Original Article

Positive zinc intake and a Japanese diet rich in *n*-3 fatty acids induces clinical remission in patients with mild active ulcerative colitis: a randomized interventional pilot study

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Zinc intake has reduced hospitalizations in patients with ulcerative colitis (UC), highlighting the need to maintain blood zinc levels. This prospective study investigated whether the promotion of zinc intake and a Japanese diet (high in *n*-3 fatty acids) could induce clinical remission in patients with mild active UC. Patients with mild active UC were randomly assigned to either (1) continue an unrestricted diet or (2) receive nutritional guidance promoting zinc intake and a Japanese diet. The primary endpoint was clinical remission at 24 weeks. Secondary endpoints were the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scores, Clinical Activity Index (CAI), Geboes Histopathology Score (GHS), and biomarkers, including zinc levels, measured at 12 and 24 weeks. Nutritional assessments were performed using the Food Frequency Questionnaire. The CAI, UCEIS, and GHS scores were significantly lower in the intervention group than in the control group, with a significantly higher proportion of patients achieving clinical remission. Furthermore, the intervention group exhibited weight gain and significantly increased blood zinc levels. The combination of promoting dietary zinc intake and a Japanese diet rich in *n*-3 fatty acids can induce clinical remission in patients with mild active UC.

***Key Words*: ulcerative colitis, zinc, *n*-3 fatty acids**

Both gut bacteria and dietary antigens play important roles in the pathogenesis of inflammatory bowel disease (IBD), and several studies have investigated the involvement of intestinal bacteria and dietary antigens in mucosal immunity.[1–4] Research has demonstrated that changes in metabolites caused by diversity in the intestinal microbiota can affect the digestion and metabolism of food, resulting in significant changes to the intestinal environment. Accordingly, a low-fat diet has been reported to maintain remission and lead to favorable outcomes in patients with Crohn's disease (CD), while high-fat formulas have been associated with poor therapeutic outcomes.[5] However, in contrast to those with CD, patients with ulcerative colitis (UC) may not experience remission-inducing effects following nutritional therapy,[6] and there is little evidence supporting nutritional therapy for the maintenance of remission in patients with UC. Therefore, unnecessary dietary restrictions should not be imposed in the maintenance phase of treatment for UC.

Patients with IBD tend to exhibit deficiencies of various micronutrients because of intestinal dysbiosis caused by diarrhea and inadequate food intake, which result from the anorexia associated with disease activity.[7] For example, Schneider *et al.*[8] revealed that the serum concentrations of copper and zinc are insufficient in a substantial proportion of patients with IBD. Other studies have reported that intestinal mucosal permeability increases in patients with IBD,[9] while zinc intake has been shown to strengthen the function of the intestinal barrier via its effects on tight junctions.[10] Furthermore, the administration of zinc in patients with UC increases the blood levels of thymulin, which plays a role in immunity, decreases the activity of natural killer cells, and normalizes intestinal permeability.[11] Finally, a multicenter study of dietary habits in patients with new-onset UC reported that the odds of new-onset UC were significantly lower in populations with high zinc intake before onset than in those with low zinc intake.[12]

Considering that supplementation with zinc preparations often causes side effects such as stomach pain and nausea, which may make continuous zinc supplementation difficult, a zinc-rich diet has been recommended over supplementation.[13]

In the past 50 years, the availability of preserved foods rich in *n*-6 polyunsaturated fatty acids has led to drastic changes in dietary habits. The rapid increase in the number of patients with IBD is undoubtedly related to these changes in environmental and dietary factors. Certain *n*-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid, which are present in seafood and marine products, have been reported to have anti-inflammatory effects. Although there are currently no consistent results suggesting that *n*-3 fatty acids can suppress intestinal inflammation and induce UC remission,[14] a higher intake of *n*-3 fatty acids has been shown to result in a lower incidence of UC (hazard ratio, 0.72). Conversely, increased intake of linoleic acid, an *n*-6 fatty acid, and decreased intake of DHA, an *n*-3 fatty acid, have been associated with an increased risk of developing UC. Therefore, a decrease in the ratio of *n*-3 to *n*-6 fatty acids and increased consumption of red meat have been reported to increase the risk of UC.[15,16]

In this study, we investigated whether the combination of nutritional guidance encouraging zinc intake and a Japanese diet rich in *n*-3 fatty acids could induce remission in patients with mild active UC who were undergoing standard treatment in our department. In addition, we prospectively examined changes in endoscopic findings, inflammatory blood biomarkers, and clinical symptoms to evaluate the effectiveness of this nutritional intervention in patients with mild active UC.

