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Dietary Interventions in Patients with Inflammatory Bowel Disease

Takayuki Yamamoto

Diet is known to have a major role in the expression of inflammatory bowel disease (IBD). Thus, dietary monitoring, mostly in small cohorts of patients' report that intake of certain nutritional constituents like fat, refined sugar, fruits, vegetables and fibre impacted on the progression of IBD. These findings are often compromised by insufficient data or methodological limitations and do not provide realistic data on any given dietary factor. Among various dietary interventions or supplements, probiotics seem to offer some benefit, albeit meta-analyses indicated no significant efficacy. Enteral nutrition appears to be effective in both active and quiescent Crohn's disease (CD). Yet, independent meta-analyses have shown enteral nutrition to be inferior to corticosteroids in the management of active CD. In conclusion, our current knowledge on dietary risk factors for IBD and the therapeutic benefit of appropriate dietary interventions need to be strengthened by future studies in large cohorts of patients.

INTRODUCTION

Inflammatory bowel disease (IBD) is a relapsing-remitting immune disorder of unknown aetiology that afflicts millions of individuals throughout the world with debilitating symptoms, which impair ability to work and quality of life. The major phenotypes of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Historically, IBD was recognised as a major health complication in developed countries notably, Northern Europe and North America, but has emerged in the rest of the world during the past few decades (1–4). The rise in the incidence and the prevalence of IBD has paralleled the social and economic development of populations and adaptation to a Western lifestyle that include changes in dietary intakes, smoking, oral contraceptives, and stress (5,6).

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Diet, as a source of luminal antigens, is thought to be an important factor in the pathogenesis of IBD, but whether antibodies against dietary antigens play a primary role in IBD aetiology or are secondary to intestinal inflammation is yet to be established. In such endeavour, epidemiologic observations may become valuable for identifying dietary factors, which are involved in the aggravation or otherwise promote disease remission. In IBD, nutritional status of patients is significantly compromised, particularly in CD. Depending on the disease activity and the assessment practice, protein-energy malnutrition is reported in 20–85% of patients with CD (7,8). Several factors can lead to protein-energy malnutrition like inadequate intake, malabsorption due to either active disease, bowel resection or bypass, increased loss (diarrhoea), due to drug based medications (salicylates, thiopurines, corticosteroids). In children with IBD, protein-energy malnutrition may cause stunted growth and delayed development. Currently various dietary interventions or supplements are available for such patients (9,10). In this article we review the current evidence for dietary constituents as risk factors for the development of IBD and critically discuss the reports on the efficacies of dietary and enteral interventions.

DIETARY RISK FACTORS FOR IBD

Several authors have reported that fats (11,12) as well as refined sugar (11,13–18) increased the risk of developing IBD, while fruits (14,19,20) and vegetables (11,14,19,20) decreased this risk (Table 1). In line with these reports, the number of patients with IBD in Japan has increased sharply during the past four decades (Figure 1). This increase is likely to reflect improved diagnostic practices as well as an increased awareness of the disease in recent years. Nonetheless, it is true to say that the actual incidence has increased. Western lifestyle is the principal actor because the genetic background of the population in Japan is fairly homogeneous and has not changed significantly in the past few decades. In contrast, total fat and more significantly protein intake during the past four decades in Japan has increased (Figure 2). In an epidemiologic study in Japan (21), univariate analysis showed that the increased incidence of CD was strongly correlated with the increased dietary intake of total fat, animal fat, n-6 polyunsaturated fatty acids (PUFAs), animal protein, milk protein, and the ratio of n-6 to n-3 fatty acid intake. Similarly, a multivariate analysis showed that the increased intake of animal protein was the strongest independent factor, and an increased ratio of n-6 to n-3 PUFAs being a weaker factor. An increased

Table 1.
Diet and risk for inflammatory bowel disease: results of cohort studies

Diet	*Crohn's disease*	*Ulcerative colitis*
Refined sugar	↑	↑
Fruit	↓	↓
Vegetables	↓	↓
Fibre	↓	?
Fat	↑	↑
Fast food	↑	↑

↑, increased risk; ↓, decreased risk.

