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Nutritional approach as therapeutic manipulation in inflammatory bowel disease

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Malnutrition is observed more frequently in patients with inflammatory bowel disease (IBD) than in the general population and associated with adverse clinical outcomes. This study aimed to review the current knowledge regarding the efficacy of dietary and nutritional intervention in IBD patients. Exclusive enteral nutrition might be inferior to corticosteroid treatment in adults with active Crohn's disease (CD) but might even be superior considering the adverse effects of corticosteroid treatment in children. Total parenteral nutrition has no advantage over enteral nutrition, which is considered a more physiologic modality in organ function. Current guidelines do not yet recommend ω3-polyunsaturated fatty acid supplementation for the prevention and maintenance of remission in IBD patients. Dietary fiber supplementation could be effective in the relief of symptoms and maintenance of remission in ulcerative colitis (UC). Although vitamin D may be favorable to clinical course of IBD and bone density. Probiotic supplementation has proven to be effective in preventing and treating pouchitis for UC but is less effective in treating CD. Nutritional interventions not only correct nutritional deficiencies but also improve symptoms and clinical courses of the disease. Hence, nutritional approaches need to be developed to significantly evaluate the effectiveness of dietary interventions used to treat IBD. **(Intest Res 2019;17:463-475)**

Key Words: Nutrition; Crohn disease; Colitis, ulcerative; Inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory disorder of the GI tract. Although the exact pathophysiology of IBD remains unknown, it has been widely acknowledged that multifactorial etiologies including interaction between genetic and environmental factors can contribute to its pathogenesis. Regarding environmental factors, accumulating data have proven that various nutritional components in diet can play a significant role in the development and clinical course of IBD.[1,2] Dietary nutrients alter the composition of the gut microbiota and intestinal permeability, influencing the interaction between the host and gut microbiota.[3]

Malnutrition, which refers to nutritional deficiencies or imbalances, has been observed in up to 75% of adults with active IBD and in up to 33% of those with remission status,[4,5] implying that malnutrition occurs more frequently in IBD patients than in the general population. Malnutrition in IBD is caused by poor nutritional intake due to anorexia or diet intolerance, increased energy requirements due to the presence of inflammatory conditions, GI losses, nutrient malabsorption, or interaction between nutrients and pharmaceutical agents.[6]

Malnutrition in IBD has been associated with several adverse clinical outcomes. IBD patients with nutritional deficiencies may present with higher mortality rate, length of stay in the hospital, infectious rate, and even thromboembolic events than those without nutritional deficiencies.[7,8] Furthermore, undernutrition in patients with postoperative conditions has been associated with increased complications such as anasto-

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motic leakage and breakdown, infection including sepsis and pneumonia, prolonged hospitalization, and increased mortality.[9]

Nutritional approach is important in the management of IBD patients. Nevertheless, pharmacotherapy has been the mainstay treatment of IBD. Pharmacological approach has clearly been considered a potential approach for both the induction and maintenance of clinical remission, but it could lead to adverse clinical outcomes and refractory period. Although nutritional approach has proven to be a key strategy for the successful management of IBD, most gastroenterologists pay less attention and provide little dietetic advice and nutritional education to IBD patients because of insufficient time in counseling IBD patients in routine clinical practice and the low-quality and inconclusive evidence-based nutritional recommendations that are often due to conflicting results. On the contrary, most IBD patients are interested in diet modification for the improvement of symptoms and frequently ask for nutritional advice.

This study aimed to promote awareness regarding the beneficial effects of nutritional therapy influencing the course of IBD to gastroenterologists. We will review the current knowledge regarding the efficacy of dietary and enteral intervention in IBD patients.

ENTERAL NUTRITION

Exclusive enteral nutrition (EEN) is a nutritional treatment that provides the whole nutritional requirements of patients with complete liquid formula via a feeding tube or orally. Although the complete mechanisms of EEN remain unknown, EEN is thought to be mediated by immunomodulation, reduction of intestinal inflammation, and modification of the microbiota and improvement of nutritional status.[10] EEN therapy potentially decreases systemic pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, and TNF-α associated with CD and increases circulating anti-inflammatory cytokines such as transforming growth factor β.[11,12] These systemic effects may result in a decrease in serum inflammatory markers, including CRP and ESR, which is observed prior to the improvement of measurements, reflecting nutritional condition after starting EEN.[13] Anti-inflammatory reaction induced by EEN that locally and directly affects the intestinal mucosa could lead to the restoration of epithelial barrier function, which decreases intestinal permeability and antigenic load.[14,15] EEN might alter the diversity and composition of metabolomics in the gut microbiome and consequently improve intestinal dysbiosis, which plays a potential role in the pathogenesis of CD.[16,17]

