Enteral Formula Containing Egg Yolk Lecithin Improves Diarrhea

Tetsuro Akashi1,*, Ayano Muto2, Yaoi Takahashi2 and Hiroshi Nishiyama2

1 Department of Internal Medicine, Saiseikai Fukuoka General Hospital, 1-3-46, Tenjin, Chuo-ku, Fukuoka 810-0001, JAPAN
2 R&D Division, Kewpie Corporation, Tokyo 182-0002, JAPAN

Abstract: Diarrhea often occurs during enteral nutrition. Recently, several reports showed that diarrhea improves by adding egg yolk lecithin, an emulsifier, in an enteral formula. Therefore, we evaluated if this combination could improve diarrhea outcomes. We retrospectively investigated the inhibitory effects on watery stools by replacing a polymeric formula with that containing egg yolk lecithin. Then, we investigated the emulsion stability in vitro. Next, we examined the lipid absorption using different emulsifiers among bile duct-ligated rats and assessed whether egg yolk lecithin, medium-chain triglyceride, and dietary fiber can improve diarrhea outcomes in a rat model of short bowel syndrome. Stool consistency or frequency of the egg yolk lecithin emulsifier did not change by adding artificial gastric juice, whereas that of soy lecithin and synthetic emulsifiers increased. Serum triglyceride concentrations were significantly higher in the egg yolk lecithin group compared with the soybean lecithin and synthetic emulsifier groups in bile duct-ligated rats. In rats with short bowels, the fecal consistency was a significant looser the dietary fiber (+) group than the egg yolk lecithin (+) groups from day 6 of test meal feedings. The fecal consistency was also a significant looser the egg yolk lecithin (−) group than the egg yolk lecithin (+) groups from day 4 of test meal feeding. The fecal consistency was no significant difference between the medium-chain triglycerides (−) and egg yolk lecithin (+) groups. Enteral formula emulsified with egg yolk lecithin promotes lipid absorption by preventing the destruction of emulsified substances by gastric acid. This enteral formula improved diarrhea and should reduce the burden on patients and healthcare workers.

Key words: lecithins, enteral nutrition, diarrhea, lipid absorption, emulsifier

1 Introduction

Enteral nutrition is the first-choice nutritional therapy for patients without impairment in the gastrointestinal tract1. Enteral nutrition is not only more physiological than parenteral nutrition but has also been shown to improve patient outcomes and decrease healthcare costs2 compared with parenteral nutrition. However, diarrhea is a common and serious complication in patients receiving enteral nutrition, with reported incidences ranging from 2% to 95% because of differences in patient populations and diarrhea definitions used3,4. Etiological factors, disease severity, and comorbidities may each contribute to the onset of diarrhea in critically ill patients (e.g., tube feeding or intensive care unit)5. Once established, diarrhea can lead to dehydration, electrolyte loss, and malnutrition, which further impair the patient’s health and may necessitate other clinical interventions that contribute to longer hospital stays and increased costs6. Therefore, not only the patient’s quality of life impaired but also the burden on health care workers is increased.

The pathogenesis of diarrhea in patients receiving enteral nutrition is multifactorial. Diarrhea in these patients is often caused by predisposing illnesses (e.g., diabetes mellitus or malabsorption), infections, gastrointestinal complications, concomitant drug therapies (e.g., antibiotics, sorbitol, or antacids), or enteral nutrition-associated factors7. Factors related to enteral nutrition include the composition of the formula, manner of formula administration, and contamination of the formula or its administration devices8–10.

Lipids in formulas may cause diarrhea, with formulas that have higher fat content being correlated with osmotic diarrhea in patients with burns8,9,10. It has also been shown that chronic diarrhea can be caused by intestinal bacterial...
disturbances such as small intestinal bacterial overgrowth (SIBO)\(^\text{13}\). Fat malabsorption may result from SIBO because of the bacterial deconjugation of bile acids and subsequent deficiency of intraluminal conjugated bile acids\(^\text{13}\). In healthy people, bile acid deconjugation begins in the distal small intestine, presumably mediated by bacteria spilling across the ileocecal valve\(^\text{13}\). In patients with intestinal stasis or other pathologic conditions promoting the growth of bacteria, bile acid deconjugation increases in the proximal intestine\(^\text{13}\). The unconjugated bile acids that are formed are absorbed passively from the small intestine, causing a decreased intraluminal concentration and impaired micelle formation\(^\text{13}\). Therefore, fat malabsorption is considered to occur. Many clinical conditions, including parenteral nutrition, diabetes mellitus, drug-induced inhibition of acid secretion, and irritable bowel syndrome, and old age are associated with SIBO\(^\text{14,15}\). SIBO is also considered frequent in patients receiving enteral nutrition and may cause excess accumulation of lipids.

