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【 ORIGINAL ARTICLE 】

Use of a Low-carbohydrate Enteral Nutrition Formula with Effective Inhibition of Hypoglycemia and Post-infusion Hyperglycemia in Non-diabetic Patients Fed via a Jejunostomy Tube

Shinji Nishiwaki [1], Hiroko Fujimoto [2], Takuya Kurobe [1], Atsushi Baba [1], Masahide Iwashita [1], Hiroo Hatakeyama [1], Takao Hayashi [1] and Teruo Maeda [1]

Abstract:

Objective As direct jejunal feeding often causes great fluctuation in glucose levels, continuous or slow infusion is recommended for jejunal tube-fed patients. However, continuous feeding results in prolonged immobility and the loss of activities of daily living. We investigated whether or not intermittent feeding of a low-carbohydrate high-monounsaturated fatty acid (LC/HM) nutrient formula reduces glucose fluctuation in patients who have undergone jejunotomy.

Methods Ten bed-ridden non-diabetic patients receiving enteral feeding via a jejunostomy tube were enrolled in this study. LC/HM formula and standard control formula were infused in cross-over order for each patient at a speed of 160 kcal/h. Blood glucose levels were monitored by a continuous glucose monitoring system during the investigation period.

Results The mean and standard deviation of the glucose concentrations and mean amplitude of glucose excursion (MAGE) were markedly lower while receiving LC/HM formula than while receiving control standard formula (104 vs. 136 mg/dL, 18.1 vs. 58.1 mg/dL, 50.8 vs. 160 mg/dL, respectively). The post-infusion hyperglycemia [area under the curve (AUC) >140 mg/dL] and peak value of the glucose level were also significantly lower in patients fed LC/HM than the control (25.7 vs. 880 mg·h/dL and 153 vs. 272 mg/dL, respectively). Reactive hypoglycemia (AUC <70 mg/dL) was also significantly lower (0.63 vs. 16.7 mg·h/dL) and the minimum value of the glucose level higher (78.4 vs. 61.8 mg/dL) in patients fed LC/HM than the control.

Conclusion The LC/HM formula is considered to markedly inhibit glycemic spikes and prevent rebound hypoglycemia in patients who receive enteral feeding after jejunostomy.

Key words: hypoglycemia, continuous glucose monitoring, glycemic fluctuation, carbohydrate restriction, jejunostomy

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Introduction

Percutaneous endoscopic gastrostomy (PEG) is a well-established method for long-term enteral feeding because of its simple and safe technique compared with the surgical placement of a gastrostomy tube. Although nutritional control via a gastrostomy tube is easy for patients with dysphagia, continuous feeding may become difficult due to complications (1). Gastroesophageal reflux is a major, life-threatening complication during gastric feeding (2, 3). Post-pyloric feeding is introduced after PEG with a jejunal extension tube (PEG-J) for patients who develop recurrent aspiration (4). Jejunal feeding is also employed for patients who are unable to undergo PEG due to anatomical reasons, such as dislocation of the stomach or a post-gastrectomy

[1]Department of Internal Medicine, Nishimino Kosei Hospital, Japan and [2]Tokai University School of Medicine, Japan
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Correspondence to Dr. Shinji Nishiwaki, pegwaki@yahoo.co.jp

