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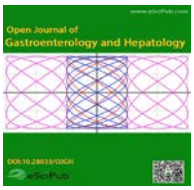

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Significance of nutritional treatment for patients with inflammatory bowel disease in the era of biologics

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ABSTRACT

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease (CD), is a chronic gastrointestinal tract inflammatory disorder. Although its etiology remains unknown, it has been reported that nutrition is involved in the onset of IBD. Patients with IBD often experience malnutrition due to malabsorption and increased energy requirements. Malnutrition is a serious issue for patients with IBD, especially in young people. Growth retardation characterized by delayed skeletal maturation and onset of puberty is a representative complication. In addition, immunosuppression, osteoporosis, and sarcopenia are important issues. Functional foods and diets have been known to alleviate gastrointestinal inflammation by modulating inflammatory cytokines. Furthermore, appropriate nutritional treatment has been reported to be effective on the induction and maintenance of remission in patients with IBD, especially with CD. Conversely, there are negative reports regarding the efficacy of nutritional therapy in patients with IBD. Recently, various new therapeutic agents such as biologics have emerged as key drugs in IBD treatment. In this new era, the efficacy of nutritional treatment, including combination therapy with biologics, should be reconsidered to improve the quality of life in patients with IBD. In this review, the nutritional treatment for patients with IBD is reviewed, and the latest evidence is provided.

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Keywords: Inflammatory bowel disease; ulcerative colitis; Crohn's disease; nutrition; biologics

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INTRODUCTION

Inflammatory bowel disease (IBD) is a disorder characterized by chronic gastrointestinal inflammation and mainly divided Crohn's disease (CD) and ulcerative colitis (UC). Its etiology remains unknown; however, genetic, environmental, and microbial factors are believed to be relevant to complex immune responses[1,2].

IBD is not curable and recently occurs more commonly at a young age. Several complications, such as delayed skeletal maturation and onset of puberty, occur in association with chronic inflammation[3]. Moreover, they often need surgery because of intestinal stenosis, perforation, and invalid medical treatment that impaired their quality of life. Thus, patients with IBD need appropriate treatment to prevent such complications. The 5-aminosalicylic acid (5-ASA) and steroids were classically used, but it has dramatically changed due to the advent of biological agents, which have continued the remission and have reduced the rate of surgical treatment[4].

Along with the increasing use of biological agents, nutritional treatment also changes the position of patients with IBD although it remains a safe, an effective, and an important clinical management for patients with IBD[5], especially in children who require normal development.

The incidence of IBD has been increasing continuously worldwide, especially in Western and Asian countries[6,7]. Therefore, it is important to understand the effectiveness of nutritional treatment for IBD and to seek clinical help. The present review focuses on the significance of nutritional treatment for patients with IBD in the era of biologics.

Pathogenesis of IBD

The definite cause of IBD remains to be determined. Its pathogenesis is thought to involve genetic predisposition[8], environmental factors such as sanitary condition or food changes, and host immune response to food antigens and microbiota. Recently, the relationship between host immunity and microbiota has been progressing dramatically due to the improvement of intestinal immunology and bacteriology. Intestinal bacteria is in harmony with the host, to exert various effects, such as the production and digestion of foods and nutrients. Aside from environmental factors such as drugs, smoking, and infection, several factors have been found to influence the composition of the intestinal flora[9]. Diet affects the composition of the gut microbiota and serves as a substrate for microbial synthesis of metabolites[10], which contribute to the change of the mucosal immune system. For example, dietary protein, particularly from meat, may increase the release of marked quantities of branched chain fatty acids and compounds such as ammonia, phenols, and nitric oxide, in addition to sulfide compounds that may have toxic effects on the mucosal epithelium[11]. Dietary fat from meat such as n-6 polyunsaturated fatty acid (PUFA) may increase the release of arachidonic acid that may be incorporated in the cell membrane and metabolized to pro- and anti-inflammatory