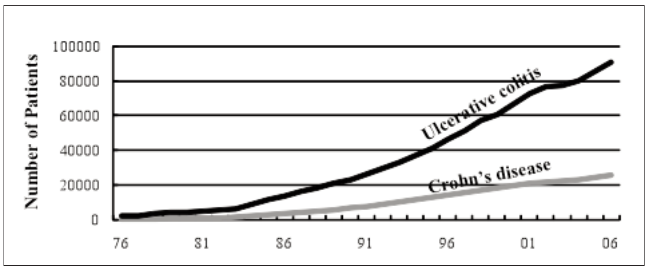

Figure 1. The increasing trend in the number of patients with inflammatory bowel disease in Japan during 1976–2006. The data are compiled by the Research Committee of Inflammatory Bowel Disease affiliated with the Ministry of Health and Welfare of Japan. Source: Yamamoto et al. (61)

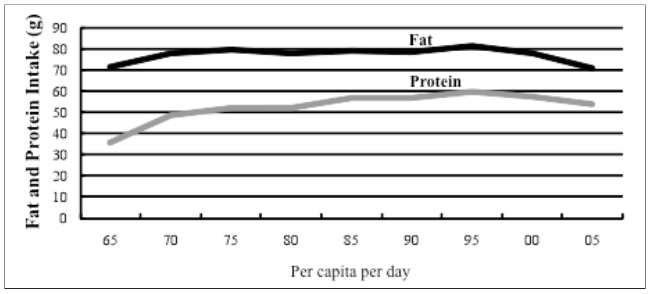

Figure 2. The trend in fat and protein intake in Japan (per capita per day). Data from the National Institute of Health and Nutrition. Source: Yamamoto et al. (61)

dietary intake of animal protein and n-6 PUFAs with less n-3 PUFAs is suspected to predispose to an increased risk of developing CD. Similar observations were reported in a Western study (20). Long-chain omega-3 fatty acids (LCN-omega-3) was negatively correlated with the expression of CD (odds ratio [OR] 0.44, 95% confidence interval [CI] 0.19–1.00). A higher ratio of LCN-omega-3/omega-6 fatty acids was significantly associated with a lower risk for developing CD (OR 0.32, 95% CI 0.14–0.71).

INTERVENTIONS

Elimination Diet

Use of an exclusion diet trial should eliminate the possibility of an adverse food reaction. In a multicentre trial (22), 78 patients who had achieved remission with elemental diet were randomly assigned to corticosteroids (n = 38) or diet (n = 40). Corticosteroid treatment started at 40 mg prednisolone daily, which was tapered and stopped after 12 weeks; this group received dietary advice on healthy eating as well. The diet group received tapered placebo and were instructed to introduce one new food daily, avoiding any food that was known to precipitate symptoms. Median remission time was 3.8 months in the corticosteroid group vs 7.5 months in the diet group, and relapse rates at 2 years were 79% in the corticosteroid group vs 62% in the diet group, significantly favouring the diet for maintenance of remission. Food intolerance was mainly to cereals, dairy products and yeast. In two small trials (23,24), remission rates in patients on elimination diet did not appear to be significantly better than the level in patients on unrestricted diet. Therefore, studies on elimination diets in CD so far have produced equivocal outcomes. Elimination diets are difficult to follow up as such studies often have a high drop-out rate and patients seem to have difficulty in identifying foods that trigger symptom exacerbation or take those with favourable effects.