Improvement of fat malabsorption is also conceivable with the use of medium-chain triglycerides (MCTs) as a countermeasure against the malabsorption of lipids. MCTs are digested and absorbed faster than long-chain fatty acids and are rapidly converted to energy and carried directly to the liver via the portal vein\(^\text{16}\). On the other hand, enteral formulas are emulsified to improve the absorption of lipids. In commercially available enteral formulas, egg yolk lecithin, soybean lecithin, and synthetic compounds are used as emulsifiers.

Recently, some reports in Japan have indicated that diarrhea could be improved (immediately in some cases) by changing the enteral formula\(^\text{18–20}\). This occurred with the use of the formula of K-2S (JANEF liquid diet NEW K-2S; Kewpie Corporation, Tokyo, Japan) or K-LEC (JANEF K-LEC; Kewpie Corporation, Tokyo, Japan) as enteral formulas\(^\text{18–20}\). Although it is unclear why this improves diarrhea, it was thought that the different components and composition have some influence. Both these enteral formulas use egg yolk lecithin as an emulsifier and contain many MCTs but do not include dietary fiber. Notably, most available enteral formulas do not contain egg yolk lecithin (Sugiura, K.; Nishiyama, H.; Muto, A. \textit{et al}. ENTERAL NU-TRIENT PCT International Patent Publication No.WO2012/121095 A1, 2012); therefore, we considered that the egg yolk lecithin is responsible for the improvement in diarrhea.

The present study was conducted to determine whether enteral formula containing egg yolk lecithin could improve diarrhea outcomes. First, we retrospectively investigated the medical records of patients who used K-LEC at the Saiseikai Fukuoka General Hospital. Second, we investigated the stability of the emulsion with artificial gastric juice \textit{in vitro}. Third, we compared lipid absorption using different emulsifiers in bile duct-ligated rats with malabsorption. Finally, we investigated whether egg yolk lecithin and other components of enteral formula could improve diarrhea outcomes in a rat model of short bowel syndrome.

2 EXPERIMENTAL PROCEDURES

2.1 Examination of medical records

2.1.1 Patients

We retrospectively analyzed the medical records of 170 patients using K-LEC between May 2011 and July 2012. The study protocol was approved by the Ethics Committee of Saiseikai Fukuoka General Hospital on July 17, 2015 (no. 2015-7-2) with the need for consent waived.

2.1.2 Nutrient composition of enteral nutrition formulas

K-LEC was introduced for diarrhea in 23 patients receiving a standard enteral formula. We excluded patients who received disease-specific or high caloric density enteral formulas before the change. The osmotic pressure and caloric density of the standard formula L-6PM (L-6PM PLUS; Asahi Kasei Pharma Corporation, Tokyo, Japan) and K-LEC are equivalent; therefore, we assessed 14 patients who were changed from L-6PM to K-LEC.

K-LEC has an osmotic pressure of 300 mOsm/L and a caloric density of 1 kcal/mL, with an energy distribution (unit/100 mL) of 3.5 g protein, 3.3 g fat, 14.1 g carbohydrate, and 0 g dietary fiber. Fat composition is 45% saturated fatty acid, 40% monounsaturated fatty acid, and 15% polyunsaturated fatty acid. L-6PM is a standard enteral formula with an osmotic pressure of 340 mOsm/L, a caloric density of 1 kcal/mL, and a synthetic emulsifier. The energy distribution (unit/100 mL) is 5.3 g protein, 2.4 g fat, 14.15 g carbohydrates, and 1.7 g dietary fiber. Fat composition is 30% saturated fatty acid, 30% monounsaturated fatty acid, and 40% polyunsaturated fatty acid.