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Materials and Methods

Study design and ethical considerations. This was a prospective, randomized, controlled trial involving 20 patients registered in an institution in Japan (clinical trial registration: UMIN000046664). The study period was from August 2018 to March 2021. The study protocol complied with the tenets of the revised Declaration of Helsinki (1989) and was approved by the institutional review board of our institution. Written informed consent was obtained from all participating patients.

Nutritional guidance. The Nutrition Department of our hospital provided three 30-min nutritional guidance sessions to patients with mild active UC. Apart from dietary intake of zinc (Table 1), patients were encouraged to eat fish rich in *n*-3 fatty acids (Table 2), flaxseed and egoma oils, and a Japanese diet. Clinical symptoms and endoscopic findings were evaluated using the Clinical Activity Index (CAI), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Geboes Histopathology Score (GHS), respectively, at 12 and 24 weeks.

Detailed nutritional assessments of food intake were undertaken using a dietary record chart and the administration of an established semiquantitative questionnaire available for clinical investigation (Food Frequency Questionnaire based on food groups, ver. 4.0; Kenpaku-sha, Tokyo, Japan). The items evaluated using the questionnaire assessed the total levels of energy, protein, fat, carbohydrate, zinc, and *n*-3 fatty acid intake.

Table 1. Zinc content in various foods

Classification		Zinc content per 100 g (mg)
Seafood	Oyster	13.2
	Scallop	2.7
	Eel	1.4
	Pacific saury	0.8
	Cod roe	3.1
	Dried sardines	7.2
Meat	Beef shoulder roast	5.6
	Beef thigh	4
	Beef liver	3.8
	Chicken liver	3.3
	Beef belly	3
	Chicken thigh	1.6
	Pork loin	1.6
Dairy products	Egg	1.3
	Milk	0.4
	Processed cheese	3.2
Soybean	Natto	1.9
	Tofu	0.6
Nuts	Cashew nuts	5.4
	Almond nuts	4.4

Table 2. *n*-3 fatty acid content in various seafoods

Seafood	*n*-3 fatty acids per 100 g (g)
Scad	1.05
Mackerel	2.12
Pacific saury	5.59
Sardine	2.1
Japanese amberjack	3.35
Young yellowtail	1.88
Tuna	0.21
Garden eel	1.42
Eel	2.42
North Pacific bluefish	1.13
Spirinchus lanceolatus	1.47
Splendid alfonsino	1.37

Patients. Patients aged ≥15 years who had mild active UC (patients with a UCEIS score of 2–4 points, CAI score of 5–6 points, and distribution of the UCEIS and CAI scores at admission indicating that the patient was not in remission) were enrolled in the study. The drugs prescribed for the patients are listed in Table 3. There were no additional treatments, including steroid, biologic, calcineurin inhibitor, and JAK inhibitor treatments, during this study. The enrolled patients were not administered zinc preparations during the follow-up period.

Details of this study were explained to the patients both verbally and in writing, and those who provided written consent were eligible for inclusion.

Patients undergoing colonoscopy without pretreatment; those with difficulty following nutritional guidance; those with intestinal obstruction, fistula, history of colorectal surgery, moderate-to-severe active-phase UC, diverticulitis, or massive colorectal bleeding; and those with anemia or other underlying conditions except UC were excluded (Fig. 1).

Randomization. The patients were randomly assigned in a 1:1 ratio to undergo nutritional guidance (intervention group) or to the control group via block randomization using computerized lists. Anonymity was ensured by allocating study-specific codes instead of using personal information, such as patient name or ID, during randomization.