Probiotics

It is now widely acknowledged that the intestinal bacterial flora together with genetic predisposing factors significantly contribute to the immunopathogenesis of IBD as reflected by mucosal immune dysregulation. Recently, there has been an increased interest in nutraceutical therapies, including probiotics, prebiotics or a combination of these called synbiotics as therapeutic options for patients with UC, CD and pouchitis (25–27). A number of clinical trials (28–34) reported that probiotics like Escherichia coli Nissle 1917, VSL#3, Lactobacillus GG and bifidobacteria-fermented milk have shown some benefit in inducing and maintaining remission of UC. However, the Cochrane review (25) on the efficacy of probiotics for induction of remission in UC concluded that conventional therapy combined with a probiotic did not improve the overall remission rate in patients with mild to moderate UC. Therefore, there is limited evidence in favour of adding probiotics to standard therapy in patients with mild to moderately severe UC. Likewise, whether or not probiotics are effective in patients with severe and extensive UC, or can be used as an alternative to existing therapies is yet to be shown (25). Probiotics were reported to be efficacious in the prevention and treatment of pouchitis in UC (35–38). Several studies (39–42) found that Saccharomyces boulardii, Lactobacillus GG and VSL#3 were useful in inducing and maintaining remission of CD as well. However, other studies (43–47) failed to observe any benefit. The Cochrane review (26) assessed the efficacy of probiotics for induction of remission in active CD. However, only a small study (n = 11) (45) was included in their review. The analysis did not show any clinical benefit for probiotics in patients with active CD. Another Cochrane review (27) investigated the efficacy of probiotics for maintenance of remission in patients with quiescent CD. Seven small studies (40,41,43–46,48) were reviewed, but there were significant disparities in the type of probiotics, methodology and medication regimens. Therefore, the studies were not pooled for statistical analysis. There was no significant benefit of Escherichia coli Nissle for reducing the risk of relapse as compared to placebo (relative risk [RR] 0.43, 95% CI 0.15 to 1.20) (43), or Lactobacillus GG after surgically-induced remission (RR 1.58, 95% CI 0.30 to 8.40) (44) or medically-induced remission (RR 0.83, 95% CI 0.25 to 2.80) (45). Cochrane's conclusion indicated that there was no evi-

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dence suggesting probiotics are beneficial in maintaining remission in patients with quiescent CD (27). All of the reviewed studies had small numbers of patients and might have lacked statistical power to show any significant difference (27). In summary, further well designed, larger randomised controlled trials are warranted to see if probiotics benefit patients with IBD, or can be used as alternatives to current medications.

Dietary Fibre and Prebiotics

In a retrospective study (49), 32 patients with CD, treated with a fibre-rich, unrefined-carbohydrate diet had a reduced rate of hospital admission and surgeries as compared with 32 patients in the non-diet-treated group. The outcome suggested that treatment with a fibre-rich, unrefined-carbohydrate diet has a favourable effect on the clinical course of CD. Germinated barley foodstuff (GBF) is a prebiotic that effectively increases luminal butyrate production by stimulating the growth of protective bacteria. Several open-label trials have reported that oral GBF reduced clinical activity (50,51), and prolonged remission time in patients with UC (52). However, further large clinical trials are necessary to validate the efficacy of dietary fibre as prebiotics in the management of IBD.

Fish Oil Supplement

A fish oil-rich diet has been associated with elevated eicosapentanoic and docosahexanoic acids levels of the intestinal mucosal lipids in patients with IBD, while reducing the level of arachidonic acid in the lipids (53,54). Similarly, fish oil supplementation was found to reduce inflammation, the dose of anti-inflammatory drugs, and promote weight gain in patients with IBD (53,54). In one study (55), fish oil supplementation was followed by clinical improvement in patients with mild to moderate active UC, without a significant reduction in the mucosal tissue leukotriene B_4 production, as compared with placebo. Another study by Loeschke et al. (56) reported that the level of n-3 fatty acids temporarily fell without an impact on UC relapse rate, while a placebo-controlled study reported that n-3 fatty acids were effective in reducing the rate of relapse in patients with quiescent CD (57). Contrary to this finding, in two larger cohorts (58,59), treatment with omega-3 fatty acids did not reduce relapse rates in patients with CD. Therefore, there is no convincing evidence in favour of omega 3 fatty acids as maintenance therapy in CD.

