 experiments is decided randomly. *ONS*, oral nutritional supplement.

80% for free fatty acids (SPSS SamplePower, IBM Co., Armonk, NY, USA). A Wilcoxon signed-rank test was conducted using statistics 22 (IBM Co., Armonk, NY, USA). Values of $p < 0.05$ were taken to represent statistically significant differences in the analysis.

## 4. Results

Six healthy male participants were included in the study with an average age of 32 years old and a range between 27 and 35 years of age. The average BMI was 22.5 with a range between 19.5 and 29. All participants were healthy, without any chronic medical problems, history of smoking or prescription medications (Table 1).

We assessed the absorption of the jelly ONS via ultrasonography. The gastric antrum appeared flat (anterior and posterior walls juxtaposed), with an ovoid shape in the supine position (Fig. 3A). Immediately after ingestion of a jelly, the antrum became round and distended, with hyperechoic inhomogeneous content (Fig. 3B). Thirty minutes after intake of the jelly, similar images to baseline were observed suggesting complete absorption of the ONS.

Decreases in fat and protein catabolism was observed in the ONS group. Significantly lower serum free fatty acid (FFA) levels [control: 327 (305, 377) μEq/L, ONS: 100 (95, 105) μEq/L, $p = 0.027$, median (25th, 75th percentile); Fig. 4A], total ketone bodies levels [control: 83 (53, 126) μmol/L, ONS:15 (13, 17)

**Table 1**
Characteristics of the volunteers.

| No. | Gender | Age (yr) | BMI (kg/m$^2$) |
|---|---|---|---|
| 1 | Male | 27 | 21.3 |
| 2 | Male | 32 | 19.5 |
| 3 | Male | 32 | 21.8 |
| 4 | Male | 33 | 22.1 |
| 5 | Male | 34 | 21.0 |
| 6 | Male | 35 | 29.0 |

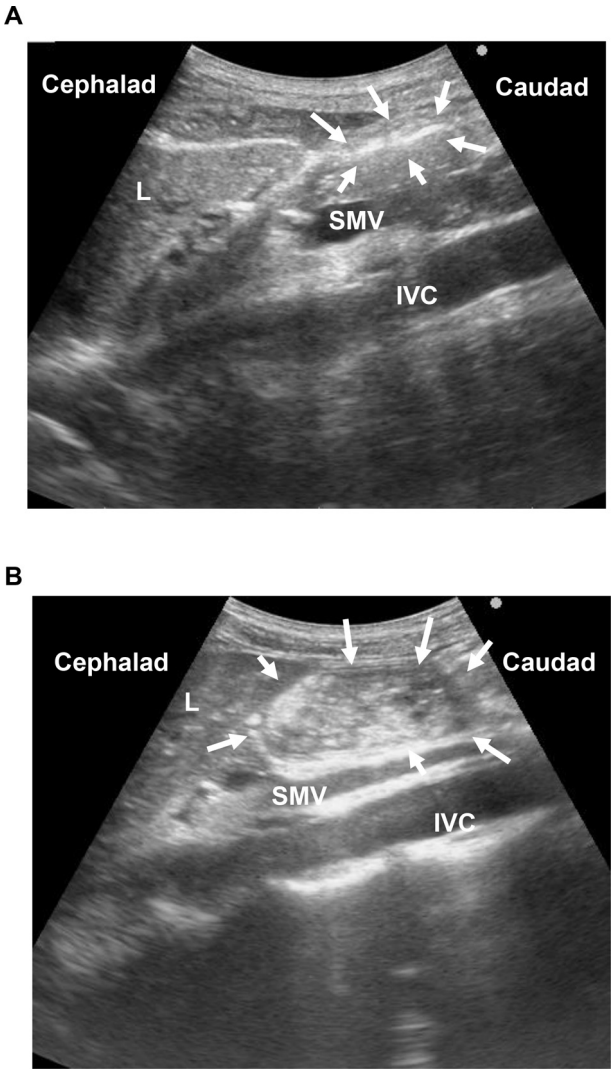


**Fig. 3. Antral images**. (A) at baseline and (B) immediately after ingestion of the jelly. *IVC*, inferior vena cava; *SMV*, superior mesenteric vein, L = liver. Arrows = gastric antrum.

