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ORIGINAL ARTICLE

Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet

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Abstract

AIM: To investigate whether semi-vegetarian diet (SVD) has a preventive effect against relapse of Crohn's disease (CD) in patients who have achieved remission, who are a high-risk group for relapse.

METHODS: A prospective, single center, 2-year clinical trial was conducted. Twenty-two adult CD patients who achieved clinical remission either medically (n = 17) or surgically (n = 5) and consumed an SVD during hospitalization were advised to continue with an SVD and avoid known high-risk foods for inflammatory bowel disease. The primary endpoint was clinical relapse defined as the appearance of active symptoms of CD. Kaplan-Meier survival analysis was used to calculate the cumulative proportion of patients who had a relapse. A 2-year analysis of relapse rates of patients who followed an SVD and those who did not (an omnivorous diet group) was undertaken.

RESULTS: SVD was continued by 16 patients (compliance 73%). Remission was maintained in 15 of 16 patients (94%) in the SVD group *vs* two of six (33%) in the omnivorous group. Remission rate with SVD was 100% at 1 year and 92% at 2 years. SVD showed significant prevention in the time to relapse compared to that in the omnivorous group (P = 0.0003, log rank test). The concentration of C-reactive protein was normal at the final visit in more than half of the patients in remission who were taking an SVD, who maintained remission during the study (9/15; 60%), who terminated follow-up (8/12; 67%), and who completed 2 years follow-up (7/10; 70%). There was no untoward effect of SVD.

CONCLUSION: SVD was highly effective in preventing relapse in CD.

Key words: Crohn's disease; Inflammatory bowel disease; Vegetarian diet; Recurrence; Lifestyle

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INTRODUCTION

The etiology of inflammatory bowel disease (IBD), which is a collective term for Crohn's disease (CD) and ulcerative colitis (UC), is unknown but is believed to be

multifactorial, whereby development of the disease in genetically susceptible subjects is triggered by environmental factors[1]. IBD is a complex polygenic disease in which the contribution of each gene to the onset of disease is small[2]. IBD incidence increases along with wealth[3,4]. The above two main features of IBD are exactly the same as those for other chronic diseases such as diabetes mellitus, coronary heart disease, and obesity in developed countries[5]. A large part of chronic diseases is related to lifestyle, including food and being sedentary. Some of the environmental factors that have been observed in association with IBD include cigarette smoking, the use of oral contraceptives, and appendectomy[3]. However, these environmental factors are thought to play only a mediating role in IBD. A real key environmental factor has not been identified. Consequently, there is no particular recommendation on lifestyle in guidelines except for smoking in CD[6-9].

Recent studies have clarified that the presence of gut indigenous microflora is a prerequisite for gut inflammation[10,11], and susceptible IBD genes identified are thought to play a role in recognition of microbial agents, immunoregulation, and inflammation[2]. Therefore, IBD is thought to result from an inappropriate response of the mucosal immune system to the intestinal microflora in a genetically susceptible individual[2]. An imbalance of gut microflora, a decrease in beneficial (preventive) bacteria, and an increase in potentially pathogenic bacteria, called dysbiosis, is observed in patients with IBD[12-14]. Dysbiosis can be a trigger for onset and relapse of IBD[15].

There is enough evidence to indicate that IBD is a diet-related disease. Epidemiology shows that IBD is prevalent in wealthy nations[3,4,16] where dietary westernization inevitably occurs[17,18]. Dietary westernization is characterized by increased consumption of animal protein, animal fat, and sugar, with decreased consumption of grains. A dietary study during dietary transition in Japan incriminated an increased intake of animal fat and animal protein in the increase in CD[19]. Pre-illness case-control studies, including those in Japan, have reported increased intake of sugar[20-23], fast foods, chocolate, and cola drinks in IBD[24,25], and a decrease in total fruit and vegetable fiber in CD[20,26]. Case-control studies in Japan are consistent; western foods including bread are a risk factor, whereas traditional Japanese foods are a preventive factor[27-29]. The same tendency has recently been reported in pediatric CD cases in Canada: a positive association with a western diet (meats, fatty foods, and desserts) and an inverse association with a prudent diet (vegetables, fruits, olive oil, grains, and nuts)[30]. Diets rich in animal protein and animal fat cause a decrease in beneficial bacteria in the intestine[31,32]. Probiotics that consist of beneficial bacteria can prevent and are effective against pouchitis, which is ileal inflammation after proctocolectomy in UC[33,34]. These pieces of evidence are consistent with the notion that a westernized diet is linked to an increase in IBD. Therefore, we regard IBD as a lifestyle-related disease that is mediated by mainly a westernized diet[35,36]. Consequently, if a suitable diet is identified and patients stick to the diet, we believe that the majority of IBD patients could be free from relapse without medication.

The conventional recommended diet for IBD is a low-residue diet[37]. A fear of irritating the bowel with dietary fiber has led to a low-residue diet. However, there is no evidence that such a diet is ideal for IBD. A low-residue diet that lacks non-digestible carbohydrates might accelerate the dysbiosis in IBD. Meals *per se* are thought to cause gut inflammation. Therefore, about half of the daily energy intake is provided by an elemental diet, which is a standard regimen in quiescent CD in Japan[38,39]. At present, it is unknown what kind of diet is suitable for IBD.

Therefore, we designed a diet that hopefully increases the number of beneficial bacteria. Limited foods are known to increase beneficial bacteria: green tea and unrefined brown rice[40,41]. However, most prebiotics are extracts of plants[42]. Therefore, we thought that a vegetarian diet would be suitable for IBD. Considering that excessive restriction in foods can be less acceptable, a semi-vegetarian diet (SVD) could be appropriate. Therefore, an SVD has been provided to IBD patients in our hospital since 2003[35,36]. SVD, which is rich in dietary fiber, is quite opposite to conventional low-residue diets in IBD[37].

The biggest problem in practice in IBD is a lack of a safe, long-lasting modality for relapse prevention. Relapse in CD is far more untenable than in UC[43]. The risk of relapse in CD is influenced by the interval of remission: a higher risk among patients with recently achieved remission than among patients in remission[44].

In this study, an SVD was provided throughout the induction phase in CD patients, or after intestinal surgery. After their discharge, they were immediately followed up in the IBD outpatient department. The aim of this study was to investigate whether an SVD has a preventive effect against relapse in high-risk patients who have recently achieved remission.