eicosanoids[12]. Specific amino acids, such as glutamine and arginine, are thought to be immunomodulatory and might be involved in mediating responses to metabolic stress, such as in inflamed intestines[13]. Other nutrients, such as vitamin D and fiber, are thought to be involved in the pathogenesis of IBD[14,15]. The gut microbiota is involved greatly in T-cell differentiation[16], and while intestinal mucosa is exposed constantly to intestinal bacteria and dietary antigens, intestinal tract macrophages contribute to the maintenance of homeostasis[17-19]. Dysbiosis changes the microbial function, by decreasing the metabolism of butyric acid, butanoate, and propanoate and increasing the oxidative stress, toxin secretion, amino acid, and sulfate transport[20-22] (Figure 1).

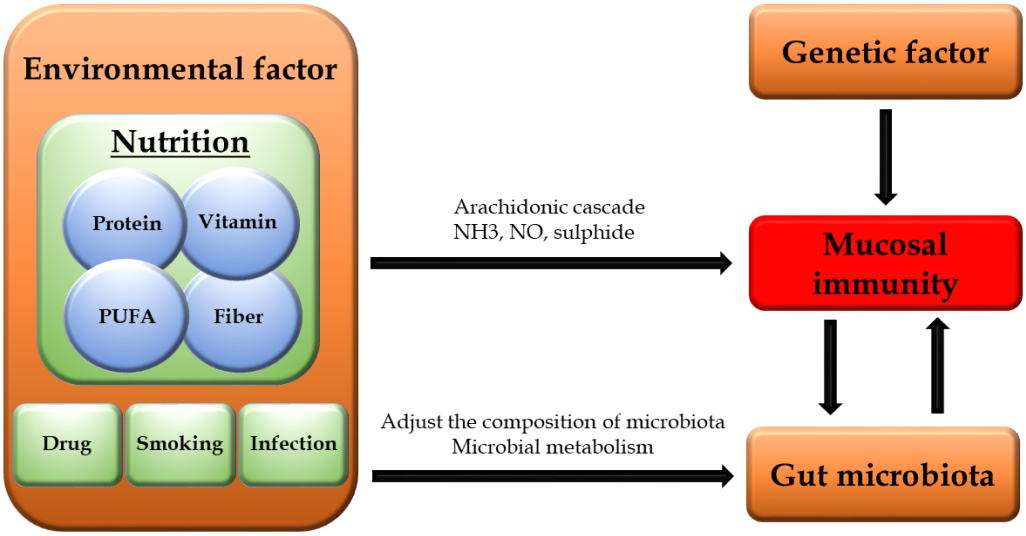

Figure 1 Relationship between IBD pathology and nutrition. Environmental factors, including nutrition, genetic factor, and gut microbiota are greatly involved in the onset of IBD. PUFA: polyunsaturated fatty acid, NO: nitric oxide

Nutritional issue in IBD

Malnutrition is common especially in pediatric patients with IBD. Clinical symptoms such as abdominal pain, diarrhea, and fever reduce the dietary intake, and catabolism is accelerated. Additionally, it causes protein leakage from digestive and absorption disorders such as lipids and trace elements and from erosions and ulcers during the active phase. Altered energy and nutritional requirements, malabsorption, and increased gastrointestinal losses are additional factors[23].

(1) Growth failure

Delayed puberty and growth failure are additional features that complicate the clinical management further in pediatric patients with IBD. Approximately one-third of children with CD have growth retardation at diagnosis[3]. Cytokines produced by chronic inflammation reduce the sensitivity of growth hormone, thereby suppressing the IGF-1 expression and further reducing the function of bone cells.

Growth failure is greater due to worsened CD than due to steroid use[24]. Suboptimal nutritional intake is the main determinant of undernutrition, although activation of the immune system and secretion of proinflammatory cytokines exert additional independent effects.