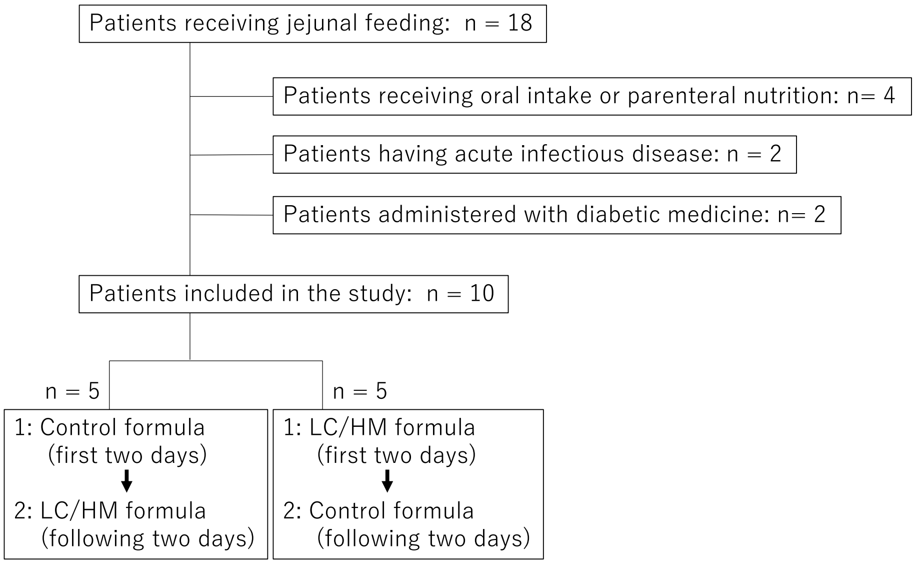

Figure 1. Diagram of the study flow. LC/HM: low-carbohydrate high-monounsaturated fatty acid

Table 1. Compositions of Enteral Nutrition Formulae Applied.

	LC/HM formula	Control formula
Energy (kcal)	100	100
Protein (g)	4.2	5
Fat (g)	5.6	2.3
Carbohydrate (g)	9.7	15.7
Dietary fiber (g)	0.9	1.2
Water (mL)	85	85

LH/HM: low-carbohydrate with high-monounsaturated fatty acid

state (5, 6). However, enteral feeding via a jejunostomy tube may cause more complications than that via a gastrostomy tube. Diarrhea and dumping syndrome are frequently occurring symptoms in patients after PEG-J (7). Therefore, careful observation during continuous jejunal feeding is recommended at its initiation (8). In addition, continuous or extended drip infusion through a jejunostomy tube reduces the physical activity of patients due to the prolonged bed-rest period necessary during feeding.

Diabetes-specific nutrition formulae with a low glycemic index, such as high-complex carbohydrate formulae or low-carbohydrate with high-monounsaturated fatty acid (LC/HM) formulae, have been introduced for glycemic control in diabetic patients (9). LC/HM formulae were reported to markedly reduce glycemic fluctuation compared with the standard nutrient formula for gastric tube-fed patients (10). However, there has been no report on the influence of a diabetes-specific LC/HM formula on jejunostomy tube-fed patients.

We herein report the effects of LC/HM formulae for glycemic control in patients receiving jejunal feeding.

Materials and Methods

The present study's flow chart is shown in Fig. 1. The subjects were 18 in-patients hospitalized at Nishimino Kosei Hospital who were fed with a standard composition of enteral liquid nutrients through a jejunostomy tube between June 2017 and November 2018. The exclusion criteria were as follows: Patients who (1) had received the combination of an oral intake and parenteral nutrition (2), had an acute infectious disease or administration of antibiotics within one week of enrollment (3), had an HbA1c level greater than 6.3% (4), had been administered diabetic medicine, or (5) refused to participate in this study. A total of 10 patients were enrolled in this study.

The concept of the study, study designs, and method of obtaining informed consent were approved by the ethics committee of our institution prior to the start. The study protocol was also registered at the University Hospital Informational Network (UMIN) Clinical Trials Registry (UMIN CTR, ID=000037496). Informed consent was received from the patients or their families after detailed explanation of the nature of this study.

Enteral nutrients

The enteral LC/HM feeding formula used in this study was based on carbohydrate-restricted nutrients (Glucerna-Ex™ or Glucerna-Rex™; Abott Japan, Tokyo, Japan). The control formula was Hine™ (Otsuka Pharmaceutical Factory, Tokushima, Japan). The compositions of the nutrition formulae are shown in Table 1. The energy percentages of the carbohydrate content in LC/HM and the control formulae were 33% and 60%, respectively, and those of the fat content were 51% and 20%, respectively. The test formulae were administered at the same energy level and times a day as prior to enrollment for each patient. The administration rate of feeding was fixed at 160 kcal/h for 4 days. This was because the speed of the control formula sometimes caused reactive hypoglycemia without adverse symptoms in our preliminary study. The daily cycle of intermittent feeding was started at 5 : 30 in the morning, 11 : 30 in the daytime, and

Table 2. Clinical Background of 10 Subjects.