MATERIALS AND METHODS

Study design

This was a prospective clinical trial with 2 years follow-up to establish whether an SVD has a preventive effect against relapse in high-risk patients who have recently achieved remission. This study was approved by the Ethical Committee of Nakadori General Hospital and all patients gave written informed consent.

Subjects

SVD was first introduced in our institution in 2003, and it has been provided to all patients with CD. From April 2003 to December 2008, 25 active adult CD patients over 19 years old were admitted to the Division of Gastroenterology, Nakadori General Hospital, Akita, Japan.

Table 1 Details of patients' data

Case No.	Sex	Age (yr)	Type of disease	Anal lesion		Disease duration	Previous segmental resection	Initial onset or relapse	Hospitalization						
				Fistula	Tag				On admission		Main medication	Duration of SVD (d)	On discharge		
									CDAI	CRP (mg/dL)			CDAI	CRP (mg/dL)	Morphology
1	F	52	C	-	-	< 1 mo	-	I	161	0.6	Sulfasalazine	58	25	0.9	Active (CS)
2	M	22	C	+	+	4 yr and 3 mo	+	R	264	3.1	Infliximab	55	62	0	NT
3	F	21	EC	+	-	5 yr and 8 mo	-	R	133	6.3	Infliximab	48	38	0	NT
4	M	22	EC	+	-	5 yr and 3 mo	-	R	679	5.9	Infliximab	82	72	0.1	Remission (CS)
5	M	23	EC	+	-	< 2 mo	-	I	235	1.5	Infliximab	55	98	0.1	Near remission (CS)
6	M	28	C	-	-	2 mo	-	I	88	2.5	Infliximab	68	59	0.5	Near remission (CS)
7	F	77	C	-	-	1 yr and 10 mo	-	R	233	13.8	Infliximab	49	39	0	Remission (CS and BE)
8	M	30	C	+	-	6 mo	-	I	281	4.6	Infliximab	50	39	0.1	Remission (CS)
9	M	55	C	+	+	8 mo	-	I	172	1.0	Infliximab	46	67	0.5	Remission (CS and BE)
10	M	19	EC	+	-	4 mo	-	I	147	0.8	Infliximab	43	40	0	Remission (CS and BE)
11	F	21	EC	-	+	3 mo	-	I	335	6.0	Infliximab	49	47	0.3	Improved still active (CS and BE)
12	F	50	E	-	-	1 mo	-	I	488	5.1	Infliximab	43	53	0	Remission (CS)
13	M	28	C	-	-	3 mo	-	I	52	0.6	Infliximab	50	2	0	Remission (CS)
14	M	19	EC	+	+	2 yr and 1 mo	-	I	193	0.8	Infliximab	43	35	0	Near remission (CS and BE)
15	M	29	C	+	-	1 yr and 4 mo	-	I	126	0.2	Infliximab	43	8	0	Improved still active (CS)
16	M	30	C	+	-	1 yr and 1 mo	-	I	211	11.8	Infliximab	47	28	0.8	Near remission (CS and BE)
17	F	21	EC	-	+	6 yr and 2 mo	-	R	544	3.7	Infliximab	46	64	0.3	Improved still active (BE)
18	F	45	EC	-	-	13 yr	+	R, PO 21st d	143	0.2	Metronidazole	19	105	0.1	NT
19	M	21	EC	+	+	2 yr	-	I, PO 13th d	217	1.1	Metronidazole	18	166	0.1	NT
20	M	34	EC	-	-	17 yr	-	R, PO 12th d	146	0	Metronidazole	24	108	0.1	NT
21	M	25	C	-	+	13 yr	-	R, PO 17th d	372	7.1	Metronidazole	21	149	0	NT
22	F	23	EC	-	-	8 yr	-	R, PO 25th d	151	8.0	Metronidazole	83	141	0.8	NT

F: Female; M: Male; EC: Enterocolitis; C: Colitis; E: Enteritis; R: Relapse; I: Initial onset; PO: Postoperative; CDAI: Crohn's disease activity index; CRP: C-reactive protein (normal range ≤ 0.3 mg/dL); SVD: Semi-vegetarian diet; CS: Colonoscopy; BE: Barium enema study; NT: Not tested.

Diagnosis of CD was made by established criteria[45]. Two patients did not achieve remission: one patient was referred to another hospital for surgery, and the other patient was discharged part way through treatment at his request. There were three smokers. Two of them accepted the doctor's advice and stopped smoking after admission. One patient resumed smoking again after discharge, and this patient was excluded from this study. Therefore, 22 patients who achieved clinical remission medically (n = 17, No. 1-17, Table 1) or surgically (n = 5, No. 18-22, Table 1) were included in this study. Clinical remission was defined as the disappearance of active symptoms of CD. Male patients predominated over female patients (14:8). Ages ranged from 19 to 77 years old (median: 26.5 years). The number of patients with enterocolitis, enteritis, and colitis was 11, 1, and 10, respectively. Fourteen patients had perianal fistulas and/or anal tags. Eleven patients with anal fistulas had draining pus. Disease duration of medically treated patients ranged from 1 to 74 mo (median: 8.0 mo). That of surgically treated patients was > 8 years except for case 19, who underwent surgery on his initial visit after 2 years with the disease. Two of the 22 patients underwent previous intestinal resection for CD. Thirteen cases were initial onset and nine were relapses. Crohn's disease activity index (CDAI)[46] on admission in medically treated patients ranged from 52 to 679 (median: 211). Five cases showed CDAI < 150, which is arbitrarily defined to be remission in many studies, but they were definitely suffering from active symptoms. Two cases showed very low CDAI, i.e. 88 in case 6 and 52 in case 13, but they had active symptoms: diarrhea for 2 mo and loose stools and lower abdominal pain for 3 mo, respectively. In surgically treated patients, CDAI score on transfer to our division after surgery was