Definitions. For this study, zinc deficiency was defined according to the Japanese Society of Clinical Nutrition's recently issued Japan's Practical Guideline for Zinc Deficiency 2018 as follows: (a) one or more symptoms of zinc deficiency or low serum alkaline phosphatase, (b) ruling out of other diseases, (c) low serum zinc level, and (d) alleviation of symptoms upon zinc administration. Serum zinc levels of <60 μg/dl and 60–80 μg/dl were considered to indicate zinc deficiency and marginal zinc deficiency, respectively.[17]

Disease remission was defined according to the UCEIS. Travis *et al.*,[18,19] who proposed the UCEIS, did not define effectiveness based on therapeutic evaluation or endoscopic remission (i.e., mucosal healing). In contrast, they noted that a UCEIS score of 0 was the best definition of endoscopic remission. Similarly, they concluded that a decrease in the Mayo Endoscopic Subscore by at least 1 or the UCEIS score by at least 2 was an appropriate definition of endoscopic response.[20] The UCEIS was evaluated by two expert endoscopists.

A CAI score of ≥6 and an endoscopy score of ≥4 were defined as clinically active disease, whereas a CAI score of ≤4 was defined as clinical remission.[21]

Histological assessment of disease activity was performed using the GHS. As there is no consensus on the definition of remission yet, we defined remission as a GHS score of 2 or less and set remission score as 2 or less.[22,23]

Outcome measurements. The primary outcomes included the rate of remission at 24 weeks after the initiation of nutritional guidance, as determined based on the CAI score, endoscopic activity findings (UCEIS), and GHS score. Secondary outcomes included patient weight, body mass index (BMI), energy intake, protein intake, lipid intake, *n*-3 fatty acid intake, zinc intake, blood zinc level (fasting), percentage of patients with blood zinc levels of >80 μg/dl, blood albumin level, white blood cell count, and C-reactive protein level.

Statistical analyses. Categorical data are presented as numbers and percentages (%) and were analyzed using Fisher's exact test. Continuous data are presented as means ± SD. Repeated-measures analysis of variance models with between-

Table 3. Patient characteristics

	Intervention (n = 10)	Control (n = 10)	p value
Age	37.5 ± 16.1	38 ± 19.2	0.95[a]
Sex (male:female)	5:05	5:05	0.673[a]
Body weight (kg)	48.3 ± 6.7	54.3 ± 8.5	0.097[a]
BMI (kg/m^2)	18.7 ± 1.9	21 ± 3.5	0.086[a]
Energy (kcal)	1,667.5 ± 509.4	1,740 ± 361.7	0.718[a]
Protein (g)	57.2 ± 19.7	61 ± 17.5	0.656[a]
Fat (g)	50.3 ± 20.5	53.4 ± 21.6	0.745[a]
n-3 fatty acids (g)	1.5 ± 0.8	2 ± 0.6	0.124[a]
Zinc (g)	7 ± 2.1	7.6 ± 1.8	0.492[a]
Alb (mg/dl)	3.7 ± 0.6	3.6 ± 0.9	0.662[a]
WBC (×10^3)	7.3 ± 2.7	7.5 ± 2.1	0.874[a]
CRP (mg/dl)	1.2 ± 2.3	3.5 ± 6.5	0.298[a]
Blood zinc (g/dl)	72.1 ± 17.8	72 ± 14.5	0.989[a]
Partial Mayo score	0.8 ± 0.4	0.9 ± 0.3	0.556[a]
UCEIS score	2.5 ± 0.7	2.1 ± 0.6	0.18[a]
CAI score	7.7 ± 3.4	5.8 ± 0.9	0.105[a]
GHS	2.6 ± 0.5	2.4 ± 0.5	0.398[a]
Base drug			
Mesalazine	8	8, 80	>0.999[b]
Azathioprine	5	5, 50	>0.999[b]
Biotherapy			0.553[b]
Adalimumab	3	1	
Infliximab	2	0	
Golimumab	0	1	
Tofacitinib	0	2	
Ustekinumab	0	1	
Vedolizumab	2	1	
None	3	4	

Alb, albumin; BMI, body mass index; CAI, Clinical Activity Index; CRP, C-reactive protein; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; WBC, white blood cell. p value, [a]unpaired t test, [b]Fisher's exact test. Data are represented as means ± SD or numbers and percentages.