(2) Anemia

Anemia is a common manifestation of patients with IBD. Iron deficiency anemia primarily occurred due to gastrointestinal tract bleeding and iron malabsorption, followed by anemia due to chronic diseases[25]. In a population-based cohort study, the incidence rate of anemia was 19.3 per 100 person-years with the prevalence of 28.7% in CD, compared with 12.9% and 16.5% for UC. In CD, anemia was associated with both increased risk and worse outcomes[26]. Regarding the treatment of anemia, the effectiveness of iron supplementation has been confirmed. According to a systematic review, intravenous iron supplementation is considered effective when rapid correction of anemia occurred, and if it is mild anemia, oral intake is considered adequate [27]. Vitamin B12 and folate deficiency are caused by malabsorption and deficiencies in vitamin B12 and folate that can lead to macrocytic anemia[28].

(3) Osteopenia

Bone loss and osteopenia have been found, which are potentially caused by malnutrition, poor calcium intake or absorption, and use of corticosteroids[29]. The prevalence of osteoporosis in pediatric patients with IBD is approximately the same as in adult patients and already present before steroid treatment[30]. A small number of studies list CD (rather than UC) and vitamin D deficiency as risk factors of osteopenia and osteoporosis[31]. Male sex and low BMI were associated with increased risk for metabolic bone disease in IBD[32].

(4) Sarcopenia

Approximately half of the patients with IBD are sarcopenic, who are mostly normal or overweight and would not be identified as malnourished by traditional measures[33,34]. Sarcopenia is a predictor of surgery[33,35,36] and is also a predictor of osteopenia in patients with IBD[37]. A retrospective cohort study has suggested that low muscle mass at the induction of an anti-TNF agent is a risk factor for treatment failure[38].

(5) Vitamin and mineral deficiency

Fat-soluble vitamins such as vitamins A and D play protective roles against the pathogenesis of IBD. Accumulating evidence suggests that patients with IBD are frequently diagnosed with low levels of fat-soluble vitamins, and, therefore, specific supplementation of these vitamins are often recommended[39]. Patients with IBD require vitamin D because it is involved in anti-inflammatory pathways. Vitamin D promotes epithelial cell resistance to injury and suppresses inflammatory response to luminal antigens. Ananthakrishnan et al.[40] showed that predicted levels of prediagnosis plasma 25 (OH) D are associated with significant reduction in the risk of developing CD and not significant reduction in the risk of UC. Garg et al.[41] revealed that vitamin D supplementation was associated with reduced intestinal inflammation in patients with active UC. Additionally, they reported that oral vitamin D intake improved symptom-based activity scores. Continuous diarrhea decreases serum magnesium and potassium levels. Magnesium deficiency complicates electrolyte abnormalities such as hypocalcemia, hypophosphatemia, and hypokalemia. Oral supplementation is necessary while measuring blood concentration. Furthermore, zinc deficiency occurs due to diarrhea. Approximately 15% of patients with IBD have zinc deficiency[42], characterized by

facial rashes, glossitis, hair loss and delayed wound healing. Zinc deficiency may be diagnosed as a result of taste disorder. Recent studies suggest that zinc deficiency is a risk factor for hospitalization, surgery, and complications in patients with IBD[43].