Since the 1970s, the time when EEN was initially used, there have been several studies evaluating the effect of EEN on IBD. These studies mostly demonstrated that compared with corticosteroid treatment, EEN has at least equal effects in the induction of remission and leads to better improvements in endoscopic mucosal healing during the active stage of pediatric CD.[13,18-21] Objective measures, such as body weight, lean mass, anemia, albumin, iron, several micronutrient deficiencies, and even growth marker (insulin-like growth factor 1), of nutritional status in the serum improve in EEN treatment.[22-25] Furthermore, EEN treatment instead of corticosteroid treatment in the induction period of clinical remission prevents the occurrence of various adverse effects of corticosteroid. Growth impairment and maturation failure of secondary sexual characteristic are considered as the most serious complications of corticosteroid treatment in pediatric CD. There is a significant difference in the reduction of linear growth failure between EEN and corticosteroid treatment (26% vs. 7%, $P=0.02$) following the induction in pediatric CD during a 2-year follow-up.[26] Compared with corticosteroid treatment, EEN induction therapy over a 6-year follow-up period is more effective in achieving early remission without an increased need for biologic therapy or surgical intervention.[27] The latest prospective study focusing on long-term outcomes reported that compared with those treated with corticosteroids at 78 weeks, pediatric CD patients treated with EEN had more favorable prognosis in growth status measured by reduction of mean height Z scored and better remission rate.[28] Therefore, several guidelines, including the European Crohn's and Colitis Organisation and the European Society for Parenteral and Enteral Nutrition (ESPEN), recommend EEN as the first-line treatment modality in children and adolescents with active CD.[29,30] Although the ability of EEN to induce clinical remission in CD has been established, EEN as a therapy for the maintenance of remission for a prolonged period is not yet determined and has been known to be ineffective for UC.[31]

The enteral formulas were classified as elemental (free amino acids), semi-elemental (peptides or protein hydrolyzed), and polymeric (whole proteins) according to the form of protein. The elemental formula is unnecessary to degradation and digestion prior to absorption, whereas the polymeric requires this process, but is more palatable and has favorable flavor. A Meta-analysis of 11 trials (n=378) demonstrated the absence of difference in the induction of remission in CD when com-

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paring the efficacy of elemental versus non-elemental formulas.[18] Protein composition as a nitrogen source does not influence the effectiveness of enteral nutrition (EN) in the treatment of active CD.[18] An analysis of 7 trials, including 209 patients treated with EN formulas with different fat contents (low fat [<20 g/1,000 kcal] vs. high fat [>20 g/1,000 kcal]), demonstrated the absence of difference in remission rates.[18] Very low-fat content (<3 g/1,000 kcal) and very low long-chain triglycerides demonstrated higher remission rates than the higher content EN formulas. The quantity or type of fat might affect the therapeutic potential of EN.

Most of the trials with adult CD patients showed that corticosteroid was more beneficial than EEN.[18] There results are based on the fact that EEN is more adherent in pediatric CD and is significantly effective in the early course of the disease.[32,33] Poor adherence could be the main barrier in achieving successful EEN therapy. A total of 41% of adults with CD receiving EEN treatment withdrew from this therapy, with even significantly higher dropout rate than those receiving corticosteroid.[10] These findings could also be supported by the previous studies stating that new-onset adult CD had similar efficacy between EEN therapy and corticosteroid treatment.[34] EEN has a lower efficacy in distal diseases such as colonic or perianal involvement and more beneficial effects in possibly small bowel involvement than corticosteroid treatment.[10,35] Hence, EEN might be helpful in the management of adult CD with certain condition, e.g., newly diagnosed or involved only in small bowel.

EN has also been used for the maintenance of remission in CD patients. However, the quantitative assessment of studies was insignificant due to the short duration of intervention, insufficient follow-up period, and small sample size.[36] EEN therapy has the following disadvantages for the maintenance of remission: patients' low adherence to EEN caused by poor palatability of the EN formula and inability to continue solid-free diet for a prolonged period.

Interestingly, EN in addition to standard medical treatment could be applicable to adult CD. A meta-analysis of 4 studies (n=342) revealed that the remission rate was significantly higher ($P<0.01$) in patients receiving EN therapy in combination with infliximab (109/157, 69.4%) than in those receiving infliximab monotherapy (84/185, 45.4%).[37] Furthermore, 74.5% of patients receiving both EN and infliximab therapies and 49.2% of patients receiving infliximab monotherapy remained in remission status after 1 year ($P<0.01$). In the recent trial comprising complicated adults with CD with fistulas, strictures, or abscesses, 12 weeks of EEN could achieve full clinical remission in 80.5%, fistula closure in 75%, and resolution of intra-abdominal abscess in 76% of patients.[38] Another study reported marked improvement in inflammatory bowel strictures with clinical remission in 81.4% of patients and 331% increase in cross-sectional area of the lumen.[39] The efficacy of EEN in adult IBD might result in positive outcomes in the preoperative setting and prevent postoperative complications.[40,41] The valuable role of EEN remains significant in adult CD based on accumulating evidence and knowledge. The EEN as one of non-pharmacological approach should be attempted considering individual situations in adult IBD in distinction from pediatric CD. Further studies in adults are required to evaluate the potential roles of EEN in the management of CD.