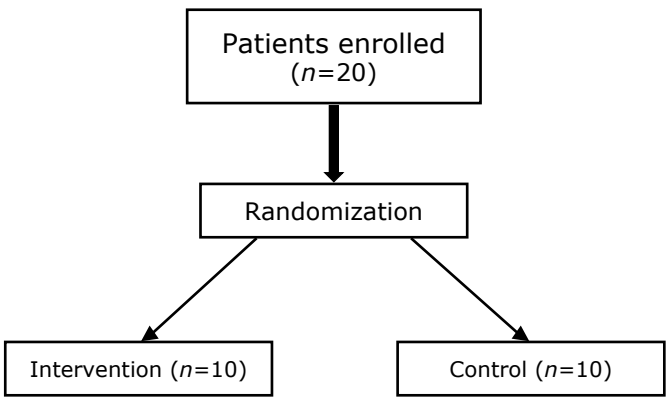

Fig. 1. Flowchart of patient enrollment.

subject (group) and within-subject (time) factors and interactions were performed. The factors of treatment group, subject, and time were included in the model. Interactions between group and time (among time) were calculated for each variable. Between-group comparisons for continuous variables were performed using unpaired t tests. Within-group comparisons for continuous variables were performed using paired t tests. Bonferroni correction was used to account for the multiplicity of comparisons between the groups. A two-sided p value of ≤0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows ver. 26.0 (IBM Japan, Tokyo, Japan).

Results

Ten patients each were allocated to the intervention and control groups. There was no significant difference in patient background between the intervention and control groups. The Partial Mayo Score (Mayo Endoscopic Subscore) was approximately 1 in both groups. The UCEIS score was approximately 2, indicating that mucosal healing had not occurred. The CAI score was >4 in both groups (intervention group: 7.7 ± 3.4, control group: 5.8 ± 0.9; p = 0.105), indicating that clinical remission had not been achieved. GHS was >2 in both groups (intervention group: 2.6 ± 3.4, control group: 2.4 ± 0.5; p = 0.398), indicating that histological remission had not been achieved (Table 3).

At 12 and 24 weeks, the nutritional guidance intervention significantly increased body weight and BMI [body weight (baseline, 12 weeks, 24 weeks): 48.8 ± 6.7 kg → 52.4 ± 6.8 kg → 53.2 ± 7.5 kg vs 54.3 ± 8.5 kg → 55.3 ± 9.3 kg → 55.4 ± 9.5 kg in the control group, p = 0.032; BMI (baseline, 12 weeks, 24 weeks): 18.7 ± 1.9 kg/m^2 → 20.2 ± 1.5 kg/m^2 → 20.4 ± 1.5 kg/m^2 vs 21.0 ± 3.5 kg/m^2 → 21.3 ± 3.1 kg/m^2 → 21.4 ± 3.3 kg/m^2 in

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Table 4. Changes in study variables in each group