Age (mean±SD years)		86.7±7.4
Gender (Males/Females)		3/7
Height (mean±SD cm)		148.5±9.8
Body weight (mean±SD kg)		39.4±6.7
Body mass index (kg/m^2)		17.9±2.89
Estimated energy requirement (mean±SD kcal/day)		878±76
Fasting glucose level (mean±SD mg/dL)		91.8±8.1
HbA1c (mean±SD %)		5.72±0.33
Total energy of feeding (mean±SD kcal/day)		1,080±193
Type of jejunostomy	DPEJ (n)	6
	PEG-J (n)	4
Reason for jejunal feeding	Gastroesophageal reflux (n)	4
	Dislocation of the stomach (n)	3
	Post-gastrectomy (n)	3

SD: standard deviation, DPEJ: direct percutaneous endoscopic jejunostomy, PEG-J: percutaneous endoscopic gastrostomy with a jejunal extension tube

16 : 30 in the evening. Daytime feeding was skipped for patients who were to be fed two times a day. For five patients, LC/HM formula was administered for the first two days, and then the control formula was administered for the following two days. The remaining five patients received the reverse order of the two formulae, i.e. the control formula was administered for the first two days, and then LC/HM formula was administered for the following two days.

Blood glucose measurement and analyses

Glucose monitoring was continuously conducted using a glucose sensor (FreeStyle Libre™; Abbott Diabetes Care, Alameda, USA). Three days after attachment of the glucose sensor, one test formula was administered for two days, and the other formula was administered for the following two days. Glucose levels were monitored every 15 minutes per day for a total of 96 times, and data measured on the second day for each formula administration were employed for analyses to eliminate the influence of the prior formula. The average and standard deviation (SD) of glucose levels and mean amplitude of glucose excursion (MAGE) were calculated. The area under the curve (AUC) for greater than 140 mg/dL and less than 70 mg/dL was assessed using all of the obtained glucose values. The proportions of the period in hyperglycemia (>140 mg/dL) and hypoglycemia (<70 mg/dL) were calculated as the total time in hyperglycemia or hypoglycemia within 24 hours. Peak and minimum glucose values were also selected from the daily glucose values.

Statistical analyses of each parameter comparing the LC/HM and control formulae were conducted using Wilcoxon's signed-rank test. All data were analyzed using a statistical software program (JMP for Windows Version 5.1.1; SAS Institute, Cary, USA).

Results

The clinical background of the patients in the present study is shown in Table 2. The total energy of the fed formulae ranged from 800-1,200 (1,080±193) kcal/day, which were intermittently infused through a jejunostomy tube 2 times (3 patients) or 3 times (7 patients) a day. All patients were administered more energy than the estimated energy requirement. Among the 10 patients, 6 had direct percutaneous endoscopic jejunostomy (DPEJ) because they were not indicated for PEG due to the state of dislocation of the stomach or their history of gastrectomy, whereas 4 patients underwent PEG-J due to repeated aspiration events after PEG.

Continuous glucose monitoring (CGM) for 48 hours in the patients administered LC/HM and the control formulae are shown in Fig. 2A and B, respectively. The peak glucose values were observed around the end of infusion (8 : 00, 14 : 00 and 19 : 00) in both formulae, showing the highest value at the evening feeding time. The peak glucose values with the LC/HM formula were 130 and 132 mg/dL for days 1 and 2, respectively, whereas those with the control formula were 240 and 236 mg/dL for days 1 and 2, respectively. The rapid decline in the glucose level was observed immediately after the end of the control formula administration and reached its nadir around two hours after the end of administration (Fig. 2B).

Table 3 shows the number of patients who had reactive hypoglycemia (<70 mg/dL) after infusion by CGM analyses. Only a few patients demonstrated reactive hypoglycemia using LC/HM formula, whereas many patients demonstrated reactive hypoglycemia using the control formula after morning and evening administration.

