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Dietary Perceptions among Patients with Crohn's Disease in Clinical Remission: Comparison with an Era Preceding the Availability of Biologic Therapy

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Keywords
Biologics · Crohn's disease · Dietary perceptions · Food avoidance · Maintenance of remission · Restrictive eating

Abstract
Introduction: Dietary temperance significantly affects the quality of life of patients with Crohn's disease (CD) and remains a major concern. However, perceptions of diet in remission may have changed from the era when treatment options were limited. Therefore, we compared the dietary perceptions and treatment of patients with CD in remission with previously published data from the time biologic therapy was not introduced. ***Methods:*** We compared the data of 254 patients with CD in remission who completed a questionnaire survey in 2022 with those of 76 patients with CD in remission collected in 2003, when biologics were not used for maintenance therapy in Japan. Remission was defined as a CD activity index of 150 or less in both studies. Perceptions of diet (degree of eating whatever one likes) were assessed using single-item nominal scale responses. ***Results:*** The percentage of patients receiving enteral nutrition therapy had decreased (past vs. present: 43.4 vs. 12.6%), while the proportion of patients receiving biologic therapy increased (0 vs. 88.6%, respectively). The percentages of patients who responded "not at all," "sometimes," and "mostly" when asked if they could eat whatever they liked had changed, respectively, from 9.2%, 46.1%, and 44.7% in the past to 4.3%, 25.2%, and 70.5% in the present. ***Conclusion:*** The proportion of those who ate whatever they liked and the mean body mass index increased in comparison with the corresponding values 20 years ago. With the advent of biologic therapies, the number of patients with CD who can enjoy eating has increased.

Introduction

Crohn's disease (CD) is an idiopathic inflammatory disorder that is attributable to genetic, immunological, and environmental influences [1]. Although the cause of CD is unknown, it has been reported to be associated with some dietary factors [2–4]. Despite limited evidence, the role of diet in inducing and/or maintaining remission in CD has been acknowledged [1, 4–6]. Various dietary approaches have been suggested and have gained attention, including partially elemental diets, Crohn's disease exclusion diet, or low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diets [7]. During the active phase, dietary

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restriction is often advised to provide rest for the flared bowel. However, during periods of remission, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend adherence to the principles of healthy dietary patterns while avoiding individual nutritional triggers and adjusting the diet only if some clinical problems persist during the remission phase [6]. Despite this recommendation, a systematic scoping review regarding the dietary behavior of patients with IBD showed a high prevalence of food avoidance or restrictive dietary behaviors, and these dietary beliefs or behaviors have been shown to affect patients' quality of life (QOL) [8].

Over the past 25 years, the emergence of novel and potent therapeutic agents has led to advancements in CD treatment. One pivotal milestone was the arrival of infliximab as a breakthrough treatment option. Infliximab, a monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), first entered clinical practice in the 1990s for induction therapy in moderate-to-severe CD [9] and was thereafter administered for maintaining remission [10]. It subsequently gained approval for use in CD treatment under Japanese National Health Insurance coverage in 2002 for induction and in 2007 for maintenance. A recent study using a medical claims database in Japan reported that approximately one-third of CD patients were introduced to biologics within 6 months of a new diagnosis [11]. Another report from a multicenter cohort in Japan showed that the percentage of patients who received biologics in IBD expert facilities was approximately 80%, which was significantly higher than that in community hospitals [12]. Thus, the use of biologics has expanded rapidly, encompassing a broader patient population and significantly enhancing the QOL of those living with CD.

As disease control improves with the expansion of treatment options for CD, patients' perceptions of their diet may change. Previous studies on dietary behaviors in IBD identified some factors associated with dietary behaviors, such as food avoidance or restrictive eating, including perceived active disease [8]. Restrictive eating and living with the fear of an adverse event or disease relapse negatively influenced patients' enjoyment of food and QOL [13]. Examining the dynamic interplay of disease activity, treatment, and dietary adjustments is essential for healthcare providers seeking to provide comprehensive care. By clarifying patients' updated perspectives on diet, healthcare providers can better guide and support patients with CD in optimizing their QOL. Therefore, this study focused on patients with CD in clinical remission and relatively enjoyable eating and compared their dietary perceptions and treatment with previously published data from a time when biologic therapy was not introduced [14].