	n	T1. On admission	T2. 12 weeks later	T3. 24 weeks later	*p* value	*p* value (group comparison)			*p* value (intragroup comparison)	
					rmANOVA	T1.	T2.	T3.	T1. vs T2.	T1. vs T3.
Bodyweight (kg)					0.032	0.097	0.433	0.561		
Intervention	10	48.8 ± 6.7	52.4 ± 6.8	53.2 ± 7.5					0.013	0.015
Control	10	54.3 ± 8.5	55.3 ± 9.3	55.4 ± 9.5					0.749	0.55
BMI					0.014	0.086	0.325	0.414		
Intervention	10	18.7 ± 1.9	20.2 ± 1.5	20.4 ± 1.5					0.01	0.011
Control	10	21.0 ± 3.5	21.3 ± 3.1	21.4 ± 3.3					0.854	0.505
Energy (kcal)					0.875	0.718	0.622	0.351		
Intervention	10	1,667.5 ± 509.4	1,781.0 ± 327.1	1,796.6 ± 342.9					0.896	0.708
Control	10	1,740.0 ± 361.7	1,871.6 ± 467.8	1,970.0 ± 458.6					0.83	0.419
Protein (g)					0.682	0.656	0.15	0.399		
Intervention	10	57.2 ± 20.5	60.1 ± 10.2	63.1 ± 12.7					>0.999	0.551
Control	10	61.0 ± 17.5	69.8 ± 17.8	68.3 ± 13.8					0.351	0.494
Fat (g)					0.814	0.745	0.324	0.142		
Intervention	10	50.3 ± 20.5	54.5 ± 15.7	53.2 ± 11.5					>0.999	>0.999
Control	10	53.4 ± 21.6	61.5 ± 15.4	61.6 ± 12.9					0.408	0.539
n-3 fatty acids (g)					0.007	0.124	0.87	0.17		
Intervention	10	1.5 ± 0.8	2.0 ± 0.7	2.3 ± 0.6					0.01	0.002
Control	10	2.0 ± 0.6	2.1 ± 0.8	1.9 ± 0.6					>0.999	>0.999
Zinc intake (g)					0.049	0.492	0.086	0.112		
Intervention	10	7.0 ± 2.1	12.1 ± 6.3	11.9 ± 6.1					0.057	0.066
Control	10	7.6 ± 1.8	8.3 ± 2.0	8.6 ± 1.8					0.753	0.392
Alb (g/dl)					0.508	0.622	0.194	0.461		
Intervention	10	3.7 ± 0.6	4.1 ± 0.3	4.2 ± 0.2					0.16	0.09
Control	10	3.6 ± 0.9	4.3 ± 0.4	4.3 ± 0.3					0.067	0.068
WBC ($\times 10^3$)					0.596	0.874	0.607	0.195		
Intervention	10	7.3 ± 2.7	5.4 ± 1.7	5.4 ± 1.0					0.074	0.139
Control	10	7.5 ± 2.1	5.0 ± 1.8	6.3 ± 1.7					0.127	0.45
CRP (mg/dl)					0.34	0.298	0.419	0.339		
Intervention	10	1.19 ± 2.3	0.11 ± 0.0	0.12 ± 0.1					0.337	0.346
Control	10	3.5 ± 6.5	0.1 ± 0.1	0.4 ± 0.9					0.272	0.355
Zinc (mg/dl)					0.008	0.989	0.672	**0.02**		
Intervention	10	72.1 ± 17.8	73.6 ± 10.3	92.1 ± 23.2					>0.999	0.073
Control	10	72.0 ± 14.5	75.5 ± 9.4	71.4 ± 10.9					0.917	>0.999
UCEIS score					0.07	0.18	0.264	0.306		
Intervention	10	2.5 ± 0.7	1.7 ± 0.7	1.6 ± 0.7					0.021	0.02
Control	10	2.1 ± 0.6	2.0 ± 0.5	1.9 ± 0.6					>0.999	0.887
CAI score					≤0.001	0.105	≤0.001	≤0.001		
Intervention	10	7.7 ± 3.4	5.0 ± 0.7	4.0 ± 0.0					0.077	0.015
Control	10	5.8 ± 0.9	6.4 ± 0.7	6.9 ± 0.6					0.01	0.002
GHS					0.209	0.525	0.478	0.172		
Intervention	10	2.6 ± 0.5	2.0 ± 0.8	1.0 ± 0.7					0.048	0.0008
Control	10	2.4 ± 0.5	2.2 ± 0.4	1.6 ± 1.0					0.894	0.071

Alb, albumin; BMI, body mass index; CAI, Clinical Activity Index; CRP, C-reactive protein; GHS, Geboes Histopathology Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; WBC, white blood cell. *p* value, rmANOVA; repeated-measures ANOVA [between groups and among times (T1, T2, T3)]; group comparison, unpaired *t* test; intragroup comparison, paired *t* test (Bonferroni correction). Data are represented as mean ± SD.

the control group, $p = 0.014$] relative to that observed at admission, respectively. There was also a significant difference in zinc intake between the intervention and control groups [intervention (baseline, 12 weeks, 24 weeks): 7.0 ± 2.1 g → 12.1 ± 6.3 g → 11.9 ± 6.1 g vs control: 7.6 ± 1.8 g → 8.3 ± 2.0 g → 8.6 ± 1.8 g, $p = 0.049$], and the blood zinc level was significantly higher in the intervention group than in the control group [intervention (baseline, 12 weeks, 24 weeks): 72.1 ± 17.8 μg/dl → 73.6 ± 10.3 μg/dl → 92.1 ± 23.2 μg/dl vs control: 72.0 ± 14.5 μg/dl → 75.5 ± 9.4 μg/dl → 71.4 ± 10.9 μg/dl, $p = 0.008$]. Although there was no difference in fat intake, *n*-3 fatty acid intake was significantly greater at 12 and 24 weeks than at admission [12 weeks: 1.5 ± 0.8 g vs 2.0 ± 0.7 g ($p = 0.010$) and 24 weeks: 2.3 ± 0.6 g ($p = 0.002$)] (Table 4).