ENTERAL NUTRITION

What Is Expected from Enteral Nutrition

The precise role of enteral nutrition in IBD remains to be validated. In 2006, the European Society for Parenteral and Enteral Nutrition (ESPEN) (60) published guidelines on the role of enteral nutrition in patients with IBD. Enteral nutrition (oral nutritional supplements including tube feeding) in addition to delivering normal food is indicated in undernourished patients with CD or UC to improve nutritional needs. In children with active CD, enteral nutrition is the first line therapy and should be used as sole therapy in adults, essentially when treatment with corticosteroids has complications. Likewise, during remission, an oral nutritional supplement is recommended only in steroid dependent patients with CD. In Japan, enteral nutrition is the first line therapy for both active and quiescent CD in accord with the guidelines of the Ministry of Health, Labour and Welfare (Figure 3). However, the role of enteral nutrition in CD might have changed as infliximab is currently approved for clinical application in patients with CD (61–63).

A serious limitation of enteral nutrition is inadequate patient compliance (61–64). Potential factors that

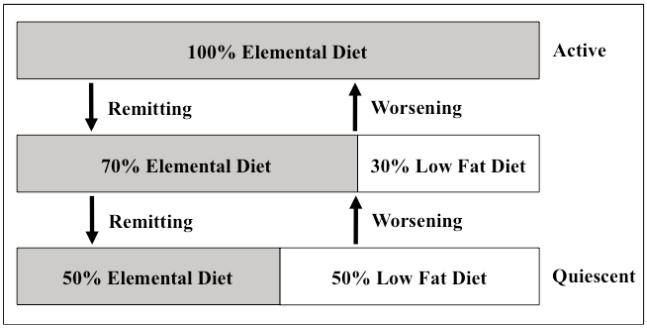

Figure 3. Enteral nutrition is a major therapeutic objective in patients with active Crohn's disease in Japan. This figure outlines the practical steps in clinical settings. Source: Yamamoto et al. (61)

militate against successful completion of enteral nutrition are poor palatability and inability to stay on a solid-free diet for a long period. It is a challenge for the enteral nutrition producing industry to provide products that are appetizing and appealing to patients. In line with this thinking, a large number of taste-enhancing flavours are now available. Additionally, the application of a nasogastric tube is useful and recommended. In clinical practice in Japan, many patients receive elemental diet by a self-inserted nasogastric tube and can continue treatment over a long period if necessary (61–64). Economic realities (the high cost of enteral formulae) may also be important considerations. In Japan, enteral nutritional therapy for CD has been covered by the national health insurance scheme. We are not aware if a similar scheme for enteral nutrition is practiced in other developed countries.

Induction of Remission in Patients with CD

Several studies compared the efficacies of different types (elemental, semi-elemental or polymeric diet) of enteral formulae in the management of active CD. A recent Cochrane meta-analysis (65) of ten trials (66–75) showed no statistically significant difference between patients treated with elemental diet (n = 188) and non-elemental diet (semi-elemental or polymeric diet; n = 146) (OR 1.10, 95% CI 0.69–1.75). Further, we are not aware of any systematic review showing one type of enteral formula being superior to others. However, the current evidence indicates that the protein composition does not influence the therapeutic potential of enteral nutrition. Given the assertions that the quantity or type of fat could influence the production of pro or anti-inflammatory factors, the fat in an enteral formula is perceived to be an important determinant of its therapeutic potential (69,74,76–78). It has been widely recognized that high-fat formulae are associated with poorer outcome, while low-fat formulae are associated with more favourable therapeutic outcomes. Additionally, fatty acid chain length is thought to influence the clinical response to an enteral formula. One study (69) suggested that long-chain triglycerides (LCTs) reduce the efficacy of enteral nutrition in patients with active CD. Similarly, a previous meta-analysis (69) of enteral nutrition trials showed a negative correlation between remission rate and LCT. However, a recent Cochrane meta-analysis (65) of seven clinical trials (66,69–74) showed no statistically significant difference between patients treated with low fat (< 20 g/1000 kcal, n = 105) and high fat (> 20 g/1000 kcal, n = 104) enteral formulae (OR 1.13, 95% CI 0.63–2.01). Similarly, a subgroup analysis carried out on four trials (66,72–74) comparing very low fat (< 3 g/1000 kcal, n = 68) and high fat (> 3 g/1000 kcal, n = 68) content demonstrated no statistically significant difference (OR 1.55, 95% CI 0.75–3.23) except that there was a weak trend favouring the very low fat formulae. Subgroup analyses (65) were performed on the basis of LCT content in feeds (in terms of percentage of total energy); the LCT content was classified as low (< 10% LCT) or high (> 10% LCT). Meta-analysis (65) of six trials (66,71,72,74,76,78) showed no statistically significant difference between patients treated with low LCT (n = 111) and high LCT formulae (n = 99) (OR 1.39, 95% CI 0.78-2.48). Further analyses using different cut-off values for LCT (5% or 15%) did not impact the results except a weak and non-significant trend favouring < 5% LCT containing diets (OR 2.07, 95% CI 0.57–7.48) (66,72,76,78). Based on these outcomes, the quantity or type of fat may not affect the therapeutic potential of enteral nutrition except a weak trend favouring very low fat (< 3 g/1000 kcal) and very low LCT (< 5%) containing diets. The possibility that the fat composition of diet renders an immunomodulatory and therapeutic effect in active CD warrants further investigations in large cohorts of patients.