2.1.3 Stool assessment

We assessed stool consistency (on the basis of the Bristol Stool Form Scale score from type 1 to 7) and frequency (number of stools per day) on the day after the enteral formula was changed. The seven types of stools were recorded as follows: type 1, separate hard lumps, like nuts; type 2, sausage shaped but lumpy; type 3, like a sausage but with cracks on its surface; type 4, like a sausage or snake, smooth and soft; type 5, soft blobs with clear cut edges; type 6, fluffy pieces with ragged edges, a mushy stool; and type 7, watery, no solid pieces\(^\text{21,22}\).

2.2 \textit{In vitro} gastric digestion model

2.2.1 Materials

In this study, we used egg yolk lecithin, soybean lecithin, and synthetic compounds as emulsifiers. To clarify the effect of emulsifiers on lipid absorption, we made adjustments with a simple blend of emulsifiers and lipids.

Formulation of the emulsion by each emulsifier was
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shown in Table 1. Egg yolk lecithin group and soybean lecithin group were formulated so that the phospholipid contents were equal. (Approximately 4.5% as phospholipid content)

Rapeseed oil was used to equalize the triglyceride content of all groups. (Approximately 20% as triglyceride content)

2.2.2 Procedure

The three test emulsions (egg yolk lecithin, soybean lecithin, and synthetic emulsifiers) were weighed in 100-mL beakers and subjected to a disintegration test in artificial gastric juice (pH 1.2, set to 1.000 mL by dissolving 2.0 g sodium chloride in 7.0 mL of hydrochloric acid and water[2]) while slowly stirring until pH 2 was reached. Then we measured the particle size distribution and mean particle diameter using a particle size analyzer (Microtrac® MT3300EXII, MicrotracBEL Corp., Osaka, Japan). The average particle diameter was set to 50% cumulative particle diameter.

2.3 In vivo lipid absorption in rats with bile duct ligation

All procedures were performed in accordance with the Standards relating to Breeding, Care, and Reduction of Pain with regard to Experimental Animals (Ministry of the Environment Notification No. 88, April 28, 2006). This experiment was carried out in October 2008. At that time, in the Institute of Technology R&D DIV., Kewpie Corporation, diethyl ether has been used as an inhalation anesthetic. Recently, inhalation anesthesia with diethyl ether is said to be unsuitable[3]. Therefore, we have introduced inhalation anesthesia with isoflurane than November 2008 in the Kewpie Institute. At the time of use of diethyl ether, we were used in an explosion-proof fume hood. In addition, in order to avoid an explosion, animal carcasses were stored safely until the ether is volatized. The study protocol was approved by the Ethics Committee of Kewpie Institute on August 19, 2016 (no. 16-5).

2.3.1 Materials

The same emulsifiers as those in the in vitro tests were used (egg yolk lecithin, soybean lecithin, and synthetic emulsifiers). Each sample was added after stirring and homogenizing at 10,000 rpm for 5 min using a Physcotron (NS-50; Micro Tech Co., Funabashi, Japan).

2.3.2 Animals and diets

Eighteen 6-week-old male Sprague–Dawley rats weighing 110–130 g (Japan SLC, Inc., Hamamatsu, Japan) were individually housed in stainless steel cages at a temperature of 22°C–24°C, with a relative humidity of 35%–65%, and a 12-h light/dark cycle (light from 08:00 to 20:00). The rats were allowed free access to feed (certified rodent diet 5002; LabDiet®, St. Louis, USA) and drink water ad libitum. The rats were allowed 1 week to adapt to their environment before starting the experiments. After the acclimation period, rats were divided into three groups on the basis of their average body weight.

2.3.3 Procedure

We created three experimental groups on the basis of the emulsifier used: an egg yolk lecithin group, a soy lecithin group, and a synthetic emulsifier group. Blood was collected after an overnight fast. The emulsion was administered once through a gastric tube at 10 g/kg body weight and blood was withdrawn from the tail vein at 0, 2, 4, 6,
2.4 Evaluation of the in vivo improvement in diarrhea using a rat model of short bowel syndrome

All procedures were performed in accordance with the Standards relating to Breeding, Care, and Reduction of Pain with regard to Experimental Animals (Ministry of the Environment Notification No. 88, April 28, 2006). The study protocol was approved by the Ethics Committee of Kewpie Institute on August 19, 2016 (no. 16-6).