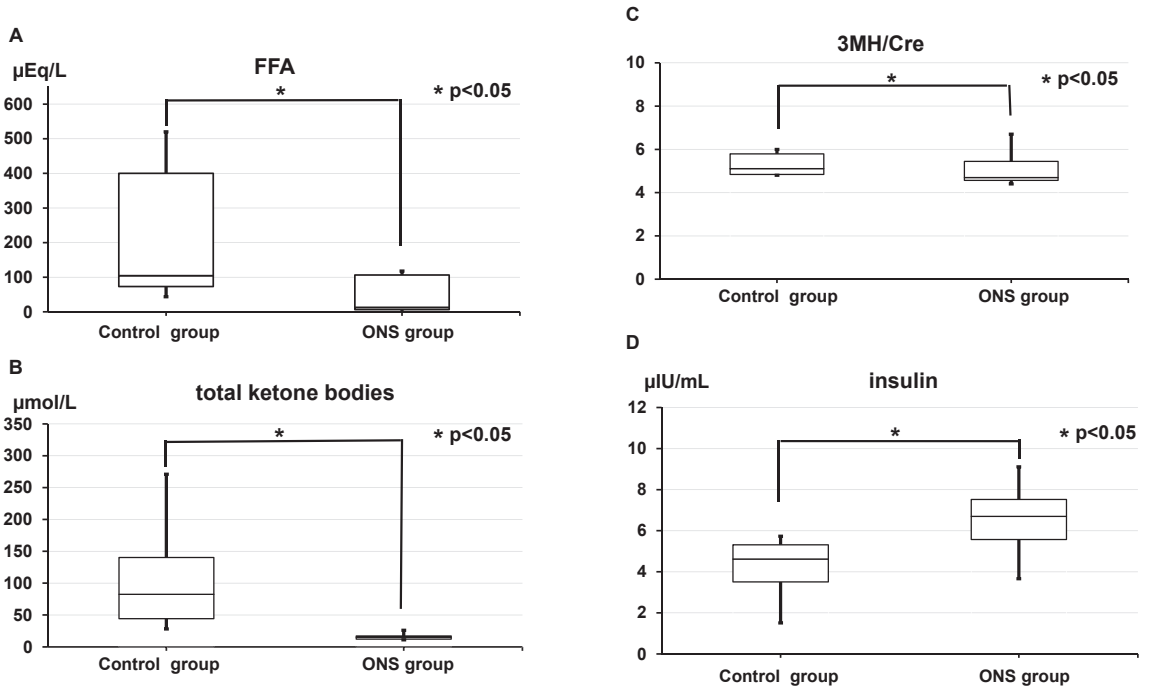


**Fig. 4. Serum concentration of (A) free fatty acids, (B) total ketone bodies, (C) 3-MH/creatinine ratio, and (D) insulin**. The boxes represent the 25th to 75th percentiles, and the horizontal lines within the boxes represent median values. The whiskers represent the lowest and highest values. *FFA*, free fatty acid; *ONS*, oral nutritional supplement; 3-MH/Cre.

μmol/L, p = 0.028, median (25th, 75th percentile); Fig. 4B], and 3-methylhistidine (3-MH)/creatinine levels [control: 5.11 (4.87, 5.62) nmol/L, ONS: 4.7 (4.6, 5.2) nmol/L, p = 0.028, median (25th, 75th percentile); Fig. 4C] were observed in the ONS group. Conversely, glucose metabolism was increased as serum insulin levels in the ONS group were significantly higher than those in the control group [control: 4.62 (3.8, 5.16) μIU/mL, ONS: 6.7 (5.85, 7.35) μIU/mL, p = 0.046, median (25th, 75th percentile); Fig. 4D]. Blood glucose, serum albumin, and serum creatinine (Cr) levels are shown in Table 2. No significant between-experiment differences were found for any of these parameters.