Nutritional treatment in IBD

(1) Enteral nutrition

Nutritional treatment was gradually accepted as internal medicine treatment for CD since the total parenteral nutrition (TPN) was reported in 1973 and elemental diet (ED) in 1980. The European pediatric CD treatment guideline also recommends complete EN therapy as the first choice of induction therapy for patients with active CD[44]. ED could involve reductions in luminal antigens and food exclusion, direct anti-inflammatory effects of the formula, improved nutrition, or changes to the gut microbiota[45,46]. Multiple clinical trials for EN have been reported (Table 1), particularly in the induction treatment for CD[47-67]. Comparative studies of EN with steroids and polymeric diets have been conducted from 1980 to 1990, and it has been reported that it has the same effect as steroids, especially in induction therapy for children. Several reports have also been made on CD maintenance therapy[68-77]. Takagi et al.[70] showed that half of ED cases had sufficient effects in a randomized controlled trial (RCT). They randomly assigned 51 patients with CD remission who received 900 to 1,200 kcal in ED and the control group freely eat meals, and the cumulative relapse rate was also examined. Then, during the average observation period of 11.9 months, the relapse rate of the half ED group was 34.6% only, whereas the control group was significantly higher at 64.0%, and by performing half ED, the hazard ratio of CD relapse was suppressed to 0.40. Esaki et al.[69] reported that 98 patients with CD remission receiving nutritional therapy for more than 1,200 kcal days had a significantly lower cumulative relapse rate than 47 patients receiving <1,200 kcal days. Not only ED but also fat digestive and semi-digestive nutrition have been confirmed to be comparable to ED, and the nutritional choices also expanded. There is also some report on the effectiveness of EN for perioperative period[78-81], and it has been suggested to reduce postoperative complications and reoperation rate. There are few reports on EN of UC[53,82], only comparison with TPN and Case series study, but both are only valid and have not been established as evidence. Meanwhile, the basic therapeutic agent for IBD is salazopyrin and steroids[83-85], and drug therapy is evolving further. In addition, infliximab (IFX), an anti-TNFα preparation, was formulated in 1993[86], followed by adalimumab and golimumab[87,88]. Recently, many other biological products with other mechanisms of action have been developed[89-91], and treatment options are expanding.

In this biologics era, the position of EN therapy has also changed. Recently, the combination use of anti-TNFα agents and EN therapy has been studied[92-100] (Table 2). Hirai et al.[96] reported that EN combination group had better cumulative remission maintenance rate than IFX alone group in their retrospective analysis of

patients with CD who received remission maintenance IFX therapy. Kamata et al.[97] reported that IFX effects on the reduction rate were low in the EN therapy combination group. Nguyen et al.[98] demonstrate that a combination of infliximab and EN is more effective at inducing and maintaining clinical remission among patients with CD than infliximab alone in a meta-analysis. Recently, it has also been reported with respect to efficacy of EN against loss of response to anti-TNFα agents[95,99,100].

Table 1 Clinical trials on enternal nutrition

Author/Reference	Year	Patient	Study method	Study design	Endopoint	Outcome
Induction for CD						
Harries [47]	1983	CD	Prospective	EN vs. ordinary diet	Disease activity, nutritional status	Effective
O'Morain et al [48]	1984	Mild-Moderate CD	RCT	EN vs. steroids	Simple activity index at 4 and 12 weeks	Effective
Giaffer et al [49]	1990	Moderate CD	RCT	EN vs. polymeric diet	Clinical remission rate at 10 and 28 days	Effective
Lochs et al [50]	1991	Mild-Moderate CD	Prospective	EN vs. combination of 6-methylpredonisolone and sulfasalazine	CDAI at 6 weeks	Not effective
Rigaud et al [51]	1991	Mild-Moderate CD	RCT	EN vs. polymeric diet	CDAI at 14, 21 and 28 days	Effective
Lindor et al [52]	1992	CD	RCT	EN vs. Steroids vs. EN+Steroids	Remission rate at 1 month	Not effective
Gonzales-Huix et al [53]	1993	Moderate-Severe UC	RCT	EN vs. TPN	Remission rate, surgical rate, and adverse effects	Effective
Gorard et al [54]	1993	Mild-Moderate CD	Prospective	EN vs. steroids	CDAI and laboratory data at 4 weeks	Effective
Fernandes et al [55]	1995	CD	Meta-analysis	EN vs. steroids or nonelemental diets	Clinical remission rate	Not effective
Griffiths et al [56]	1995	CD	Meta-analysis	EN vs. steroids or nonelemental diets	Clinical remission rate	Not effective
Zoli et al [57]	1997	Moderate CD	RCT	EN vs. steroids	Simple activity index at 2 weeks	Effective
Heuschkel et al [58]	2000	Child CD	Systematic review	EN vs. steroids	Remission rate	Effective
Verma et al [59]	2000	Mild-Moderate CD	RCT	EN vs. polymeric diet	CDAI	Effective
Ludvigsson et al [60]	2004	Child CD	RCT	EN vs. polymeric diet	PCDAI at 6weeks	Effective
Grover et al [61]	2014	Child CD	Prospective	EN vs. not EN	Clinical, biochemical, mucosal and transmural remission rate	Effective
Sigall-Boneh et al [62]	2014	Mild-moderate Child	Prospective	partial EN vs. not EN	Remission rate at 6 weeks	Effective