Clinical Evaluations of Enteral Nutrition vs Corticosteroids

Three meta-analyses (79–81) published in the mid nineties compared the efficacies of steroids and enteral nutrition for inducing remission in patients with active CD and showed that steroids produced higher efficacy rates vs enteral nutrition. Similarly, a recent Cochrane meta-analysis (65) of six trials (77,82–86) in which 192 patients had received enteral nutrition and 160 steroids yielded a pooled OR of 0.33 (95% CI 0.21–0.53), significantly favouring steroid therapy. However, unlike

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drug trials, the difficulties in double blinding enteral nutrition led to low quality scores for the majority of trials. The only two high quality studies reported conflicting outcomes, one favouring steroid therapy (83), while the other favoured enteral nutrition (82) albeit neither showing a statistically significant difference. Combining these studies (82,83) for a subgroup analysis of 34 patients in the enteral nutrition (polymeric diet) and 35 in the steroid therapy, the OR was 1.18 (95% CI 0.37–3.70). In the full publications, there were inadequate data to carry out further subgroup analyses, factoring age, disease duration and disease location. In children with active CD, two meta-analyses (87,88) compared the efficacies of enteral nutrition and corticosteroids. An initial meta-analysis (87) found that enteral nutrition was as effective as corticosteroids in inducing remission (RR 0.95, 95% CI 0.67–1.34). A recent meta-analysis (88) factored four paediatric trials (82,89–91) comparing the outcomes of enteral nutrition (n = 73) and corticosteroids (n = 71). There was no significant difference in the remission rates between the groups (RR 0.97, 95% CI 0.68–1.40, random effect model). In the same study (88), the authors analysed four paediatric trials (92–95) (n = 190) to compare the outcomes between two enteral nutrition regimens. Although three (92,94,95) of the four trials did not show a significant difference in remission rates, one trial (n = 50) (93) found that remission rate with partial enteral nutrition (50% of energy requirement as elemental formula) was significantly lower than the outcome with total enteral nutrition (15% vs 42%).

In spite of data suggesting corticosteroid therapy produces higher efficacy rate vs enteral nutrition in inducing remission (65,79–81), the outcomes in diet studies should be interpreted with reservations. There are numerous factors that potentially can influence the efficacy of enteral nutrition, like population demography, study design, compositions of enteral formulae, route of administration, patient compliance, timing of outcome assessment and definition of remission.

Enteral Nutrition to Promote Mucosal Healing

Several studies claim that corticosteroids fail to induce mucosal healing in the treatment of CD (96,97), while small uncontrolled studies showed mucosal healing with enteral nutrition (98,99). Specifically, the latter studies (98,99) reported down regulation of mucosal pro-inflammatory cytokine profiles in both the ileum and the colon after enteral nutrition; potentially very interesting observations in respect of achieving a healthy mucosal immunity. Given that the ultimate goal in the treatment of CD is mucosal healing (in addition to symptomatic improvement) (100), this advantage of enteral nutrition over corticosteroid is valuable in therapeutic decision making.