Table 2 Nutritional data and hemoglobin during hospitalization

Case No.	Dietary pattern before hospitalization	Hospitalization									
		On admission					On discharge				
		BMI (kg/m^2)	Albmin (g/dL)	Chol (mg/dL)	ChE (IU/mL)	Hemoglobin (g/dL)	BMI (kg/m^2)	Albmin (g/dL)	Chol (mg/dL)	ChE (IU/mL)	Hemoglobin (g/dL)
1	Pro-Japanese	21.1	4.7	155	4929	14.8	20.5	4.1	145	4959	13.0
2	Standard	17.2	3.8	140	4059	14.0	17.1	4.5	145	4170	15.5
3	Japanese	17.2	3.7	102	2003	8.3	19.2	4.0	152	4117	11.1
4	Pro-Japanese	18.5	2.8	100	789	8.6	17.9	3.0	116	1876	12.7
5	Pro-western	17.7	4.8	132	5592	15.8	17.0	4.2	135	5057	14.4
6	Pro-western	21.3	3.0	122	2876	10.8	20.7	4.4	192	4321	10.8
7	Pro-Japanese	17.2	2.1	95	1549	7.5	16.8	3.2	177	2633	11.6
8	Pro-western	19.2	3.2	128	3441	12.6	18.3	4.2	114	4911	14.3
9	Japanese	19.7	3.9	190	5094	13.0	18.2	4.1	221	4602	14.1
10	Pro-western	17.6	4.0	147	4505	13.5	17.6	4.5	154	4725	13.7
11	Standard	19.8	3.7	147	4081	9.5	18.4	3.9	125	4837	10.3
12	Standard	24.1	4.4	149	5156	11.0	21.4	4.3	158	6626	10.7
13	Standard	24.4	4.6	151	4599	16.2	22.5	4.4	143	4376	15.1
14	Pro-western	19.0	4.7	167	5722	15.0	18.8	4.4	138	4861	16.0
15	Pro-western	24.1	4.6	188	5755	15.4	22.4	4.5	137	5643	15.8
16	Pro-western	22.5	3.7	138	3757	12.3	21.4	4.4	116	4304	14.3
17	Standard	18.8	3.8	187	2700	10.6	18.1	4.1	209	2798	11.8
18	Pro-Japanese	21.6	4.1	126	7943	10.7	21.9	3.9	129	9098	10.8
19	Pro-western	20.1	4.1	150	3320	11.0	20.1	4.2	152	3426	11.8
20	Polymeric diet	18.1	3.9	100	3512	11.0	17.9	4.1	130	3757	13.4
21	Standard	15.6	3.5	116	3387	10.2	15.6	4.0	138	3870	11.9
22	Pro-Japanese	16.5	3.2	58	2320	9.9	16.0	2.9	78	3355	9.8

Standard: A mixture of Japanese and western diet; BMI: Body mass index; Chol: Total serum cholesterol; ChE: Cholinesterase. Normal range: BMI: 18.5 kg/m^2 ≤- < 25.0 kg/m^2; Albmin: 3.8-5.2 g/dL; Chol: 120-220 mg/dL; ChE: 3200-6500 IU/mL; Hemoglobin: M: 13.8-17.5 g/dL, F: 12.0-15.1 g/dL.

determined. The details such as sex, age, clinical types by disease location, anal lesions, disease duration, initial onset or relapse, and C-reactive protein (CRP) concentration are shown in Table 1.

Medical induction of remission: The main medication was infliximab in all medically treated patients except for case 1. Case 1 was the earliest case in this study with mild symptoms and was treated with sulfasalazine 3 g/d. Metronidazole 750 mg/d was given after admission. Patients received liquid infusion of 1500 mL/d *via* a peripheral vein for about 1 wk, without meals. Meanwhile, morphological studies including colonoscopy or contrast barium enema study, enteroclysis, and esophagogastroduodenoscopy were performed to assess clinical types and stenosis. Laboratory data were also obtained. Then, infliximab (5 mg/kg body weight; Remicade, Centocor, Malvern, PA, USA) was infused over 3 h[47]. Infliximab was further infused at 2 and 6 wk according to the standard recommendation[47]. After about 1 mo of metronidazole administration, it was switched to mesalamine 1.5 g/d or sulfasalazine 2 g/d. After the third infusion of infliximab, patients were discharged. Iron (60 mg/d saccharated ferric oxide) was given to patients with moderately severe anemia, but none of patients received a blood transfusion. No steroid hormone, immunosuppressant, or antibiotic other than metronidazole was administered.

The CDAI score of medically treated patients was significantly decreased from 255 ± 169 (mean ± SD) on admission to 46 ± 24 at week 6 after the first infusion of infliximab, i.e. before the third infusion of infliximab (paired *t* test, $P < 0.0001$, Table 1). The concentration of CRP also significantly decreased from 4.0 ± 3.9 to 0.2 ± 0.3 mg/dL ($P = 0.001$). Morphological studies by colonoscopy and/or contrast barium enema study were performed before discharge in 15 patients (Table 1). Morphological remission was achieved in seven patients. Near remission was achieved in four patients in whom redness and/or a few small aphthoid lesions without ulcer were present. In three patients, active lesions were improved, but active lesions (ulcer) were still present. In case 1, there was no improvement in active lesions. Nutritional data in patients who showed hypoalbuminemia (< 3.8 g/dL, $n = 7$) or hypocholesterolemia (< 120 mg/dL, $n = 3$) on admission were improved to a normal level at week 6: from 3.2 ± 0.6 to 3.9 ± 0.6 g/dL ($P = 0.0086$) and from 99 ± 4 to 148 ± 31 mg/dL, respectively (Table 2). Low serum cholinesterase (< 3200 IU/L, $n = 5$) improved: from 1983 ± 855 to 3149 ± 1039 ($P = 0.0233$). There was little change in body mass index (BMI) at week 6 in patients who showed abnormally low levels (< 18.5 kg/m^2, $n = 5$) on admission: from 17.4 ± 0.2 to 17.5 ± 1.0. Anemia (male < 13.8 g/dL, female < 12.0 g/dL, $n = 11$) improved from 10.7 ± 2.0 to 12.3 ± 1.6 ($P = 0.0058$). Details of individual data are presented in Table 2.