The ONS group revealed significantly lower oxidative stress surrogate markers. Results revealed significantly lower serum d-ROMs levels [control: 307 (279, 338) U.CARR, ONS: 277 (260, 290) U.CARR, P = 0.027, median (25th, 75th percentile); Fig. 5A]. In the ONS group, serum d-ROMs levels were in normal oxidative stress surrogate marker levels, whereas the control group increases in oxidative stress surrogate markers. Serum BAP levels differed significantly between groups [control: 2151 (2113, 2185) μmol/L, ONS: 2464 (2441, 2521) μmol/L, p = 0.028, median (25th, 75th percentile); Fig. 5B]. Serum BAP levels in the control group showed mild insufficiency of antioxidant capacity, but the ONS group produced suitable antioxidant capacity.

Improved participant satisfaction scores were seen in the ONS group. The VAS scores for anxiety, hunger, and thirst were higher in the control group than in the ONS group, with no differences in any other measure of subjective well-being (Table 3).

## 5. Discussion

Our results suggest that a jelly type ONS can be effectively taken and absorbed within 30 min of ingestion with minimal aspiration risk. We also show that ONS is able to decrease lipid and protein catabolism and oxidative stress surrogate markers while maintaining adequate glucose metabolism. Finally, we show that there is improved participant satisfaction with ingestion of the ONS.

Orally administered 12.6% carbohydrate loading before surgery is currently recommended in the ERAS protocol this normally consists of a liquid supplement. Previous reports have shown that intake of a preoperative carbohydrate drink was an independent predictor of positive clinical outcomes [6]. However, there are limited studies regarding the intake of preoperative jelly-type carbohydrates.

Food thickeners are commonly used in the commercial food industry falling into two main classes of starches and gums. Gums include guar, carrageenan, pectin, locust bean, and xanthum. These thickeners are used for thickening thin liquids for dysphagic individuals, and carry a low-risk of aspiration for elderly people when administered in a jelly made with gums. OS-1 jelly used in the present study contained a polysaccharide that consists of gums such as carrageenan and pectin to produce a jelly-like consistency. Additionally, OS-1 jelly is used as an oral rehydration therapy advocated by the World Health Organization as it is quickly absorbed by the body.

One of the major concerns of increasing the viscosity of a liquid is the potential of becoming an aspiration risk especially peri-operatively. Here we evaluate the specific risk of OS-1 jelly and its ability for gastric emptying. Previously, Perlas et al. suggested that sonographic assessment of the gastric antrum provides qualitative information about gastric content (empty or not empty) [9]. In their study, a cross-sectional image of the antrum was obtained *via* ultrasonography and the antrum was imaged in the epigastric area in the parasagittal plane using the left lobe of the liver, the inferior vena cava, and the superior mesenteric vein as internal landmarks. Similarly, in this study, participants in ONS group were scanned at baseline (fasting state), immediately after intake of the jelly, and 30 min after intake of the jelly. Our results suggested complete resolution and emptying of the gastric contents within

**Table 2**
Physiological data.

| | Control group | ONS group | P value |
|---|---|---|---|
| Glucose (mg/dL) | 99 (90, 101) | 97 (87, 108) | 0.753 |
| Albumin (g/dL) | 5.1 (4.8, 5.3) | 4.9 (4.8, 5.0) | 0.144 |
| Creatinine (mg/dL) | 0.815 (0.775, 0.875) | 0.76 (0.735, 0.875) | 0.102 |

Data shown as median (25th, 75th percentile).