Materials and Methods

Study Design and Participants

This cross-sectional study compared patient data obtained in a survey to previously reported data collected by the first author [14]. We conducted a questionnaire survey and a medical record review of patients with IBD from a specialized IBD clinic, where more than 1,000 patients with IBD were followed up, in Osaka from June to July 2022. All patients who visited the clinic during this period were recruited consecutively. The study size was determined by the 2-month survey duration when more than half of the patients visited because this was an exploratory study. The data obtained from 254 patients with CD in remission were compared with previously reported data from 76 patients with CD in remission collected from a university hospital leading IBD research in Tokyo from June to October 2003, when biologic therapy was not used for maintenance therapy in Japan. The eligibility criterion for this study was a Crohn's disease activity index (CDAI) [15] of <150. We excluded patients who were aged <20 years, who did not answer questions about their diagnosis, and who had data with identical responses to all items or missing outcome variables.

Variables of Interest

The survey included questions regarding basic demographics, disease background, treatment, body mass index (BMI), and dietary perceptions. Data on disease type, CDAI score, and C-reactive protein (CRP) levels were collected from medical records. The following data were collected using a questionnaire: age, sex, disease duration, current treatment, height, weight, and dietary perceptions. Dietary perceptions were assessed by evaluating the degree of dietary temperance using the following single-item question with nominal scale responses: I eat whatever I like (not at all/sometimes/mostly). This approach for assessing the degree of dietary temperance was identical to the Japanese questions and response options used in the previous study [14]. We also asked participants about their awareness of their symptom-inducing foods using the following single-item question with nominal scale responses: I know what foods cause symptoms for me (there may be none/I know/I kind of know/I do not know). In addition, participants who were aware of their symptom-inducing foods were asked a question about the degree of coping: I avoid my symptom-inducing foods (not at all/sometimes/mostly). For the current treatment, we asked whether they were using each of the following: oral 5-aminosalicylic acid (5-ASA), immunomodulators, oral corticosteroids, enteral nutrition, and biologics. This involved providing examples of the trade names of the major drugs. Enteral nutrition included elemental diet and oral nutritional supplements, whether drunk or applied via a tube.

Statistical Analysis

For descriptive statistics, continuous variables were presented as mean and standard deviation, and categorical variables were presented as frequency and percentage. For comparisons of the two groups, differences between present and past data were compared by Student's *t* test with summary statistics or the χ^2 test.

Table 1. Participants' background and treatment data: comparison between the present and past studies

	Present survey (n = 254)				Previous report (n = 76)[1]			
	n	mean	SD	(range)	mean	SD	(range)	p value
Age, years	253	41.2	11.1	(21–75)	35.3	9.9	(20–66)	0.000
Disease duration, years	251	16.6	7.9	(1–46)	8.2	5.7	(0.4–25.5)	0.000
CDAI	254	41.7	43.9	(−78–149)	76.2	41.1	(−4.8–148.5)	0.000
CRP, mg/L	252	0.22	0.7	(0.00–5.38)	0.58	0.92	(0.02–6.00)	0.003
BMI, kg/m^2	254	22.7	3.5	(16.4–35.4)	21.2	3.0	(16.0–29.8)	0.001
		n	%		n	%		p value
Sex								
Male		186	73.2		61	80.3		0.313
Female		67	26.4		15	19.7		
Missing		1	0.4					
Type								
Ileitis		37	14.6		22	28.9		0.056
Colitis		48	18.9		13	17.1		
Ileocolitis		169	66.5		41	53.9		
Previous surgery (bowel resection)		108	42.5		41	53.9		0.079
Previous surgery (anal fistula)		62	24.4		21	27.6		0.570
History of fistula		94	37.0		49	64.5		0.000
Current treatments								
Oral 5-ASA		26	10.2		73	96.1		0.000
Immunomodulators		39	15.4		26	34.2		0.002
Oral corticosteroids		19	7.5		10	13.2		0.239
Enteral nutrition		32	12.6		33	43.4		0.000
Biologics		225	88.6		0	0.0		0.000

SD, standard deviation; CDAI, Crohn's disease activity index; CRP, C-reactive protein; BMI, body mass index; 5-ASA, 5-aminosalicylic acid. [1]Tanaka M., Iwao Y., Sasaki S., et al. Moderate dietary temperance effectively prevents CD relapse of Crohn disease: a prospective study of patients in remission. Gastroenterol Nurs. May/June 2007;30(3):202–210.

No imputation was performed for missing data. Statistical analyses were performed using IBM SPSS v29.0J for Windows. Statistical significance was set at $p < 0.05$.