2.4.1 Animals and diets.

Liquid diets based on K-LEC were divided into the following four groups: 1) a K-LEC group, 2) a K-LEC egg yolk lecithin (-) group, in which the emulsifier in K-LEC was changed to a synthetic emulsifier, 3) an MCT (-) group, in which the MCT content of K-LEC was replaced by plant oil, and 4) a dietary fiber (+) group, in which digestion-resistant dextrin (Fiber Sol#2; Matsutani Chemical Industry Co., Ltd. Itami, Japan) was added to K-LEC. Samples for liquid diet were prepared by emulsification with a mixer, followed by fine emulsification with a high-pressure homogenizer. Retort sterilization was performed for 15 min at 121°C.

Sixteen 7-week-old male Sprague–Dawley rats weighing 190–220 g (Japan SLC, Inc.) were again individually housed in stainless steel cages at 22°C–24°C, with a relative humidity of 35%–65%, and a 12-h light/dark cycle (light from 08:00 to 20:00). The rats were allowed free access to feed (certified rodent diet 5002; LabDiet®) and drinking water and given 1 week to adapt. Thereafter, they were given free access to commercially available liquid diet (JANEF liquid diet K-4A Kewpie Corporation, Tokyo, Japan) for 3 days to acclimatize.

2.4.2 Procedure

Rats were fasted from the night before surgery and anesthetized by the inhalation of isoflurane (Intervet K.K., Osaka, Japan). Laparotomy was performed in all rats by midline incision, we resected 40 cm small bowel from the ileocecal valve approximately 5 cm proximal, produced a model of short bowel syndrome (SBSS). After the surgery, for 5 days, rats were allowed free access to each test liquid diet to make a recovery period. Furthermore, for the following 5 days, the rats were given the same amount of each test liquid diet and we observed and analyzed the feces. Fecal consistency was evaluated and graded as follows: normal stools (1), very loose stools and remains in the form (2), fluffy pieces with ragged edges, a mushy stool (3), and watery, no solid pieces (4).

2.5 Statistical analysis

Dr. SPSS II for Windows (Japan IBM Inc., Tokyo, Japan) was used for statistical analysis, and all data were expressed as means ± SD. The differences in medical records were examined using the nonparametric Wilcoxon signed-rank test. The differences in the state of in vitro emulsification was examined using one-way analysis of variance, followed by the Dunnett’s test, to evaluate significant differences between the egg yolk lecithin and other groups. The differences in fecal consistency in animal models were examined using the nonparametric Mann-Whitney test, and comparisons between the three groups were performed using one-way analysis of variance followed by the Tukey–Kramer multiple comparison test. For all two-tailed tests, \( p < 0.05 \), \( p < 0.01 \), \( p < 0.001 \) were considered statistically significant.

3 Results

3.1 Retrospective medical record review of changes in diarrhea following change to K-LEC

We identified 14 patients who were changed from L-6PM to K-LEC during the study period (5 males and 9 females; mean age 75.0 years). The route of administration was either nasogastric intubation (12 patients) or gastrostomy (2 patients). Stool consistency or frequency improved in 13/14 patients (92.9%) on the day after the change; these patients were able to continue enteral nutrition. In the patient who did not show improvement, *Clostridium difficile* was detected in the fecal culture and treatment was necessary. Before the change to K-LEC, the mean stool type was 6.93 ± 0.07 (i.e., type 7 in 13 cases and type 6 in 1 case). After the change to K-LEC, the mean stool type had decreased to 6.00 ± 0.13; just one case remained with type 7 and there were 9 cases with type 6 stools, 1 case with type 5, and 3 cases without bowel movement. Stool consistency significantly improved (\( p = 0.004 \)).
The change in stool frequency is shown in Fig. 1. Before the change to K-LEC, mean stool frequency was 4.43 ± 1.05 per day (range 2–16). After the change to K-LEC, stool frequency improved to 2.50 ± 0.58 per day (range 0–8). Stool frequency was significantly reduced by changing to K-LEC (*p = 0.035).