		and young adult CD				
Swaminath et al [63]	2017	Pediatric CD	Systematic review	EN vs. Steroids	Remission rate	Effective
Yang et al [64]	2017	CD with complications	Prospective	EN vs. not EN	CDAI at 12weeks	Effective
Luo et al [65]	2017	Pediatric CD	Prospective	EN vs. IFX	PCDAI at 8weeks	Effective
Connors et al [66]	2017	Pediatric CD	Retrospective	EN vs. Steroids	PDAI during 4-12 weeks, avoidance of steroids over 6 years	Effective
Narula et al [67]	2018	CD	Systematic review	EN vs. not EN	Clinical remission	Effective
Maintenance for CD						
Wilschanski et al [68]	1996	Child CD	Retrospective	EN vs. not EN	Time to relapse and linear growth	Effective
Esaki et al [69]	2006	Remission CD	Retrospective	EN vs. not EN	Recurrence rate	Effective
Takagi et al [70]	2006	Remission CD	RCT	Half EN vs. not EN	Relapse rate over the 2-year period	Effective
Yamamoto et al [71]	2010	Remission CD	Systematic review	EN vs. not EN	Clinical or endoscopic relapse	Effective
Hanai et al [72]	2012	Remission CD	Prospective	EN vs. 6-mercaptopurine	Relapse rate (CDAI≧200) for 2 years	Effective
Duncan et al [73]	2014	Remission, pediatric CD	Retrospective	EN vs. not EN	Remission rate at 1 year	Effective
Grover et al [74]	2015	Pediatric CD	Retrospective	EN vs. Steroids in thiopurine	Steroid dependency, need for IFX, linear growth, surgical resection over 2 years	Effective
Kang et al [75]	2015	Severe pediatric CD	Prospective	short-term partial EN vs. not EN	Nutritional status and CDAI at 1 year	Effective
El-Matary et al [76]	2017	Remission CD	Systematic review	EN vs. not EN	Relapse rate	Effective
Akobeng et al [77]	2018	CD	Systematic review	EN vs. not EN	Clinical or endoscopic relapse	Not effective
Perioperative period for CD						
Ikeuchi et al [78]	2004	Postoperative CD	Retrospective	EN vs. not EN	Reoperation rate	Effective
Yamamoto et al [79]	2007	Postoperative CD	Prospective	EN vs. not EN	Endoscopic recurrence at 6 and 12 months	Effective
Wang et al [80]	2016	Preoperative CD	Prospective	EN vs. not EN	Postoperative complication	Effective
Brennan et al [81]	2018	Preoperative CD	Meta-analysis	EN vs. TPN	Postoperative complication	Effective
Induction for UC						
Gonzales-Huix et al [82]	1993	Moderate-Severe UC	RCT	EN vs. TPN	Remission rate, Surgical rate, Adverse effects	Effective
Klaassen et al [83]	1998	Severe UC	Prospective	EN case series study	Tolerance, laboratory data	Effective

CD: Crohn's disease, EN: enteral nutrition, RCT: randomized controlled trial, CDAI: Crohn's disease activity index, UC: ulcerative colitis, TPN: total parenteral nutrition, PCDAI: pediatric Crohn's disease activity index, IFX: infliximab