Surgical induction of remission: Five patients, cases 18-22, who had recently undergone intestinal resection for intestinal obstruction, were transferred to our division

Table 3 Lifestyle and dietary habits

	Every day	3-5 times/wk	1-2 times/wk	Rare	None
Smoking (No. of cigarettes/d)	20 ≤	6-19	1-5	Rare	P
Regular exercise	R	R	R		P
Alcohol					P
Eating between meals			P	R	R
Type of diet (D)	Semi-vegetarian (R)	Japanese	Pro-Japanese	Standard/mixed	Pro-western (P)
Food					
Rice	P				
Miso soup	P				
Pulses	R	P			
Vegetables	R	P			
Udon/soba (Japanese noodles)				P	
Ramen (Chinese noodles)			P	R	
Bread (D)	P			R	
Tea, coffee		Canned coffee (P)		R	
(Sugar in tea or coffee) (D)	Large amount (P)	Average amount	Small amount	Rare	None (R)
Juice	P			R	R
Cola/soda					P
Beef			P	R	
Pork/chicken (D)		P		R	
Minced or processed meat			P	R	
Fish				P	
Cheese/butter/margarine			P	R	
Sweets (D)	P			R	R
Ice cream/milk shake				P	
Yoghurt (plain)	R				P
Green tea (D)	R				P
Potatoes/starches (D)	R		P		
Fruits (D)	R				P

P: Your present habit (style); R: Recommended habit (style); D: Drastic alteration recommended.

when they could take solid meals. This occurred on post-operative day 12-15 (Table 1). They took metronidazole 750 mg/d for about 1 mo along with meals[48].

Patients' dietary habits: Patients' dietary habits and lifestyles before onset or relapse of the disease were obtained immediately after admission, prior to providing information about the SVD, by means of a food-frequency questionnaire[49]. The questionnaire included 45 questions that covered almost all foods or food groups in Japan. There was a question about dietary type that listed six types: western, pro-western, standard/mixed, pro-Japanese, Japanese, and SVD. A definition of dietary types was not set. There was a variety of dietary patterns before the onset or relapse of CD: pro-western (n = 8), standard/mixed of western and Japanese diet (n = 6), pro-Japanese (n = 5), and Japanese (n = 2) (Table 2). Case 20 had a 2000 kcal/d polymeric diet without meals. None of our patients' dietary pattern was SVD or a western diet. Based on the questionnaire, a summarized table was made that showed both a patient's hitherto and future recommended lifestyle and dietary habits. Such a table created for case 8 is shown in Table 3. Recommended dietary habits were consistent with SVD in the following. This table was used by the dietitian when giving dietary guidance, and it was given to the patient by the chief investigator (Chiba M) during hospitalization.

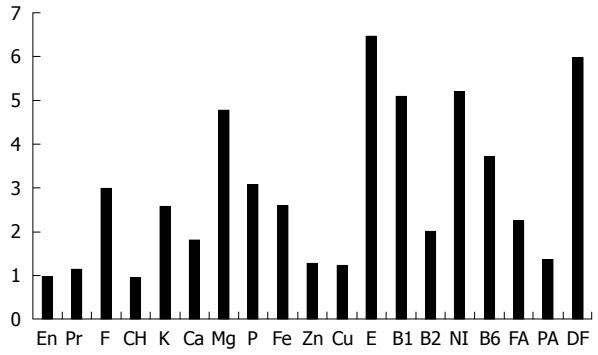

Figure 1 Nutritional elements of brown rice in comparison with white rice[50]. The amount of elements in 100 g of edible food is expressed in comparison with those in white rice, whose value is 1. Brown rice is richer in almost all elements in comparison. En: Energy; Pr: Protein; F: Fat; CH: Carbohydrate; E: Vitamin E; B1: Vitamin B1; B2: Vitamin B2; NI: Niacin; B6: Vitamin B6; FA: Folic acid; PA: Pantothenic acid; DF: Dietary fiber.

SVD: SVD was initiated on the same day as infusion of infliximab in medically treated patients. About 800 or 1100 kcal/d was given in the beginning, and calories were gradually increased to a maximum of about 30 kcal/kg standard body weight. White rice was served first for 2-5 d followed by mixed rice (70% white rice and 30% unrefined whole brown rice) for 2-5 d, and finally brown rice was served. Unrefined brown rice contains more vitamins and minerals than white rice[50] (Figure 1) and is reported to increase significantly beneficial bacteria compared to

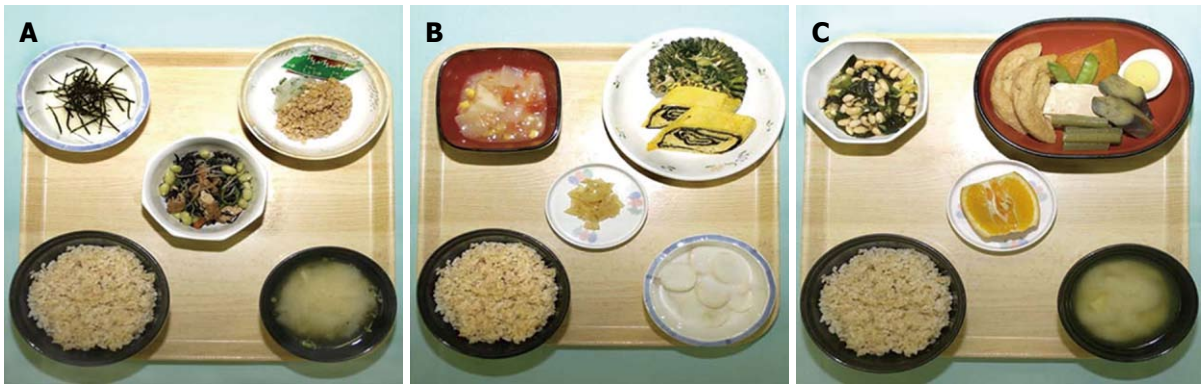

Figure 2 A sample of a 1700-kcal/d semi-vegetarian diet (SVD) for Crohn's disease (CD). From left to right, breakfast (A), lunch (B), and dinner (C). Boiled brown rice is seen at the bottom left of the tray and miso (fermented bean paste) soup is at the bottom right. Breakfast (A): Raw grated nagaimo (yam) and shredded toasted nori seaweed are at the top left; natto (fermented soybeans) and grated daikon (Japanese radish) are at the top right; and braised hijiki seaweed, nama-age (thick deep-fried beancurd), and edamame (young soybeans) are in the center; Lunch (B): Boiled potato, onion, and corn in tomato soup are at the top left; isomaki-tamago (dried nori seaweed inside egg roll) and boiled chrysanthemum with sesame dressing are at the top right; takuan (pickled radish) is in the center; and a mixture of banana and plain yoghurt is at the bottom right; Dinner (C): Boiled chingensai (qing gin cai), soybeans, and wakame seaweed with vinegar soy sauce dressing are at the top left; simmered ganmodoki (bean-curd-based mixture), tofu (bean curd), boiled egg, Japanese-variety eggplant, Japanese butterbur, Japanese-variety pumpkin, and snow peas are at the top right; and citrus fruit is in the center.