### 3.2 In vitro emulsification

Average particle diameters are shown in Table 2. The average particle size of the egg yolk lecithin emulsion was significantly smaller than that of soybean lecithin (p = 0.000, n = 3) and the synthetic emulsion (p = 0.000, n = 3). In addition, there was almost no change in the average particle of the size egg yolk lecithin emulsion when prepared to pH 2 with artificial gastric juice from neutral pH, whereas the average particle diameter of the soybean lecithin emulsion (p = 0.000, n = 3) and synthetic emulsifier emulsion (p = 0.000, n = 3) increased. Figure 2 shows that the egg yolk lecithin emulsion was also visibly stable 30 min after standing when compared with the other emulsions after adjustment to pH2.

#### Table 2: Change in the average particle diameter at the time of pH variation for each emulsion type.

<table>
<thead>
<tr>
<th>Study group</th>
<th>pH adjustment-free</th>
<th>pH 2.0 Adjustment</th>
<th>Δ Particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH</td>
<td>Particle size (µm)</td>
<td>pH</td>
</tr>
<tr>
<td>Egg yolk lecithin emulsion</td>
<td>6.0</td>
<td>3.9 ± 0.0**</td>
<td>2.0</td>
</tr>
<tr>
<td>Soybean lecithin emulsion</td>
<td>6.5</td>
<td>5.8 ± 0.1***</td>
<td>2.0</td>
</tr>
<tr>
<td>Synthetic emulsifier emulsion</td>
<td>6.4</td>
<td>4.4 ± 0.0***</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Values are presented as means ± SD.

***Different from the egg yolk lecithin emulsion group within each group (p < 0.001) (n = 3)

Fig. 2  Visual comparison of the state of emulsification in vitro.
A. Egg yolk lecithin emulsion. B. Soybean lecithin emulsion. C. Synthetic emulsifier emulsion. These emulsions were adjusted to pH 2 and left standing for 30 min. The egg yolk lecithin emulsion remained in the emulsified state.
3.3 Lipid absorption evaluation among rats with bile duct ligation

There was no significant difference in body weights between rats of each group at the time of experiment. At 4 h after administration, the serum triglyceride concentration in normal rats was significantly higher in the soybean lecithin group than in the egg yolk lecithin and synthetic emulsifier groups (p = 0.046, n = 6), but IAUC was not significantly different (Fig. 3A and 3B). The change and IAUC for serum triglyceride concentration in the rats with bile duct ligation are shown in Fig. 3C and 3D. At 2 h after the administration, the serum triglyceride concentration was significantly higher in the egg yolk lecithin group than the synthetic emulsifier (p = 0.013, n = 5) or soy lecithin group (p = 0.000, n = 5). Further 4 h after administration, the serum triglyceride concentration was still higher in the egg yolk lecithin group than in the soy lecithin group (p = 0.013, n = 5; Fig. 3C). IAUC in the egg yolk lecithin group was significantly higher than that in the soybean lecithin group (p = 0.054, n = 5; Fig. 3D, egg yolk lecithin group 849.8 vs soybean lecithin group 193.6).

3.4 Evaluation of diarrhea in rats with short bowels

Details of test liquid diet are shown in Table 3. Initial body weight, final body weight, average food consumption, and the length of small bowel resection were not significantly different between the groups (shown in Table 4). Changes in fecal consistency during days 2–10 of the test liquid diet were shown in Fig. 4, with images of the fecal consistency on day 10. In the K-LEC group, the fecal score was lower than that of the other groups during the test liquid diet feeding period. In the K-LEC group, the fecal score was significantly lowered on days 6 to 10 compared to the dietary fiber (+) group. Furthermore, in the K-LEC group, the fecal score was significantly lowered on days 4, 5, and 9 compared with the egg yolk lecithin (-) group. There were no significant differences between the MCT (-) and K-LEC groups.

4 Discussion

Diarrhea related to enteral nutrition is a problem that should be resolved quickly. Although many studies have tried to improve this situation, the results of inhibi-