Table 2 Clinical trials on enternal nutrition combined with anti-TNFα agents

Author/Reference	Year	Patient	Study method	Study design	Endopoint	Outcome
Matsumoto et al [93]	2005	CD	Retrospective	IFX + EN vs. IFX + TPN vs. IFX	CDAI at 2 weeks	Not effective
Tanaka et al [94]	2006	CD	Retrospective	IFX + EN vs. IFX	HBI at 16 weeks	Effective
Yamamoto et al [95]	2010	CD	Prospective	IFX + EN vs. IFX	Clinical remission rate (CDAI < 150)	Not effective
Sazuka et al [96]	2012	CD	Retrospective	IFX + EN vs. IFX	Rate of LOR	Effective
Hirai et al [97]	2013	CD	Retrospective	IFX + EN vs. IFX	Remission rate (CRP < 0.3mg/dl)	Effective
Kamata et al [98]	2015	CD	Retrospectve	IFX + EN vs. IFX	Sustaining IFX maintenance therapy	Effective
Nguyen et al [99]	2015	CD	Meta-analysis	IFX + EN vs. IFX	Inducing and maintaining clinical remission	Effective
Sugita et al [100]	2018	CD	Prospective	ADA + EN vs. ADA	Non-ADA-LOR rate	Effective
Hisamatsu et al [101]	2018	CD	Prospective	IFX + EN vs. IFX	Retention rate of IFX dose escalation therapy at 56 weeks	Effective

CD: Crohn's disease, IFX: infliximab, EN: enteral nutrition, TPN: total parenteral nutrition, ADA: adalimumab, CDAI: Crohn's disease activity index, HBI: Harvey-Bradshaw Index, LOR: loss of response

(2) Parenteral nutrition

Since dietary antigens may be important stimulants for the mucosal immune system, bowel rest with TPN has been considered as a therapeutic option for patients with IBD. In malnutrition cases, TPN is selected first in a patient with frequent diarrhea, extensive small intestinal lesions, severe stenosis of the intestinal tract, slimming or abscess, and when massive bleeding occurs. Given the complications due to central venous puncture and subsequent management complications, EN therapy should be transferred as soon as possible. TPN as a primary therapy aimed to achieve bowel rest, to correct nutritional deficits, and to remove antigenic mucosal stimuli[101]. Various studies have analyzed the effects of TPN, which was used to treat patients with moderate-to-severe CD especially in the 1980s[102-106] (Table 3). Muller et al.[103] prospectively evaluated the effects of TPN in 30 patients with CD, whereby 83% achieved remission, but relapse was common. Surgery could be avoided in 25 of 30 patients with complicated CD on 3 weeks of inpatient TPN, followed by 9 more weeks at home. Ostro et al.[104] evaluated the effects of TPN in 100 patients with CD refractory to conventional medical management. In their study, 90 patients received complete nutrient replacement and 10 received protein-sparing therapy and 77 achieved clinical remission. Greenberg et al.[106] compared the effects of TPN, partial parenteral nutrition (PPN) with supplementary nutrition with a defined formula via NG tube, or PPN with supplementary normal diet. No significant differences were observed in the remission rates of 71% in the TPN group, 58% in the PPN with defined formula diet group, and 60% in the group with PPN and normal diet. Additionally, TPN was shown to play a role in the postoperative healing of enterocutaneous fistulas arising from surgical anastomosis or complicated fistulas in patients with CD[107]. When comparing TPN and EN, TPN

is associated with higher costs and significant risks such as infection and should be restricted to patients who cannot take adequate nutrition enterally[108,109].

There are two short-term studies about TPN with severe acute UC, but the results were no effect[102,105].

Table 3 Clinical trials on total parental nutrition

Author/Reference	Year	Patient	Study method	Study design	Endopoint	Outcome
Dickinson et al [103]	1980	UC and CD	Prospective	TPN vs. not TPN	Surgical rate and response rate	Not effective
Muller et al [104]	1983	CD	Prospective	TPN case series study	Recurrence rate	Not effective
Ostro et al [105]	1985	CD	Retrospective	TPN vs. not TPN	Remission rate	Effective
McIntyre et al [106]	1986	UC and CD	RCT	TPN vs. not TPN	Operation rate, mortality rate, and surgical rate	Effective (only surgical rate in CD)
Greenberg et al [107]	1988	CD	RCT	TPN vs. EN vs. PPN	Remission rate	Not effective

UC: ulcerative colitis, CD: Crohn's disease, RCT: randomized controlled trial, TPN: total parenteral nutrition, EN: enteral nutrition, PPN: partial parenteral nutrition

Dietary treatment

As a basis of dietary treatment in IBD, high energy, high vitamin and mineral, and low-fat meals are recommended to efficiently improve the protein and energy malnutrition while resting the intestinal tract. In CD, low-fat diets and low-residue foods are the bases; however, evidence regarding the type and dose of adequate fat and dietary fiber remains unclear.