In addition, endoscopic evaluation (UCEIS) revealed significant improvements in the endoscopic mucosa (by approximately

Table 5a. Percentage of patients in remission (CAI score ≤4) in each group

	n	T1 (at admission)	T2 (12 weeks)	T3 (24 weeks)
Remission (CAI score ≤4)				
Intervention	10	0 (0.0)	2 (16.7)	9 (90.0)
Control	10	0 (0.0)	0 (0.0)	0 (0.0)
p value			0.474	<0.001

Data are represented as numbers and percentages. *p* value: Fisher's exact test. CAI, Clinical Activity Index.

Table 5b. Percentage of patients with sufficient blood zinc level (zinc >80 μg/dl) in each group

	n	T1 (on admission)	T2 (12 weeks)	T3 (24 weeks)
Zinc >80 μg/dl				
Intervention	10	5 (50.0)	5 (30.0)	5 (50.0)
Control	10	3 (30.0)	2 (20.0)	4 (40.0)
p value		0.65	>0.999	>0.999

p value, Fisher's exact test. Data are represented as numbers and percentages.

1 point) in the intervention group at both 12 and 24 weeks (2.5 ± 0.7 to 1.6 ± 0.7, $p = 0.020$). The CAI decreased by 3.7 points in the intervention group at 24 weeks (7.7 ± 3.4 to 4.0 ± 0.0 $p = 0.015$), indicating clinical remission. CAI was significantly higher in the control group.

The GHS score significantly decreased in the intervention group after 24 weeks (2.6 ± 0.5 to 1.0 ± 0.7 $p = 0.0008$; Table 4).

The percentage of patients in clinical remission (i.e., CAI score ≤4) was 0% in the control group and 90% in the intervention group at the 24-week assessment ($p<0.001$). However, there was no significant difference in the percentage of patients whose blood zinc levels were maintained above 80 μg/dl (not zinc deficient). No exacerbation of symptoms was observed in either group, and no patient required intensive treatment (Table 5).

Discussion

In this study, we investigated whether nutritional guidance that promotes a diet rich in zinc combined with *n*-3 fatty acids could induce clinical remission in patients with mild active UC. The CAI and UCEIS scores were significantly lower in the intervention group than in the control group, with a significantly higher proportion of patients achieving clinical remission. Furthermore, the intervention group exhibited significant weight gain at 12 and 24 weeks, as well as significant increase in the blood zinc levels at 24 weeks. In this study, we treated only mild UC to avoid influencing the outcomes of any therapeutic intervention other than nutritional guidance. The treatment regimen, besides nutritional guidance, remained unchanged in all patients.

Although it is unclear to what extent the improvement in blood zinc levels in this study contributed to the improvement in the pathophysiology of UC, we believe that addition of zinc loading to the existing treatment for mild UC is expected to have an add-on effect on treatment.

There was no difference in total calorie, fat, and protein intake between both groups, even after nutritional guidance. However, *n*-3 fatty acid and zinc content was significantly higher in the intervention group, suggesting that the improvement in CAI was due to *n*-3 fatty acid and zinc intake.

Abnormal composition of the intestinal microbiota, known as dysbiosis, may be involved in the pathogenesis of IBD.[24] Moreover, compared with healthy individuals, patients with IBD exhibit a decrease in the diversity of intestinal microbiota.[25] Apart from monogenic IBD, microbial and other environmental exposures are more crucial in the development and progression of IBD than genetic susceptibility to the disease.[26] Diet is among the major environmental factors contributing to the epidemiological surge in IBD and mental stress.[27] In patients with UC, nutritional guidance, including that which promotes a low-fat diet, has not been considered a major contributor to the maintenance of remission. During the active disease phase, however, nutritional disorders do occur, including a loss of body weight (by 18–62%) and hypoalbuminemia (by 26–50%).[28]