The analyses of CGM data for our 10 patients on the second day of LC/HM or the control formula are summarized in Table 4. The mean and SD and MAGE were significantly lower with the LC/HM formula than with the control formula. The period, AUC, and peak value of hyperglycemia were significantly lower with the LC/HM formula than with the control formula. The period and AUC of hypoglycemia

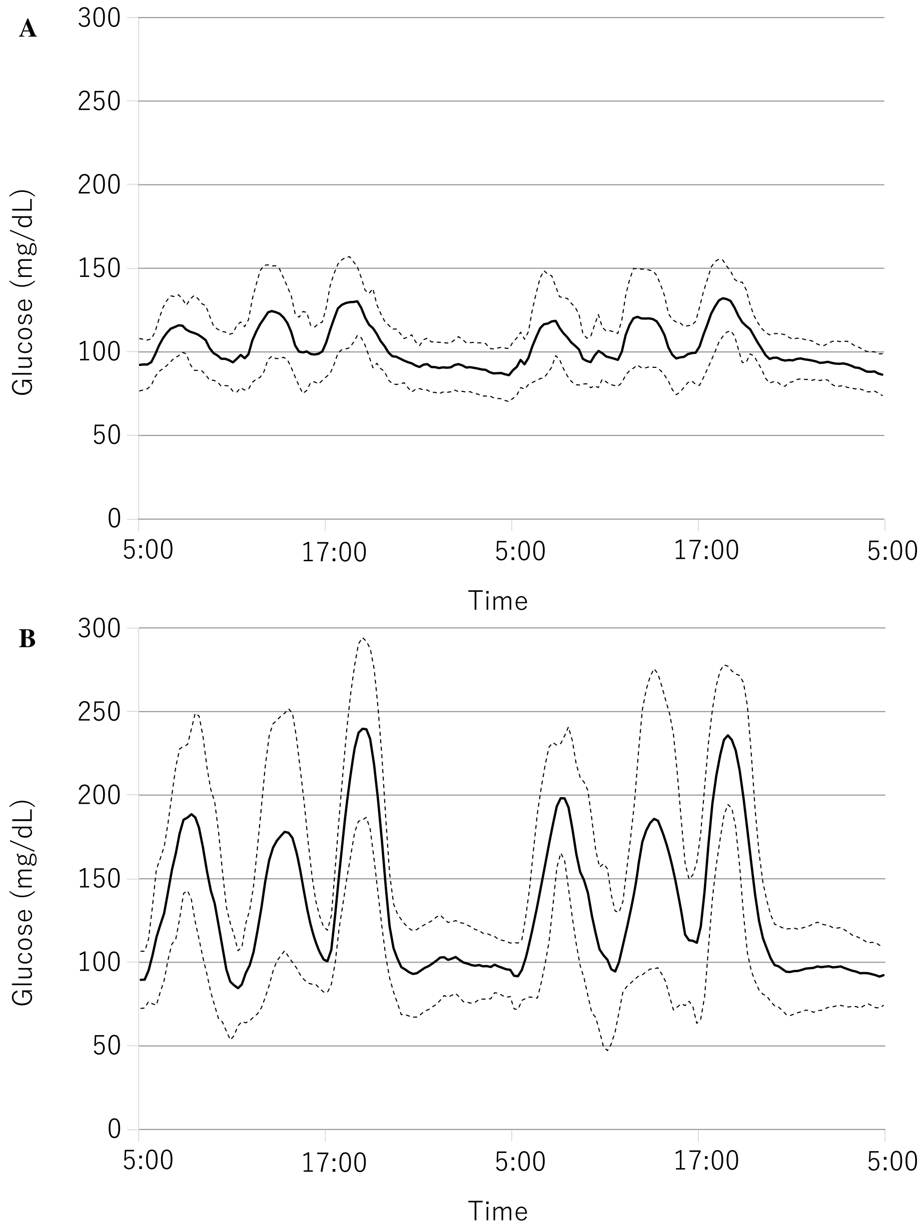

Figure 2. **Glucose levels monitored during two-day administration of the LC/HM formula (A) and the control formula (B) in all patients. The solid line indicates the mean value, and the dotted lines indicate the standard deviations. LC/HM: low-carbohydrate high-monounsaturated fatty acid**