(1) Fatty acid

High fat diets have been shown to increase the severity of colitis in mice, while plant polysaccharides and resistant fiber plant components have been shown to reduce UC symptoms. It is believed that the mechanism increases the production of short-chain fatty acids and increases the barrier function by serving as an energy source for intestinal mucosa. Butyrate (BT) especially regulates innate and adaptive immune cell generation and function. BT has an anti-inflammatory effect by inhibiting the recruitment and proinflammatory activity of neutrophils, macrophages, dendritic cells, and effector T cells and by increasing the number and activity of regulatory T cells. Gut microbial dysbiosis has reduced BT concentration that is linked to a marked increase in the number of proinflammatory immune cells in the gut mucosa in patients with IBD. The anti-inflammatory effect of BT includes inhibiting the recruitment and proinflammatory activity of neutrophils, macrophages, dendritic cells, and effector T cells and increasing the number and activity of regulatory T cells. Therefore, gut microbial dysbiosis has been shown to reduce BT concentration that is linked to a marked increase in the number of proinflammatory immune cells in the gut mucosa in patients with IBD[110,111]. High intake of dietary n-3 PUFA is associated with decreased risk of UC and CD[112,113]. A case-control study has suggested that the association between dietary n3: n6 PUFA intake and risk of UC may be modified variants at CYP4F3. High n3: n6 PUFA intake was associated with reduced risk of UC in individuals with GG/AG genotype at a single

nucleotide polymorphism in CYP4F3[114]. Barnes EL et al.[115] reported that increased intake of multiple fatty acids was associated with increasing odds of relapse and specific fatty acids, i.e., myristic acid (commonly found in palm oil, coconut oil, and dairy fats) that may associate with an increasing risk of flare. n-6 fatty acids found in the fat oils of beef, pork, and poultry are limited because they will exacerbate inflammation, whereas those found in fish oil tend to reduce inflammatory leukotrienes and exert anti-inflammatory action. A RCT found no effects on n-3 fatty acid supplementation during the 1 year prevention of CD relapse[116], whereas other studies found it to be associated with absence of CD relapse[117].

(2) Amino acids

Amino acids have been reported to have an anti-inflammatory effect on intestinal inflammation animal model, with glutamine as the most common. The effects of glutamine on enteritis were confirmed by its oral administration to trinitrobenzenesulfonic acid-induced enteritis rats[118] and dextran sulfate sodium (DSS)-induced enteritis rats[119]. Its scavenger effect on intestinal epithelial cells, improvement of barrier function, and inhibition of local inflammatory cytokine production are considered as the mechanism of action. Biogenic amines such as histamine, an important regulator of physiological gut functions, might also affect the immune response in patients with IBD. Histamine is derived from the amino acid histidine, and dietary histidine can reduce symptoms of immune-mediated colitis in mice. Andou et al.[120] revealed that histidine suppresses the production of TNFα from macrophages through NF-κB signal suppression. Tryptophan is a precursor of an immunomodulating biogenic amine that promote T-regulatory cells development and immune tolerance. Additionally, threonine could enhance barrier function by enhancing the production of intestinal mucus. Tryptophan and threonine supplements have been shown to reduce colitis symptoms in mice. Glycine has been reported to inhibit the production of local inflammatory cytokines and chemokines against DSS-induced enteritis rats, thereby preventing the progression of enteritis[121].