Table 4 Content of semi-vegetarian diet (2000 kcal/d)

	SVD	DRI
Energy		
Protein (%)	16.1 ± 0.5	< 20
Fat (%)	18.6 ± 1.4	20-30
Carbohydrate (%)	66.1 ± 1.6	50-70
Content		
Protein (g)	80.3 ± 3.0	M 60, F 50
Fat (g)	41.4 ± 3.6	
Carbohydrate (g)	330.2 ± 11.4	
Dietary fiber (g)	32.4 ± 2.1	M 20, F 17
Soluble dietary fiber (g)	6.8 ± 0.7	
Insoluble dietary fiber (g)	23.3 ± 1.6	
Calcium (mg)	873.7 ± 65.2	M 600-650, F 600
Phosphorus (mg)	1882.7 ± 101.8	M 1050, F 900
Iron (mg)	19.3 ± 1.3	M 7.5, F 10.5
Sodium (mg)	4492.9 ± 342.1	600
Kalium (mg)	4281.7 ± 250.6	M 2000, F 1600
Vitamin A (μgRE)	1416.6 ± 360.9	M 750, F 600
Vitamin B1 (mg)	2.0 ± 0.2	M 1.4, F 1.1
Vitamin B2 (mg)	1.3 ± 0.2	M 1.6, F 1.2
Niacin (mg)	26.6 ± 3.1	M 15, F 12
Vitamin C (mg)	133.1 ± 23.4	100
Vitamin D (μg)	3.2 ± 1.0	5
Vitamin E (mg)	12.3 ± 1.9	M 9, F 8
Cholesterol (mg)	285.9 ± 72.1	M < 700, F < 600
NaCl (g)	10.9 ± 0.8	M < 10, F < 8
Polyunsaturated fatty acid (g)	13.9 ± 1.9	
Monounsaturated fatty acid (g)	9.3 ± 0.9	
Saturated fatty acid (g)	7.1 ± 0.9	
P:S ratio	2.0 ± 0.2	

SVD: Semi-vegetarian diet, Figure is mean ± 1SD of 28 d; DRI: Dietary reference intakes for Japanese[52], Figures for ages above 18 are shown; P:S: Polyunsaturated fatty acids:saturated fatty acids.

well-milled white rice[41]. Eggs and milk were used. In other words, our diet was a lacto-ovo-vegetarian diet[51]. Miso (fermented bean paste) soup, vegetables, fruits, legumes, potatoes, pickled vegetables, and plain yoghurt were served daily. Fish was served once a week and meat once every 2 wk, both at about a half the average amount. Patients were provided with several different 4-wk menus on a rotational basis. Figure 2 shows what an SVD looks like. Details of the contents of nutritional elements including minerals, vitamins, and fatty acids in an SVD are shown in Table 4. These figures were obtained by HOPE/COMETY-NT (Fujitsu, Tokyo, Japan). The rate of fat in total calories (18.6%) was < 20%, which is the lower limit of Dietary Reference Intakes for Japanese (DRI)[52]. The amounts of dietary fiber and iron in the SVD were above the DRI. Those of most of the other elements in the SVD were comparable to DRI (Table 4). Coarse tea was served along with the meal service. During hospitalization, foods other than the meal service were discouraged. Drinking of green tea was encouraged. Participant days of SVD ranged from 43 to 82 d (median: 49 d) in medically treated patients (Table 1). In surgically treated patients, they were shorter, about 3 wk. Case 22 was exceptionally long, 83 d, due to a postoperative complication of subcutaneous abscess formation. In all 22 cases, there were no adverse effects such as gaseous distress, abdominal discomfort, or diarrhea as a result of the SVD.

At the end of hospitalization, a qualified dietitian gave dietary guidance to the patient and the meal preparer. It included how to boil brown rice. The responsible doctor (Chiba M) also gave patients an SVD guide (Figure 3) and advised them to continue the diet after discharge. Foods that have been shown to be a risk factor for IBD in or outside Japan, including sweets[20-23,28-30], bread[27], cheese[27-29], margarine[27], fast foods, carbonated beverages, and juices[24,25,29], were discouraged. Healthy habits were encouraged: no smoking, regular physical activity, moderate or no use of alcohol, regularity of meals, and not eating between meals[53].

Follow-up study

Twenty-two patients who achieved remission either medically or surgically were followed up for 2 years. Medication was mesalamine or sulfasalazine (Table 5). None of