Table 3. **Number of Patients Demonstrated Reactive Hypoglycemia (<70 mg/dL) by Continuous Glucose Monitoring.**

	LC/HM formula		Control formula	
feeding time	day 1	day 2	day 1	day 2
morning (n=10)	1	0	6	5
noon (n=7)	0	1	0	0
evening (n=10)	0	1	3	3

LC/HM: low-carbohydrate with high-monounsaturated fatty acid

were significantly lower with the LC/HM formula than with the control formula, and the minimum value of hypoglycemia was significantly higher with the LC/HM formula than with the control formula. The incidence of adverse symptoms, such as abdominal distension, nausea, vomiting, and diarrhea, did not notably differ between the test periods with both formulae.

Discussion

Jejunostomy was initially conceived as an additional procedure during upper gastrointestinal, hepatobiliary, or pancreatic surgery for the purpose of enteral feeding (11). After the introduction of the PEG technique, PEG-J and DPEJ were subsequently developed for jejunal feeding (4-6). The major indications of jejunal feeding are post-operational nutrition support, gastroesophageal reflux after gastrostomy, gastroparesis, gastric outlet obstruction, pancreatitis, and an inability to conduct PEG due to a history of gastrectomy or dislocation of the stomach from the abdominal wall (12).

Table 4. Continuous Glucose Monitoring Data of LC/HM or Control Formula Administration.

	LC/HM formula	Control formula	p value
24-h mean glucose level (mean±SD) mg/dL	104±12.3	136±21.3	<0.01
Standard deviations of 96 glucose levels for 24 h (mean±SD) mg/dL	18.1±5.2	58.1±12.1	<0.01
MAGE, (mean±SD) mg/dL	50.8±15.4	160±42	<0.01
Period with glucose level more than 140 mg/dL (mean±SD) %	8.01±8.49	35.8±9.4	<0.01
Total AUC for glucose level greater than 140 mg/dL (mean±SD) mg·h/dL	25.7±32.0	880±796	<0.01
Period with glucose level less than 70 mg/dL (mean±SD) %	0.61±1.2	6.75±7.21	<0.01
Total AUC for glucose level less than 70 mg/dL (mean±SD) mg·h/dL	0.63±1.28	16.7±22.3	<0.01
Peak value for glucose (mean±SD) mg/dL	153±15	272±40	<0.01
Minimum value for glucose (mean±SD) mg/dL	78.4±15.6	61.8±13.9	<0.05

LC/HM: low-carbohydrate with high-monounsaturated fatty acid, SD: standard deviation, MAGE: mean amplitude of glucose excursions, AUC: area under the curve

Although the complications of jejunostomy depend on the methods and devices used, enteral and metabolic complications during feeding are common.

The pathophysiological conditions of patients with jejunostomy tube feeding are similar to those of patients who have undergone gastrectomy or gastric bypass operation. Nausea, vomiting, abdominal distension, and diarrhea are often observed after the rapid inflow of foods or liquid nutrition formulae into the small intestine (7, 13, 14). Micronutrient and vitamin deficiencies due to malabsorption are complications of the long-term nutritional maintenance of patients who undergo gastric surgery and placement of a jejunal feeding tube (15-17).

Glucose absorption and metabolism are also impaired in such patients (18, 19). Breitman et al. reported that the postprandial glucose curve was shifted to the left in patients with jejunal feeding compared with gastric feeding, although the incremental AUC did not differ markedly between the two routes (20). They also reported that the glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) levels were increased, and the peak insulin response was faster and higher in patients receiving jejunal feeding than in those receiving gastric feeding. Reactive hypoglycemia followed by postprandial hyperglycemia and hyperinsulinemia, known as late dumping syndrome, is the major symptom following rapid inflow into the jejunum. In patients who undergo jejunostomy, rapid or bolus feeding causes hyperinsulinemia, and induced reactive hypoglycemia may result in late dumping syndrome (21). Hyperplasia of islet β-cells in gastric-bypass surgery is considered to induce hyperinsulinemia and consequent hypoglycemia (22). Hirakawa et al. reported that hypoglycemia and increased glucose fluctuation may induce macrovascular and microvascular events (23). Therefore, the fluctuation of plasma glucose levels should be suppressed. Alfa-glucosidase inhibitors are known to be effective for suppressing post-prandial elevation of glucose, insulin, and GLP-1 levels (24).