(3) Specific-carbohydrate diet

Certain carbohydrate diets, involving strict restriction of cereals, most dairy products, and refined sugars, are of interest in the medical community, but has not been widely studied. Evidence on the role of poorly absorbed short-chain carbohydrates on gastrointestinal symptoms increased in the 1980s. These incompletely absorbed carbohydrates and polyols are summarized in the term FODMAPs, which is an acronym that stands for: Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols[122]. FODMAPs can also induce gastrointestinal symptoms when fermented by intestinal bacteria and produce large amounts of gas[123,124]. Several trials have demonstrated the effects of FODMAP-reduced diet for the treatment of irritable bowel syndrome (IBS)[125]. As patients with IBD experienced IBS-like symptoms, a FODMAP-reduced diet might also be a therapeutic option[122,126].

(4) Prebiotics

Prebiotics are indigestible foods that selectively promote the growth of effective gut bacteria and promote the host's health status. Some oligosaccharides and dietary fibers are food ingredients qualified as prebiotics, such as the growth promoting effects of *Lactobacillus* and *Bifidobacteria*[127]. Dietary fiber undergoes fermentation by the intestinal bacteria and produces SCFAs such as BT and propionic acid acetate and becomes an energy source of mucosal epithelial cells and small intestine villi, activating specific intestinal bacteria. Dietary fiber intake stimulates the intestinal tract by promoting secretion of intestinal motility and digestive juice, which can cause symptoms such

as diarrhea and abdominal pain. Therefore, low residual food has been recommended in patients with IBD. However, as its physiological effects become apparent, the views on dietary fiber for patients with IBD have also changed. For UC, Mitsuyama et al.[128] reported the clinical utility by administering a powder derived from malt rich in glutamine and dietary fiber to mild-to-moderate UC.

Heaton et al.[129] restricted intake of refined carbohydrates against CD; CD patients who ingested diet rich in dietary fiber such as raw vegetables and fruits had shorter hospitalization for patients with CD who ingested low residual food. In addition, Ananthakrishnan et al.[130] reported that long- term intake of dietary fiber, particularly from fruit, is associated with risk of CD but not UC. On the other hand, Levenstein et al.[131] divided the patients with CD without stenosis into low residual food group and normal food group, including fresh vegetables and fruits; there was no difference in symptoms, need for hospitalization, complication, nutritional status, and recurrence after surgery. Although it should be avoided when there is active lesion or stenosis, intake of dietary fiber is useful for improving the patient's quality of life.

(5) Probiotics

Probiotics are defined as live bacteria showing beneficial effects on the host when ingested at an appropriate amount; the most common are *Lactobacillus* and *Bifidobacteria*. Probiotics can reduce harmful microorganisms and maintain the microbial balance inside the gut by blocking the site of adhesion, competing for nutrients, and killing pathogenic microorganisms[132]. In addition, probiotic bacteria can function as anti-inflammatory agents by modulating the NF-κB signaling pathway, inflammatory cytokines, and regulatory T-cell response[133]. VSL#3 is as a probiotic with UC remission induction effect[134,135]. In patients with mild-to-moderate UC, VSL#3 is said to have some effects on reducing the disease activity[136]. Takeda et al.[137] reported immunoregulatory effect of Bifidobacterium longum in UC. In addition, it was demonstrated that Bifidobacterium longum 536 (BB536) improves UC disease activity index, endoscopic index, and Mayo subscores in a randomized controlled trial[138]. Taken together, some probiotics could be a therapeutic option in IBD treatments.

CONCLUSION

Enternal and parenteral nutrition for patients with IBD is effective in some condition. Several food components such as vitamin D, n-3 PUFA, and amino acids have been effective in treating gastrointestinal inflammation and modulating factors involved in the pathogenesis of IBD. Functional foods can modulate inflammatory cytokines and can interact with the immune system to produce anti-inflammatory functions against IBD. Furthermore, probiotics and prebiotics have anti-inflammatory effects against IBD. Based on these clinical data, nutritional treatment may induce and maintain remission especially in patients with CD. On the other hand, its evidence in UC remains unclear.

In recent years, biologics have appeared one after another and medical treatment in IBD has

been diversified. However, we are required to recognize the importance of the nutritional and dietary treatment once again in the era of biologics, and to accumulate further evidence in the future.

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