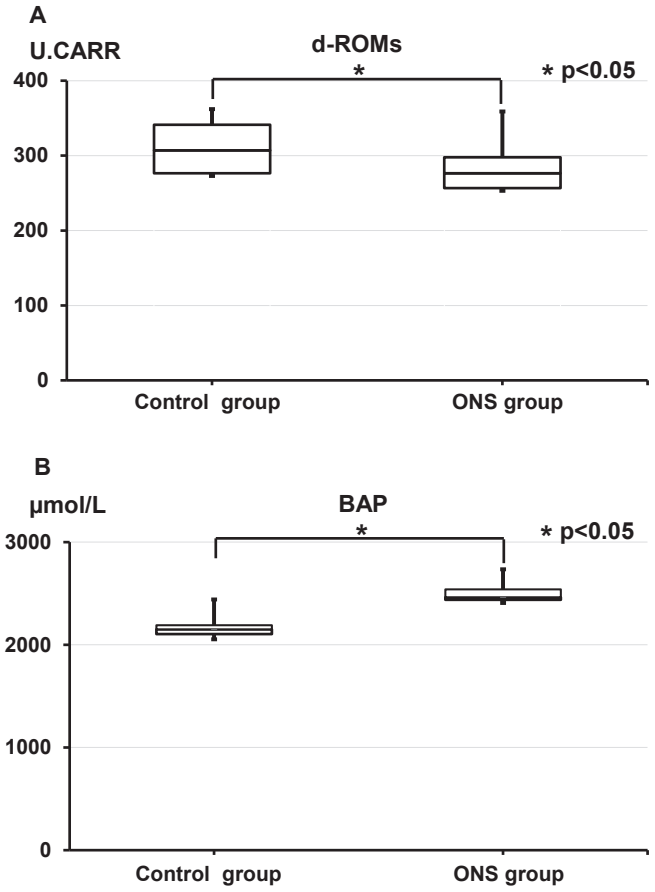


**Fig. 5. Oxidative stress and antioxidant**. (A) Serum d-ROMs levels. (B) Serum BAP levels. *U.CARRd-ROMs*, derivatives of reactive oxygen metabolites; *BAP*, biological antioxidant potential.

30 min, which strongly suggests that an intake of an OS-1 jelly-type carbohydrate supplement 2 h before the induction of anesthesia would safe without an increased risk of aspiration.

Starvation-induced physiologic changes occur with short-term or overnight fasting. Lipolysis, ketone body synthesis, and endogenous glucose production and uptake are promoted by starvation [14]. Adipose tissue is a major alternative fuel source during periods of starvation. Starvation promotes the metabolism of triglycerides into fatty acids. As fatty acids are used to yield energy ketone bodies are produced. The number of total ketone bodies reportedly increases during starvation [14]. In the present study, serum levels of FFA and total ketone bodies were significantly lower in the ONS group than in the

**Table 3**
Visual analog scale score.

| | Control group | ONS group | P value |
|---|---|---|---|
| Anxiety | 15 (10, 70)* | 5 (0, 30) | 0.042 |
| Depression | 0 (0, 60) | 0 (0, 30) | 0.18 |
| Hunger | 75 (60, 90)* | 20 (0, 30) | 0.026 |
| Malaise | 30 (0, 60) | 10 (0, 50) | 0.258 |
| Nausea | 0 (0, 0) | 0 (0, 0) | 1.0 |
| Thirst | 30 (10, 80)* | 10 (0, 30) | 0.041 |

Data shown as median and range in parenthesis. * indicates $p < 0.05$ between groups.

control group. The decrease in plasma FFA concentration can be explained by a decrease in fat oxidation, leading to decrease in ketone production. Because of the powerful inhibitory effect of insulin on lipolysis [15], the increase in serum insulin levels results in a decrease in serum FFA levels and a subsequent decrease in fat oxidation and ketone production. The present study demonstrated that serum insulin level in the ONS group were significantly higher than those in the control group. The serum insulin levels in the ONS group confirmed that lipid catabolism was inhibited.