Fig. 3 Changes in serum triglyceride (TG) concentration and area under the blood concentration time remain. Values are the mean ± standard error (A, B: n = 6; C, D: n = 5). a-c Labeled means without a common letter indicate significant differences (p < 0.05). ■: Egg yolk lecithin emulsion given. ◆: Soybean lecithin emulsion given. ▲: Synthetic emulsifier emulsion given. A. Changes in serum TG concentration during normal health. B. IAUC of serum TG during normal health. C. Changes in serum TG concentration after bile duct ligation. D. IAUC of serum TG after bile duct ligation.
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...tory effect on diarrhea by various methods have been inconsistent. Given that patients receiving enteral nutrition can suffer from malabsorption of fat (e.g., SIBO), we focused on a stable emulsion of egg yolk lecithin and showed that K-LEC created a rapid clinical effect, with most of the patients being able to continue enteral nutrition. In a patient who did not show improvement, *C. difficile*, which is known to be associated with tube feeding only, was detected in the fecal culture...
vitro study, the particle size of the egg yolk lecithin emulsion was less than 5 μm, but the average particle size of fat in enteral formula has been reported to be approximately 1 μm (Sugiura K, Nishiyama H, Muto A, et al. ENTERAL NUTRIENT PCT International Patent Publication No.WO2012/121095 A1, 2012). According to a report by Flezer, a particle size of less than 0.5 μm is directly absorbed without being digested. Thus, we assumed that fat absorption was helped by emulsification with egg yolk lecithin, which prevented destruction by gastric acid. In addition, egg yolk lecithin contains phospholipids, phosphatidylcholine, and cholesterol, which are all components of bile juice and may help with micelle formation. Therefore, emulsification by egg yolk lecithin may help to improve the nutritional statuses of patients with deficient bile secretion (e.g., in obstructive jaundice or external choledochostomy).

Finally, we investigated whether egg yolk lecithin and the other components of enteral formula contributed to the improvement in diarrhea outcomes. Although stimulation of the intestine formulated dietary fiber (e.g., water-soluble dietary fiber such as indigestible dextrin) was assumed to be small, diarrhea was observed in this study. Other researchers have commented that the quantities of fiber included in food must be controlled because indigestible carbohydrates generally reach the large intestines undigested and unab sorbed and may elevate osmotic pressure and induce osmotic diarrhea. Thus, dietary fiber can cause diarrhea in digestive malabsorption states. Therefore, egg yolk lecithin and free dietary fiber were assumed to improve diarrhea outcomes by different mechanisms, and the improvement using K-LEC was considered to be an effect of both free dietary fiber and egg yolk lecithin. Depending on the quantity, dietary fiber may not cause diarrhea. The possibility of diarrhea-suppressant effect is suggested by the efficacy of a new enteral formula, K-5S (JANEF K-5S; Kewpie Corporation, Tokyo, Japan), which has minimum amount of dietary fiber added. Also in the MCT group, the fecal score decreased after the 8th day and showed the same value as the K-LEC group. Because of high digestion and absorption, MCT is often used for liquid diet. However, it is also known to cause diarrhea when ingested in large quantities at once. It is thought that the presence of MCT also affects fecal scores. Our study has a few limitations. First, diarrhea is a multifactorial disorder, and our conclusions may not be valid for all patients. Although we showed that diarrhea improved in most clinical cases, lipid malabsorption is possible. It is possible that this mechanism was causative in a considerable number of patients receiving enteral nutrition.
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vation is necessary to determine whether the improvement in diarrhea after administration of enteral formula containing egg yolk lecithin is related to the shortening of the disease recovery or nutritional status improvement. Despite these limitations, enteral formula containing egg yolk lecithin was shown to be an effective treatment for diarrhea.

5 CONCLUSION
We showed that the egg yolk lecithin emulsion was stable after the addition of artificial gastric juice, which may have contributed to the improved fat absorption in rats with bile duct ligation who received egg yolk lecithin. We hypothesize that the emulsification of enteral formula using egg yolk lecithin promotes lipid absorption by preventing the destruction of emulsified substances by gastric acid, as summarized in Fig. 5. In clinical cases and model rats with short bowel syndrome, switching to K-LEC, which is emulsified with egg yolk lecithin, was associated with improvement in diarrhea. This change to K-LEC is a simple and rapidly effective method that should be considered as a suitable first step in the management of diarrhea related to enteral nutrition. Consequently, this change has the potential to reduce the burden on patients and healthcare workers as well as medical costs by shortening hospital stays. Further knowledge of lipid absorption and its role in the management of intractable diarrhea is required.

Acknowledgments
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Conflicts of Interest
Tetsuro Akashi declares that he has no conflict of interest. Ayano Muto, Yayoi Takahashi, and Hiroshi Nishiyama are employees of Kewpie Corporation.

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