Diabetes-specific formulae have also been employed for glucose control during enteral feeding for diabetic patients. The addition of dietary fiber, an increased proportion of sucrose or fructose, or LC/HM formulae are effective for glycemic control in type 2 diabetic patients (25). The use of Glucerna™, an LC/HM formula, for tube-fed diabetic patients has been shown to effectively neutralize glycemic fluctuation without significant gastrointestinal complications (26, 27). Furthermore, the daily insulin requirement can be reduced for diabetic patients using LC/HM formulae (11, 28). Carbohydrate-restricted meals also successfully improved hyper-insulinemic hypoglycemia for patients who underwent Roux-en-Y gastric bypass (29). However, there has been no report on the administration of diabetes-specific formulae to patients receiving jejunal feeding.

In the present study, we used an LC/HM formula for patients with jejunal feeding in order to suppress glucose level fluctuations. Although the total energy of the LC/HM formula was equivalent to that of the control formula, the mean glucose level, MAGE, and glucose fluctuation were markedly decreased with the LC/HM formula than with the control formula. The peak glucose value was also markedly lower with the LC/HM formula, leading to an increased minimum glucose value. As there were no diabetic patients in our study, with all patients considered to have a normal insulin secretory capability, hypoglycemia may have been caused by hyperinsulinemia during feeding with the control formula. Although our patients showed minimal symptoms of hypoglycemia or late dumping, their planarized glucose level by LC/HM formula was considered to have prevented these symptoms.

Fat-rich diets reduce lower esophageal sphincter pressure and inhibit gastric motility, which may subsequently cause abdominal distension, nausea, or vomiting (30, 31). Although jejunal feeding is also considered beneficial for preventing regurgitation of nutrients because the feeding site is located more distally than that for gastric feeding, we should take care to prevent vomiting of gastric juice (32). Several reports on the gastrointestinal tolerance of LC/HM formula for gastric tube feeding found no significant complications (26-28). When administering a fat-rich formula to jejunal feeding patients, steatorrhea may be caused by a lack of bile or pancreatic juice. We observed no gastrointestinal symptoms, including vomiting and diarrhea, associated with the jejunal administration of LC/HM formula during the test period.

The LC/HM formula also influenced the lipid metabolism. Mottalib et al. reported that postprandial free fatty acid and triglyceride levels with the LC/HM formula did not differ markedly from those with their control oatmeal formula (33). Intermediate-term tube feeding of an LC/HM formula for several months has been reported to reduce triglyceride levels in diabetic patients (27, 28); thus, this diet may be useful for preventing arteriosclerosis. Although continued metabolic analyses and clinical observations are necessary, LC/HM formulae for jejunal feeding may help reduce the rate of cardiovascular events.

Several limitations associated with the present study warrant mention. First, the sample size was small, and the study was conducted at a single institution. A multi-institutional study with a greater number of subjects is desired to further verify our findings. Second, the present study was an open-label study, possibly causing unintentional bias. Third, the administration periods of the control and test formulae were only two days. If LC/HM formula is administered over a longer period, not only the glycemic levels but also the lipid and amino acid metabolism may change. However, our results may provide an option for administering LC/HM formula to jejunostomy patients and thus expand our knowledge regarding the effects and safety of the long-term administration of LC/HM formula.

In conclusion, LC/HM formulae for jejunal feeding improve glycemic level control and inhibit hyperglycemia and subsequent reactive hypoglycemia. Further clinical analyses are necessary to evaluate the effects of the long-term administration of LH/LM formulae.

The authors state that they have no Conflict of Interest (COI).

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