Table 5 Follow-up study

Case No.	Main medication	Dietary pattern				Days of remission	Reason for termination	On final attendance						
		Month 3	Year 1	Year 2	On relapse			CDAI	CRP (mg/dL)	BMI (kg/m^2)	Alb (g/dL)	Chol (mg/dL)	ChE (IU/mL)	Hemoglobin (g/dL)
1	SSZ for 1 yr	SVD	SVD	SVD		730	Completion	0	0.1	23.1	4.5	235	5684	14.4
2	Mesalamine	SVD	Omni		Omni	301	Relapse	193	8.2	17.5	3.8	151	3262	13.8
3	Mesalamine	SVD	Omni		Omni	367	Relapse	167	11.3	21.1	3.5	133	3551	10.0
4	Mesalamine	SVD	SVD	SVD		730	Completion	128	5.0	18.7	2.8	114	1113	9.3
5	SSZ for 1 yr	SVD	SVD			523	Moving	39	0	19.4	4.5	194	5509	15.0
6	Mesalamine	Omni			Omni	191	Relapse	192	5.7	21.7	3.9	134	3052	7.9
7	None	SVD	SVD			442	INFX for RA	61	2.0	19.6	4.0	158	5068	10.9
8	Mesalamine	SVD	SVD		SVD	635	Relapse	174	7.6	19.1	3.1	88	2678	11.3
9	Mesalamine	Omni	Omni	Omni		730	Completion	48	0.2	19.8	4.3	171	5461	15.2
10	Mesalamine	SVD	SVD	SVD		730	Completion	18	0.1	18.2	5.1	181	4659	16.3
11	Mesalamine	SVD	SVD	SVD		730	Completion	11	0	19.7	4.7	147	5215	13.9
12	Mesalamine	SVD	SVD	SVD		730	Completion	45	0	20.2	4.7	163	6268	11.3
13	Mesalamine	SVD	SVD	SVD		730	Completion	0	0	22.8	4.6	171	4770	15.6
14	Mesalamine	SVD	SVD			666	Ongoing	27	0.1	19.3	4.7	188	6084	15.1
15	Mesalamine	SVD	Omni			560	Ongoing	0	0	22.6	4.8	185	5671	16.8
16	Mesalamine	SVD	SVD			440	Ongoing	19	1.9	21.8	4.4	141	5146	14.2
17	Mesalamine	SVD	SVD			397	Ongoing	32	2.0	22.5	3.6	216	2683	11.1
18	Mesalamine	SVD	SVD	SVD		730	Completion	25	0.4	22.6	3.7	151	10222	11.1
19	Mesalamine	SVD	SVD	SVD		730	Completion	62	0	20.1	4.7	139	4391	13.3
20	None	SVD	SVD	SVD		730	Completion	37	0.7	18.2	4.5	156	5655	13.2
21	SSZ	SVD	SVD	SVD		730	Completion	16	0.1	19.0	4.9	205	6424	14.4
22	Mesalamine	SVD	Omni		Omni	630	Relapse	118	5.1	22.1	3.5	84	3596	10.1

Alb: Albumin; SSZ: Sulfasalazine; Omni: Omnivorous diet; INFX: Infliximab; RA: Rheumatoid arthritis. Normal range: CRP: ≤ 0.3 mg/dL; BMI: 18.5 kg/m^2 ≤- < 25.0 kg/m^2; Albmin: 3.8-5.2 g/dL; Chol: 120-220 mg/dL; ChE: 3200-6500 IU/mL; Hemoglobin: M: 13.8-17.5 g/dL, F: 12.0-15.1 g/dL.

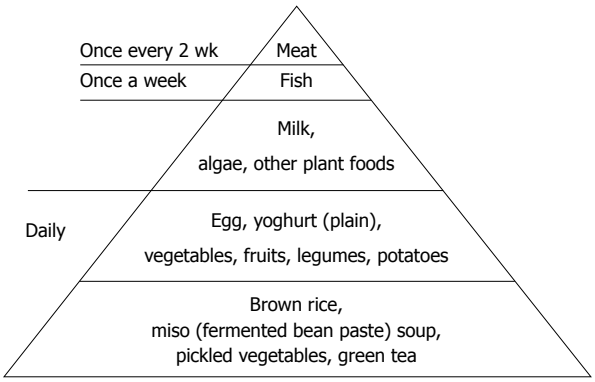

Figure 3 SVD food guide pyramid.

the patients took immunosuppressants such as azathioprine or 6-mercaptopurine. They visited the IBD outpatient department (responsible doctor: Chiba M) every 8 wk. Blood samples for measurement of CRP, complete blood counts, albumin, and transaminases were taken at each visit. The food-frequency questionnaire was obtained at month 3, at years 1 and 2, or when a patient relapsed. When remission was maintained for 1 year and a patient seemed to continue the SVD, medication was stopped if the patient so desired. Primary end point was clinical relapse that was defined as the appearance of active symptoms of CD that required treatment. Duration of remission was calculated as the number of days between discharge and the appearance of symptoms of relapse. Although the responsible doctor (Chiba M) similarly advised patients to continue the SVD, some patients did not follow the advice or abandoned it at some point. Relapse in 2 years was compared between two groups of patients: SVD group and the omnivorous diet group.

Assessment of dietary pattern in outpatients: Dietary pattern was classified into two groups: SVD and omnivorous diet. When the following two conditions were fulfilled, it was regarded as SVD in this study. One is that a patient follows the principle of SVD: daily intake of rice, vegetables, and fruits, and occasional intake of fish, meat, and other animal-based foods. The other one is that a patient refrains from foods reported as risk factors for IBD in or outside Japan as stated above[20-30]. A diet that did not fulfill these two conditions was regarded as an omnivorous diet.

Statistical analysis

Kaplan-Meier survival analysis was used to calculate the cumulative proportion of patients who had a relapse. Patients who stopped the treatment for any reason other than relapse were considered censored at the time of their last observation. Comparison of cumulative relapse rates between the SVD and omnivorous groups was tested by the log rank test. A P value of 0.05 or less was considered to indicate a statistically significant difference. Statistical analysis was performed using JMP 8 (SAS Institute Inc., Cary, NC, USA) software.

RESULTS

Eighteen patients terminated the follow-up: completion

Table 6 Maintenance therapy in Crohn's disease following induction of remission or response

	Induction therapy		Maintenance therapy		
	Subjects	Regimen	Regimen	Duration	
				1 yr	2 yr
Candy *et al*[55], 1995	CDAI > 200	PS (diminishing dose) + AZA 12 wk	AZA 2.5 mg/kg Placebo	Remission rate 42% (14/33) 7% (2/30)	
Hanauer *et al*[56], 2002	CDAI ⩾ 220 Responder to a single infusion of infliximab	Gr (1) and Gr (2) INFX 5 mg/kg at weeks 0, 2, 6 Gr (3) INFX 5 mg/kg then placebo infusion at weeks 2, 6	Gr (1) INFX 5 mg/kg every 8 wk Gr (2) INFX 10 mg/kg every 8 wk Gr (3) placebo infusion every 8 wk	Remission rate 25% (28/113) 33% (37/112) 11% (12/110)	
Sandborn *et al*[58], 2005	Mild to moderate CD	Budesonide 6 mg or 3 mg	Budesonide 6 mg or 3 mg Placebo	Relapse rate 60%-70% (In all 3 groups)	
Takagi *et al*[39], 2006	Active CD	TPN (25 cases), TEN (22 cases), PS (1 case), INFX (3 cases)	ED (half) + a free diet (half) A free diet	Relapse rate 26.9% (7/26) 64.0% (16/25)	
Regueiro *et al*[59], 2009	CD patients who had surgery	Ileocolonic resection	INFX 5 mg/kg at weeks 0, 2, 6 then every 8 wk Placebo	Remission rate 80% (8/10) 58% (7/13)	
Present study	Active CD	INFX 5 mg/kg at weeks 0, 2, 6 (16 cases), intestinal resection (5 cases), SSZ (1 case)	Semi-vegetarian diet Omnivorous diet	Remission rate 100% (16/16) 67% (4/6)	92% 25%