3-methylhistidine is an amino acid derived from skeletal muscle protein. Because of the differences in the quantity of skeletal muscle in individuals, 3-MH/creatinine ratio has been utilized as an index of catabolism of muscle protein [16–18]. In our previous study, we demonstrated that intraoperative glucose infusion did not suppress protein catabolism during minor surgery [19]. In this study, 3-MH/creatinine ratios in the ONS group were significantly lower than in the control group. Insulin promotes the uptake of glucose into the skeletal muscle. Furthermore, it also inhibits proteolysis [20]. Our results suggest that the higher insulin levels induced by ingestion of the jelly in the ONS group suppressed the starvation-induced catabolism of muscle protein.

Nitric oxide (NO) exerts important vasodilatory and antioxidant effects [21]. Insulin stimulates endothelial NO production [22,23]. In target tissues, insulin stimulates 2 major pathways: the phosphatidylinositol 3-kinase pathway and the mitogen-activated protein kinase (MAPK) pathway. After receptor binding, phosphatidylinositol 3-kinase activation is critical for insulin-mediated glucose uptake into insulin-dependent target tissues, such as skeletal muscle, the heart, and adipose tissue [24]. Furthermore, this pathway has been shown to regulate insulin-dependent endothelial NO production [25]. Insulin resistance is dependent on a defect in a specific insulin-signaling pathway, the phosphatidylinositol 3-kinase pathway [26]. A previous study reported that orally administered 12.6% carbohydrate loading led to an improvement in insulin resistance [5]. In ONS group in this study, a possible mechanism for the decrease in oxidative stress surrogate markers and increase in antioxidant capacity surrogate marker may be that insulin-stimulated endothelial release of NO had improved by the alleviation of insulin resistance.

As hospitals and clinics try to improve patient satisfaction especially in the perioperative setting, our results in the ONS group may lead to actual patient satisfaction. We observed decreases in anxiety, hunger, and thirst. Given these findings, preoperative ONS may be beneficial for improving the preoperative quality of life.

This study had several limitations. First, we demonstrate the improvement in lipolysis and proteolysis markers in healthy volunteers who did not undergo a surgery. Considering the confounding effects of mental anxiety related to surgery, whether similar improvement can be achieved postoperatively in actual patients with a jelly supplemented 12.6% carbohydrate need to be studied. Furthermore, these biological processes are complex with multiple end points and this study only addressed a subset of those. Second, the influence of age and non-prescription medications such as $H_2$ blockers on the excretion of the jelly from the stomach remains unclear. Shiraishi et al. described gastric emptying after OS-1 ingestion in morbidly obese subjects appeared to not differ from subjects with a normal BMI [27]. The safety of jelly ingestion at least 2 h before the induction of anesthesia should be investigated in a future study. Additionally, only male participants were investigated to avoid hormonal differences which could influence differences within metabolic status. Finally, we did not monitor or limit the contents of the evening meal consumed on the day before the experiment. Therefore, we cannot deny that differences in the meal consumed by each individual may have affected our data.

In conclusion, our study suggests that an intake of a OS-1 jelly-type 12.6% carbohydrate supplement might contribute to suppress the catabolism of adipose tissue and muscle protein and oxidative stress surrogate markers, while increasing fasting healthy participant satisfaction without an increased risk of aspiration. Although further clinical studies on postoperative patients are required to determine whether preoperative OS-1 jelly-type 12.6% carbohydrate supplement loading contributed to improvement in patient outcome, the results provide vital information for implementing a modified ERAS protocol.

## Author contribution

Conception and design of the study (Tsutsumi YM), acquisition of data (Oyama T, Kakuta N, and Mita N), analysis of data (Oyama T and Kakuta N), drafting the article (Oyama T, Kakuta N, and Tsutsumi YM),

revising it critically for important intellectual content (Kawahito S and Tanaka K), and all author approved final version submitted.

## Conflicts of interest

The authors do not have any conflict of interests regarding the content of the paper.

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