Major nutrients are absorbed in the small intestine, which is not involved in most UC cases. Therefore, it is not clear whether dietary factors are pathogenic or exacerbating factors. However, diets high in fruits, vegetables, and *n*-3 fatty acids and low in *n*-6 fatty acids have been associated with a lower risk of developing both CD and UC.[29] Additionally, animal studies have shown that medium-chain and long-chain fatty acids exert different effects on the antigen-presenting cells in the intestinal tract.[30] Furthermore, trans fatty acids exacerbate intestinal mucosal inflammation.[31] Although Hou *et al.*[14] commented on the inconsistency in the data regarding the effects of an *n*-fatty acid-enriched diet on intestinal inflammation and induction of remission, their results indicated that nutritional guidance might reduce the risk of developing UC.

The intake of *n*-6 fatty acids, such as arachidonic acid, is reported to exacerbate inflammation and adversely affect the body; hence, a good balance should be maintained by including more food rich in *n*-3 fatty acids than in *n*-6 fatty acids in the modern diet. Although the intervention group had a higher intake of *n*-3 fatty acid-rich foods, fatty acid composition in the blood was not measured in this study. Thus, precise evaluation of the effectiveness of *n*-3 fatty acid-rich foods was not possible.

Siva *et al.*[32] reported that 86 of 223 (38.6%) patients with UC and 326 of 773 (42.2%) with CD had low zinc levels. In addition, patients with IBD associated with hypozincemia had a higher risk of hospitalization, surgery, and complications than patients with normal serum zinc levels.[33] One factor that may have contributed to this observation is the lack of essential nutrients due to fast food consumption and dietary restrictions. Considering the above findings, maintaining the blood zinc level may help to prevent exacerbations of UC.

In this study, nutritional guidance was provided to encourage zinc intake and the adoption of a Japanese diet rich in *n*-3 fatty acids because consuming zinc-rich food can lead to excessive fat intake and insufficient intake of *n*-3 fatty acids and dietary fiber. Zinc intake increased after starting nutritional guidance. However, there was a significant difference in zinc intake between the two groups, indicating that it may be important for these patients to comply with nutritional guidance and a Japanese diet. The actual concentration of zinc in the blood increased in the intervention group, whereas it remained almost unchanged in the control group.

In the intervention group, the clinical remission rate significantly increased, whereas endoscopic activity significantly decreased. Although the clinical remission (CAI ≤4) rate was significantly higher in the intervention group, the treatment was not standardized; therefore, this effect cannot be proven to be exclusively due to zinc loading plus the Japanese diet intervention. However, no new treatments were added in this study, and there were no significant differences in the treatment at entry, indicating that nutritional guidance encouraging the addition of zinc and conversion to a Japanese diet may be effective for inducing remission.

A previous study reported that zinc deficiency exacerbates colonic inflammation via activation of the IL-23/Th17 axis and

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that zinc intake is expected to increase the remission induction rate by suppressing these cytokines.[33] In the current study, the baseline blood level of zinc ranged from 80 to 130 μg/dl, and there was a significant difference in the blood zinc level between the intervention and control groups. Indeed, the zinc level exceeded 80 μg/dl and was significantly higher in the intervention group than in the control group, which may have led to the improvements in the UCEIS and CAI scores.

This study has some limitations, including its single-center design. This study did not investigate the intestinal microbiota of each patient. It also did not account for the patient's current treatment regimen or disease duration. In addition, there was no blinding, and the sample size was small because it was a pilot study.

In conclusion, the current pilot data indicate that promotion of both zinc intake and a Japanese diet rich in *n*-3 fatty acids may help induce clinical remission in patients with mild active UC. Nonetheless, large-scale randomized controlled trials are required to validate our findings.

Author Contributions

Manuscript drafting, KM; study design, YT, HI; endoscopists, KM, YT, RS, HO, and HI; nutritionists, YI; statistical analysis, YT; supervision, HN and HI. The final version of the manuscript was read and approved by all authors.

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Abbreviations

BMI	body mass index
CAI	Clinical Activity Index
CD	Crohn's disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
GHS	Geboes Histopathology Score
IBD	inflammatory bowel disease
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflicts of Interest

No potential conflicts of interest were disclosed.

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