PS: Prednisolone; AZA: Azathioprine; CD: Crohn's disease; TPN: Total parenteral hypernutrition; TEN: Total enteral nutrition; ED: Elemental diet.

of 2-year observation in 11, relapse in five, and early termination for other reason in two (moving and infliximab therapy for associated rheumatoid arthritis in one each). Four patients are ongoing (Table 5). Dietary types that patients marked in the food-frequency questionnaire during the follow-up study were judged appropriate by other foods or food groups marked. SVD was maintained by 16 patients but not by six (compliance 73%) (Table 5). There was no untoward effect of SVD. The reason for the discontinuance of SVD in six patients was not a detrimental effect of SVD but their preference for sweets, meat, and/or fish. Case 2 continued SVD for the first 3 mo but stopped thereafter. Cases 3 and 22 consumed vegetables and fruits only once a week and ate sweets frequently. Case 6 cooked and added meat to the SVD that was prepared by his mother. Case 9 had alcohol at supper every night and frequently ate fish and sweets. Case 15 consumed animal foods more often than the standard for an SVD.

Five patients relapsed. Four were medically treated and one was surgically treated. On the final study visit, they showed elevated CRP concentration and a CDAI of > 100 (Table 5). Seventeen patients maintained remission. Among them, 11 with normal CRP concentration showed almost normal values in other nutritional data (BMI, albumin, cholesterol, and cholinesterase) and hemoglobin. Their CDAI was extremely low. Meanwhile, most of the six patients with elevated CRP, although in remission, showed some abnormality in these indices. The details are shown in Table 5.

Among the 16 patients who continued with the SVD, 15 maintained remission and one relapsed (Table 5): the remission rate was 100% (16/16) at 1 year and 92% at 2 years (Figure 4 and Table 6). Among six patients who were on an omnivorous diet, two maintained remission and four relapsed (Table 5): the remission rate was 67% (4/6) at 1 year and 25% at 2 years (Figure 4 and Table 6). Life table analysis showed that the cumulative relapse rate

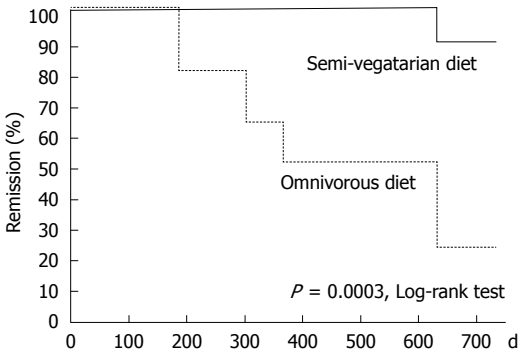

Figure 4 Life table estimate of maintaining remission with SVD or omnivorous diet.

at 2 years was significantly lower in the SVD group than in the omnivorous group (P = 0.0003) (Figure 4). The concentration of CRP was normal at the final visit in more than half of the patients in remission on an SVD; in those who maintained remission during the study (9/15; 60%); terminated follow-up (8/12; 67%), or completed 2 years follow-up (7/10; 70%).

DISCUSSION

We used mesalamine or sulfasalazine in the follow-up phase. Considering that the relapse-preventive effect of mesalamine or sulfasalazine is absent or modest at most[54], it is reasonable to conclude that the SVD protected patients from relapse but an omnivorous diet did not.

Azathioprine and 6-mercaptopurine are known to be effective and used for maintenance of remission in patients with steroid-dependent CD[6-9]. They are also used in the induction phase together with prednisolone and then used for maintenance. In such situations, Candy *et al*[55]

have reported that the remission rate at 1 year was 42% (placebo control, 7%) (Table 6). Recently, scheduled infliximab therapy every 8 wk has been shown to be effective as maintenance treatment in both adults and pediatric patients[56,57]. Remission rate at 1 year in adults was 25%-33% (placebo control, 11%) (Table 6)[56]. An elemental diet that consisted of about a half the daily energy intake has been shown recently to have a relapse-preventive effect in the Japanese study group: 26.9% relapse rate at 1 year (control free diet, 64.0%) (Table 6)[39]. Remission rates with the SVD in the present study were far better than those reported previously: 100% (16/16) remission rate at 1 year and 92% at 2 years. To the best of our knowledge, this is the best result in relapse prevention. Although our study population included mild cases, our excellent results cannot be explained solely by a difference in severity in study population, because even mild to moderate disease relapse rates are 60%-70% at 1 year (Table 6)[58]. More recently, scheduled infliximab therapy every 8 wk has been shown to be effective in postoperative patients: 80% remission rate at 1 year (placebo control, 58%) (Table 6)[59]. Successful scheduled maintenance therapy with infliximab, however, could encounter difficulty over longer periods due to a waning of efficacy, and side effects. In 2 years, more than half the patients need a shortening in the infliximab dosing interval and about 10% of patients need cessation of therapy[60]. Although the number of patients in our study was small, all four postoperative patients on the SVD maintained remission for 2 years (Table 5).

When we began thinking of IBD as a lifestyle-related disease mediated mainly by dietary westernization, we changed our modality of treatment to emphasize diet (Table 7). The menu of a conventional low-residue diet for IBD is shared by UC and CD. However, CD is apparently more tenacious than UC[43]. Therefore, the staple is refined white rice for UC and unrefined brown rice for CD. About 30 kcal/kg per day is provided in the current diet, while total calories were not individualized in the conventional diet. Dietary analysis is needed for dietary guidance in current practice (Table 7). In addition to diet, common health practices[53] are encouraged.