Results

Comparison of Participants' Backgrounds and Treatment

In the present survey, 1 patient declined to participate, and 11 patients provided invalid responses; consequently, the responses provided by 254 patients were analyzed. In the previous survey, among 85 patients who met the inclusion criteria, two declined to participate and seven failed to return the questionnaire; thus, 76 patients were analyzed [14]. The participants' background and treatment data are shown in Table 1. Significant differences were observed for some variables: age, disease duration, and BMI were higher in the present survey than in the past, and among disease activity indicators, CDAI and CRP levels were higher in the past survey than in the present. The present survey had a smaller percentage of patients with a history of fistula than the past survey. Regarding treatments, the percentages of use of 5-ASA, immunomodulators, and enteral nutrition were lower in the present survey than in the past survey. In contrast, the percentage of patients receiving biologic therapy increased from zero in the past survey to over 80% in the present survey.

Comparison of the Degree of Dietary Temperance

The relationship between patient characteristics that showed significant differences between the two groups and the degree of dietary temperance in the present

Table 2. Comparison of patient characteristics by degree of dietary temperance

		Degree of dietary temperance "I eat whatever I like"			*p* value
		not at all (*n* = 11)	sometimes (*n* = 64)	mostly (*n* = 179)	
Age (mean ± SD), years		46.4±9.6	39.0±10.6	41.6±11.3	0.084
Disease duration (mean ± SD), years		20.8±8.8	14.7±8.1	17.0±7.7	0.029
CDAI (mean ± SD)		58.5±44.2	44.6±44.2	40.4±43.8	0.410
CRP (mean ± SD), mg/L		0.07±0.11	0.15±0.48	0.26±0.79	0.417
BMI (mean ± SD), kg/m^2		22.6±3.6	22.6±3.8	22.7±3.4	0.979
History of fistula	No, *n* = 160, %	3.1%	23.1%	73.8%	0.241
	Yes, *n* = 94, %	6.4%	28.7%	64.9%	

p values are based on ANOVA or χ^2 test. SD, standard deviation; CDAI, Crohn's disease activity index; CRP, C-reactive protein; BMI, body mass index.

Table 3. Degree of dietary temperance: comparison between the present and past studies

	Present survey (*n* = 254)		Previous report (*n* = 76)[1]		*p* value
	n	%	*n*	%	
I eat whatever I like					
Not at all	11	4.3	7	9.2	0.001
Sometimes	64	25.2	35	46.1	
Mostly	179	70.5	34	44.7	

[1]Tanaka M., Iwao Y., Sasaki S., et al. Moderate dietary temperance effectively prevents CD relapse of Crohn disease: a prospective study of patients in remission. Gastroenterol Nurs. May/June 2007;30(3):202–210.

survey are shown in Table 2. Disease durations were significantly different by categories in dietary temperance.

The participants' dietary perceptions are presented in Table 3. The percentage of participants who ate whatever they liked was significantly higher in the present survey than in the past. Since many of the patients in the present survey had a long disease duration and the means differed significantly, a subgroup analysis was performed only for patients who had had the disease for less than 10 years (Table 4). The results showed that the proportion of those who ate whatever they liked was still higher in the present survey than in the past.

Awareness of Symptom-Inducing Foods

The data for awareness and avoidance of symptom-inducing foods are shown in Table 5. A total of 166 (65.4%) patients were aware of their symptom-inducing foods; among them, 94% avoided their symptom-inducing foods sometimes or mostly. The influence of background factors assumed to be related to the perception of symptom-inducing foods was examined, but no statistically significant relationship was demonstrated (Table 6).

Discussion

This is the first study to compare patient perceptions of diet and treatment before and after the introduction of biologics as a clinical treatment option. As expected, the proportion of those who ate whatever they liked increased, and the mean BMI also increased in comparison with the corresponding values obtained approximately 20 years ago. In addition to the use of biologics, the usage rates of 5-ASA, immunomodulators, and elemental diets also changed significantly. Despite the vigorous interest among patients and healthcare providers regarding effective eating in IBD management, evidence is limited owing to the difficulties in research on this topic. In this context, a comparative study of past and present patients with CD in remission using the same questionnaire items would be valuable.

Before the introduction of biologics, maintenance therapy for CD consisted mainly of 5-ASA, immunomodulators, and an elemental diet. In particular, elemental diets were widely used as both primary and secondary treatment options for CD in Japan based on the Japanese guidelines, which recommended the amount of enteral nutrition used to cover a relatively high percentage of patients' daily energy requirements [16]. The current guidelines also state that home enteral nutrition is

Table 4. Degree of dietary temperance: comparison between the present (subgroup with disease duration of less than 10 years) and past studies

	Present survey (n = 63)		Previous report (n = 76)[1]		p value
Disease duration (mean±SD)	7.7±2.6		8.2±5.7		
	n	%	n	%	
I eat whatever I like					
Not at all	1	1.6	7	9.2	0.046
Sometimes	23	36.5	35	46.1	
Mostly	39	61.9	34	44.7	

SD, standard deviation. [1]Tanaka M, Iwao Y, Sasaki S., et al. Moderate dietary temperance effectively prevents CD relapse of Crohn disease: a prospective study of patients in remission. Gastroenterol Nurs. May/June 2007;30(3):202–210.