Enteral Nutrition as Maintenance Therapy in Patients with Quiescent CD

Enteral nutrition is intended for inducing remission as well as for maintenance therapy to sustain remission in patients with CD. Accordingly, there have been several studies assessing the efficacy of enteral nutrition for maintenance of medically (101–109) or surgically (110–112) induced remission. However, among these, only two studies (105,108) had randomised controlled design; most were not even prospective. Therefore, in a recent Cochrane systematic review (113), the authors included the only two randomised trials (105,108), and presented the outcome in the individual study, but pooled statistical analysis was not possible because there was significant disparity between the studies. Four prospective trials (one randomised (105) and three non-randomised (104,107,112)) compared maintenance of remission between patients who received enteral nutrition (elemental diet) and those who did not (Table 2). In these studies, patients used enteral nutrition as a supplement (104,105) or as a nocturnal tube feeding (105,107,112) in addition to their routine food. In Japan, three studies treated patients with "half elemental diet" (approximately half of the calories from the elemental diet and the other half from low fat food (< 30 g/day) (107,112) or unrestricted food (105). In all of these studies (104,105,107,112), the clinical remission rate was significantly better in patients who had been treated with elemental diet, and notably, in one of these studies (107), elemental diet therapy was associated with an improvement of the endoscopic disease activity index. In another study (112), after resection, endoscopic recurrence rate was significantly lower in patients who were given enteral nutrition as

Table 2.
Four prospective trials compared maintenance of remission between patients who received enteral nutrition (EN group) and those who did not (Non-EN group)

Author	*Outcomes*	
Verma et al. (104)	EN group (n = 21) Clinical remission rates at 1 year 48% P<0.0003 (on an intention-to-treat basis)	Non-EN group (n = 18) 22%
Takagi et al. (105)	EN group (n = 26) Crude clinical remission rates 65.4% P = 0.03 (on an intention-to-treat basis) Cumulative clinical remission rates: Significant (P not reported)	Non-EN group (n = 25) 36.0%
Yamamoto et al. (107)	EN group (n = 20) Clinical remission rates at 1 year 75% P = 0.03 (on an intention-to-treat basis) Cumulative remission rates: P = 0.01 by the log-rank test	Non-EN group (n = 20) 35%
Yamamoto et al. (112) Post-operative setting	EN group (n = 20) Clinical remission rates at 1 year 95% P = 0.048 Endoscopic remission rates at 1 year 70% P = 0.027	Non-EN group (n = 20) 65% 30%

compared with patients who were not given. Additionally, the mucosal cytokines (interleukin [IL]-1b, IL-6 and tumour necrosis factor [TNF]-a) levels significantly increased with time in patients who were not given enteral nutrition, but not in those who were given (107). This observation suggested that enteral nutrition may alleviate mucosal inflammation, and this effect should promote better remission outcome. However, although the evidence level is not striking, the available data are in favour of enteral nutrition for maintaining remission in patients with CD. Needless to say that large randomised controlled trials are necessary if one is to obtain a solid efficacy outcome with enteral nutrition in the maintenance of remission. Such outcome could reduce the use of corticosteroids and other immunosuppressive drugs, which often are associated with serious adverse side effects.

CONCLUDING REMARKS

Identifying dietary constituents as risk factors or otherwise as remission inducers should be of major clinical interest as such information can help to evade a relapse and spare pharmacologic preparations routinely used to induce remission in patients with IBD. Among various dietary modifications or supplements as therapeutic formulae, as yet, there is none showing convincing efficacy. Looking at enteral nutrition, the clinical benefit of this practice in the management of patients with active CD has been realised in several studies. However, a number of meta-analyses showed that enteral nutrition was inferior to corticosteroids, particularly when assessed on an "intention-to-treat" basis, but corticosteroid adverse effects can be a serious concern. Although the evidence level is not striking, the available data are in favour of enteral nutrition

for maintaining remission in patients with CD. Further well designed large trials are necessary to support the current knowledge on enteral nutrition including long-term benefits of these interventions. ■

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