SVD is initiated after about 1 wk of fasting, on the same day as infliximab infusion. By this time, symptoms such as diarrhea, abdominal pain, and fever subside, and patients want to eat. SVD that contained a moderate amount of dietary fiber was not detrimental but useful for induction of remission of CD. It improved hypoalbuminemia, hypocholesterolemia, and anemia during hospitalization. Although clinical remission could be obtained by one or two infusions of infliximab, we believe that a certain period of time is needed for recovery of morphological changes in the intestine. Therefore, three infusions of infliximab in 6 wk[47] were given, not at the outpatient clinic but during hospitalization. This period of hospitalization was also useful for patients to become familiar with the SVD. Compliance with the SVD in outpatients in this study was about 75%, which indicates that an SVD could be applicable to the majority of CD patients. An SVD is completely natural and safe. There is no need to fear side effects, as with steroid hormones or immunosuppressants such as infliximab, azathioprine, 6-mercaptopurine, or methotrexate.

Table 7 Conventional and current diet in IBD at Nakadori General Hospital

	Conventional	Current
Diet	Low-residue diet	Semi-lactoovovegetarian diet
Menu	Common for UC and CD	SVD for UC (staple: white rice) SVD for RUC (staple: white rice 70%, brown rice 30%) SVD for CD (staple: brown rice)
Refrainment	Fiber-rich diet	Minced or processed meat, bread, fast foods, sweets, cola/soda, juices
Dairy products	Refrainment	Egg, milk: no refrainment Refrain from cheese/butter/margarine
Calories	2000 kcal/d	About 30 kcal/kg standard body weight/d
Dietary analysis	Absent	Food-frequency questionnaire
Dietary guidance	Absent	Guidance by doctor and registered dietitian

UC: Ulcerative colitis; RUC: Refractory ulcerative colitis.

Fifteen of 16 patients who continued the SVD were free from relapse in our study. In addition, more than half of the patients in remission showed normal CRP levels. CRP is a sensitive indicator for predicting relapse[61]. Judging from CRP levels, it seems that more than half of the patients who continue the SVD will be free from relapse as long as they maintain the diet. However, the rest of the patients in remission with elevated CRP might relapse in the long term, which seems a limitation of the SVD. Our study clearly shows that the dietary pattern influences the relapse rate in CD. Therefore, trials of the preventive effect of medications in CD should be designed in consideration of diet.

There have been trials for prevention of relapse in CD with diets or supplements. Excellent results with an exclusion diet of intolerant foods[62], an unrefined-carbohydrate, fiber-rich diet[63], or fish oil supplement[64] have not been reproduced in other studies[65-67]. Therefore, none of the dietary modifications has been widely accepted. Currently, manipulation of gut microflora with probiotics and/or prebiotics has emerged as an attractive therapeutic modality in IBD[11,15,33,34]. The rationale of an SVD, i.e. enhancement of beneficial bacteria in the gut, is the same as that of probiotics and prebiotics. There is a limitation to mere addition of probiotics, prebiotics or food stuffs and exclusion of potentially untoward food stuffs[65-68]. We believe that, not partial, but comprehensive food control is needed for patients who are genetically predisposed to IBD. Therefore, our SVD encourages consumption of grains, vegetables, and fruits, while limiting intake of animal foods that tend to decrease beneficial bacteria[31,32] and other foods reported to be risk factors for IBD[20-30]. However, no food item is prohibited.

Although we designed our SVD with gut bacterial flora in mind, both plant-only (vegan) and plant-based (lacto-ovo-vegetarian, semi-vegetarian) vegetarians are shown to have low rates of cancer, cardiovascular disease, obesity, and total mortality[51,69]. Plant-based diets are recommended for prevention of cancer and other lifestyle-related chronic diseases[70]. Therefore, SVD will not only be effective for gut inflammation, but also promote the general health of IBD patients.

Since we are aware that an SVD is effective for relapse prevention, we are concerned with rapid, safe and reliable induction of remission. This is now attainable by infliximab[47]. Therefore, we use infliximab as the first choice of therapy in all newly diagnosed active CD cases. So far, there has been no failure in induction of remission with infliximab (Chiba *et al*, article in preparation). Therefore, since the advent of infliximab and SVD, we feel that CD has been much more controllable than before.

In conclusion, this study shows that an SVD is safe and has a preventive effect against relapse of CD. Normal CRP levels are maintained in more than a half of the patients with an SVD. This supports our notion that IBD is a lifestyle-related disease that is mediated mainly by a westernized diet. The concept that IBD is a lifestyle-related disease is lacking in present practice. We believe that without introduction of this concept, a major breakthrough in the prevention of relapse in CD is not attainable. Whether gut microflora are indeed enriched in beneficial bacteria by an SVD needs to be clarified. Our new findings require verification in large, randomized, controlled clinical trials.

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COMMENTS

Background

Crohn's disease (CD) is a chronic disease of the intestine. The peak incidence is between the ages of 15 and 25 years. Remission is induced by drip infusion or elemental diet (amino-acid-based) without meals, by drugs such as prednisolone and infliximab, by resection of the involved intestine, or by a combination of these. The biggest problem in practice in CD is frequent relapse and difficulty in maintaining remission. At 1 year, the relapse rate is around 60%-70% and the remission rate is 25%-42%. A low-residue diet has been conventionally recommended without evidence of improving remission rates. Because meals inevitably cause relapse, the use of elemental diet is popular in countries like Japan.

Research frontiers

Although the etiology of CD is unknown, there is some evidence to indicate that it is a lifestyle-related disease that is mediated mainly by a westernized diet: increased consumption of animal protein, animal fat, and sugar, with decreased consumption of grains. Therefore, the authors designed a semi-vegetarian diet (SVD) which hopefully increases beneficial (preventive) bacteria in the intestine. In this study, the authors examined whether the SVD had a preventive effect against relapse in high-risk patients with CD who had recently achieved remission.

Innovations and breakthroughs

The SVD was highly effective in preventing relapse in CD. Remission rate with the SVD was 100% at 1 year and 92% at 2 years. This is the best result in relapse prevention. The concentration of C-reactive protein, an indicator of inflammation, was normal at the final visit in more than half of the patients on the SVD, which indicated that more than half of the patients who continue the SVD will be free from relapse as long as they maintain the diet.

Applications

SVDs can be provided anywhere in the world. Ulcerative colitis (UC) is another chronic inflammatory bowel disease that displays a less harsh clinical course than CD. An SVD can also be applied to UC.

Terminology

The SVD in this study was a lacto-ovo-vegetarian diet in which eggs and milk were used. Fish was served once a week and meat once every 2 wk, both at about half of the average amount.

Peer review

This is an excellent paper with clear scientific data in a clinical area of extreme importance.

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