Table 5. Awareness and avoidance of symptom-inducing foods

Awareness of symptom-inducing foods (N = 254)	n	(%)
I know	**63**	**24.8**
I kind of know	**103**	**40.6**
I do not know	25	9.8
There may be none	63	24.8
Avoidance of symptom-inducing foods (N = 166*)	**n**	**(%)**
Not at all	8	4.8
Sometimes	51	30.7
Mostly	105	63.3
Missing	2	1.2

*Respondents in bold font proceeded to the next question, and only 166 patients (65.4%) who were aware of their symptom-inducing foods answered the question "I avoid my symptom-inducing foods."

effective in maintaining CD remission [4]. However, this recommendation of enteral nutrition therapy for the maintenance of clinical remission in adults differs from the ESPEN guideline, "Neither enteral nutrition nor parenteral nutrition can be recommended as primary therapy for maintaining remission in IBD." [6], and a current Cochrane review, "No firm conclusions regarding the efficacy and safety of enteral nutrition in quiescent CD can be drawn." [17]. In contrast, a previous Cochrane review published before the introduction of biologics as a clinical treatment option concluded that "The available evidence suggests that supplementary enteral nutritional may be effective for maintenance of remission in CD. Whilst larger studies are needed to confirm these findings, enteral nutritional supplementation could be considered as an alternative or as an adjunct to maintenance drug therapy in CD" [18]. The number of current therapy options has increased, and patients' perceptions of their diet or eating habits have also changed. On the basis of these considerations, our results are reasonable.

In the past, continuing clinical remission for a long time was difficult; healthcare providers tended to ask patients to restrict their diet to low-fat and low-residue meals to avoid worsening of symptoms. In addition to assessing dietary perception, the previous study also evaluated dietary intake using a validated food frequency questionnaire, and the results showed that while the mean fat intake was 20.6%, among patients practicing strict temperance, it was 10.7% [14]. The increase in mean BMI in the present survey in comparison with the past survey

Table 6. Comparison of patient characteristics by degree of awareness of symptom-inducing foods

	Awareness of symptom-inducing foods				*p* value
	I know (*n* = 63)	I kind of know (*n* = 103)	I do not know (*n* = 25)	there may be none (*n* = 63)	
Disease duration (mean ± SD), years	17.0±8.1	15.5±7.3	19.1±11.3	17.0±6.8	0.183
Disease type					
Ileitis (*n* = 37), %	32.4	40.5	8.1	18.9	0.681
Colitis (*n* = 48), %	18.8	45.8	6.3	29.2	
Ileocolitis (*n* = 169), %	24.9	39.1	11.2	24.9	
Previous surgery (bowel resection)					
No (*n* = 146), %	21.2	42.5	8.9	27.4	0.346
Yes (*n* = 108), %	29.6	38.0	11.1	21.3	
Previous surgery (anal fistula)					
No (*n* = 192), %	25.5	37.5	10.9	26.0	0.332
Yes (*n* = 62), %	22.6	50.0	6.5	21.0	
History of fistula					
No (*n* = 160), %	23.8	38.8	10.6	26.9	0.669
Yes (*n* = 94), %	26.6	43.6	8.5	21.3	

p values are based on ANOVA or χ^2 test. SD, standard deviation.

may reflect changes in dietary behavior. Since the present survey did not investigate dietary intake, we could only compare dietary perceptions, but we believe these findings are informative enough to characterize the significant changes in dietary behaviors in patients with CD in clinical remission. People eat various types of meals every day and at every time, and the nutrient content of each food varies and cannot be controlled. Although dietary surveys based on self-administered questionnaires or dietary records are commonly used, their validity and reliability are limited by recall bias, over-/under-reporting bias, and/or the calculations used for evaluating nutrients. Since the impact of diet on symptoms varies from person to person, a dietary survey, which requires considerable effort and expense, may not be an appropriate approach.

The present survey showed an increase in the percentage of patients who ate whatever they liked, which may reflect a favorable change in the patients' QOL. Concurrently, eating whatever the patients' liked also did not indicate a lack of care about diet, since 65.4% of our participants were aware of their symptom-inducing foods, and most avoided them. Individual food intolerances and their avoidance are frequently reported in patients with IBD [6, 8], and their removal is considered helpful in prolonging remission [19]. However, for patients whose disease is well controlled by treatment, recommendations of excessive nutritional therapy and restrictive diets by healthcare providers may require reassessment. Individually tailored eating with care, adjustment, and joy is important to optimize the QOL of patients with CD in remission.

This study had several limitations. First, the two surveys showed significant differences in some background variables rather than in treatments. Although both sets of data were from CD patients in remission defined by a CDAI of ≤150, age and disease duration were higher in the present survey than in the past, and CDAI and CRP levels were higher in the past than in the present. Therefore, the differences in dietary perceptions may not be solely due to differences before and after the introduction of biologics as a clinical treatment option but also because of the influence of such background differences. Second, the two surveys were conducted at different facilities. Opinions or approaches to CD treatment and nutritional therapy vary between institutions and physicians because of differences in the amount of knowledge and experience and different beliefs or values. Although both sets of data were collected from IBD-specialized outpatient clinics with experienced doctors and other health professionals, surveying the same facility may have been more preferable. Third, the generalizability of our findings is limited. We believe that our results are applicable to Japanese patients with CD treated by IBD experts. Since treatment strategies for IBD have been reported to differ between experts and non-experts, particularly in relation to immunomodulators and biologics, which are

predominantly prescribed in expert hospitals [12], a similar survey at a non-expert hospital may have yielded different results. Furthermore, if the survey were conducted outside Japan, the results may have been different because of Japan's unique medical system. In Japan, a certain number of rare diseases are designated intractable diseases to promote research to clarify the pathogenesis of these diseases and to develop treatments and financially support patients with these diseases. CD is one such designated disease [20]. This allows Japanese patients with CD and physicians to select treatments with minimal expenses. Finally, the methods used to assess dietary perceptions were not validated. In addition, the relationship between dietary perceptions and consequent disease control is uncertain, and prospective studies are needed to support effective and acceptable dietary management in patients with CD in remission.

In conclusion, the proportion of those who ate whatever they liked as well as the mean BMI increased in comparison with the corresponding values recorded approximately 20 years ago. With the advent of biologic therapies, the number of patients who can continue to enjoy food has increased. Our results showing that many patients ate whatever they liked with individual strategies to avoid symptom-inducing foods under the condition that their disease is well controlled provide helpful insights for shared decision-making when considering potent therapeutic agents such as biologics.

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Statement of Ethics

This study conformed to the principles outlined in the Declaration of Helsinki of 1964. The study protocol was reviewed and approved by the Ethics Review Committee of the Faculty of Medicine of Tokyo Dental and Medical University and the Kinshukai Hanwa-Sumiyoshi Hospital Ethics Committee (Approval Numbers: M2021-396 and 2022-8). Patients received information regarding the purpose, methods, risks, and benefits of the study as well as the voluntary nature of participation and their right to refuse participation with no disadvantages. Written informed consent to participate was not directly obtained but inferred by ticking the box indicating agreement.

Conflict of Interest Statement

Makoto Tanaka received lecture fees from Takeda Pharmaceutical and Mitsubishi Tanabe Pharma and received collaborative research funds from Takeda Pharmaceutical. Aki Kawakami has no conflicts of interest to declare. Kayoko Sakagami received lecture fees from Takeda Pharmaceutical, Mochida Pharmaceutical, Janssen Pharmaceutical, AbbVie, Pfizer, EA Pharma, Zeria Pharmaceutical, and Gilead Sciences. Hiroaki Ito received lecture fees from Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Janssen Pharmaceutical, AbbVie, Mochida Pharmaceutical, Pfizer, EA Pharma, Zeria Pharmaceutical, Nippon Kayaku, Gilead Sciences, Kyorin Pharmaceutical, and Nippon Shinyaku.

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Author Contributions

Project lead, development of the research protocol, data curation, formal analysis and interpretation of the results, visualization, writing – original draft, funding acquisition, and project administration: Makoto Tanaka; conceptualization of the research: Makoto Tanaka, Aki Kawakami, Kayoko Sakagami, and Hiroaki Ito; methodology: Makoto Tanaka and Aki Kawakami; investigation: Kayoko Sakagami; resources: Makoto Tanaka and Hiroaki Ito; and writing – review and editing: Aki Kawakami, Kayoko Sakagami, and Hiroaki Ito.

Data Availability Statement

The data that support the findings of this study are not publicly available due to Ethics Committee formalities but are available from the corresponding author upon reasonable request.

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