PARENTERAL NUTRITION

Total parenteral nutrition (TPN) is a therapeutic option for achieving bowel rest, correction of nutritional deficiency, and removal of dietary antigen-stimulating mucosal immune system.[42] Recently, interest in the role of TPN, such as being a treatment option, is scarce because TPN has not been found to be effective as a primary therapy for the induction and maintenance of remission in IBD.[31]

Intervention trials evaluating the effect of TPN in IBD patients were conducted mainly in the 1980s.[43-47] Achieving remission rate greater than 80% and avoiding surgical treatment are considered the initial effects of TPN, but delayed relapse is commonly developed after cessation of TPN.[47] There was no significant difference in the effects of TPN, partial parenteral nutrition (PN) with supplementary EN, and PN with normal diet.[45] Additionally, there were no significant differences in the remission rate between TPN and EN.[48] TPN is rather expensive, with infection and thromboembolism due to venous catheter and hepatobiliary complication being considered independent risk factors.[49,50] TPN is ineffective in treating patients with severe UC.[43,46] Therefore, this modality should be restricted to IBD patients with insufficient oral or tube feeding due to the dysfunction of the GI tract or to CD patients with short bowel syndrome, with several surgery, with obstructed bowel where there is no possibility of placement of a feeding tube beyond the obstruction or where this has failed, or with complications such as a proximal fistula and/or a high-output intestinal fistula or anastomotic leak.[30]

Preoperative TPN improves body weight and serum albumin in CD patients and decreases postoperative complications in IBD patients with severe malnutrition despite the limitation

of retrospective studies.[51,52] Conversely, other studies found that preoperative TPN had little beneficial effects on postoperative morbidity and mortality, prolonged hospitalization, and was significantly prevalent in sepsis.[53] Current guidelines recommend that PN in the perioperative period in IBD patients should be usually used as a supplementary therapy to EN and should only be used if EN is contraindicated due to intestinal obstructions or ileus, severe shock, and intestinal ischemia or if EN is not possible in the absence of access, severe vomiting, or diarrhea.[30] Based on the studies that have been currently conducted, it was known that TPN has lesser advantages than EN, which is considered a more physiologic modality in organ function as regards mucosal healing, maintenance of remission, and surgical treatment. However, TPN was still the preferred treatment modality in real clinical practice to supply nutrients, improve intestinal permeability and fistula healing, and reduce inflammation. Hence, additional studies are required to determine the exact role of perioperative PN in IBD patients, although it is difficult to consider TPN as a single therapeutic modality for disease control.

OMEGA-3 POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) of the ω3 series, mainly found in dietary fish oils, are essential nutrients because they cannot be produced by humans.[54] Epidemiological studies and several randomized controlled trials (RCTs) demonstrate a positive association between the consumption of ω3-PUFAs and improvements in various inflammatory conditions compared with the consumption of ω6-PUFA with pro-inflammatory effects.[55] Molecules synthesized from ω3-PUFAs are able to not only play a protective role against inflammatory response but also resolve existing inflammatory reactions mediated by specialized proresolving mediators such as resolvins, protectins, and maresins.[56] It has been significantly considered that the administration of ω3-PUFA may be beneficial to IBD patients. However, there have been conflicting results in clinical and experimental studies focusing on the development of clinical outcomes of IBD.

Various studies of experimental colitis models have shown that ω3-PUFA had protective effects in decreasing colonic damage and inflammation.[57-62] Based on these evidences, several epidemiological studies and clinical trials in humans have been conducted on the roles of ω3-PUFA for the prevention and treatment of IBD. Regarding the development of IBD, epidemiological studies showed that there was a significant strong association between consumption of lower ratio of ω6/ω3-PUFA and decreased incidence of UC, but not CD.[63,64] Several intervention trials revealed that there was significantly protective association between ω3-PUFA and risk of IBD.[64-66] On the contrary, some studies failed to determine any significant association between ω3-PUFA intake and development of IBD.[67,68] The latest meta-analysis of observational studies showed that dietary ω3-PUFA consumption obtained from fish was inversely related to the risk of CD.[69] Moreover, there was a strong inverse association between dietary ω3-PUFA and the risk of UC.[69] With respect to ω3-PUFA as an IBD therapy, previous large multicenter RCTs revealed that daily administration of 4-g ω3-PUFA is not beneficial in preventing disease relapse.[70] Meta-analysis of RCTs demonstrated that ω3-PUFA supplementation was probably ineffective for the maintenance of remission in IBD.[71-73] Nevertheless, the intervention study revealed that higher ratio diet of ω3/ω6-PUFA in IBD patients for 18 months was significantly effective in the maintenance of remission.[74] Another study found that UC patients who consumed higher ω3-PUFA levels using salmon had better activity index measured using the simple clinical colitis activity index score than those who did not consume higher ω3-PUFA levels.[75]

Although experiments of animal models show the significant efficacy of ω3-PUFA, clinical trials in human demonstrate its weak evidence of benefits in clinical courses of IBD patients. These conflicting results might be due to inconsistency in study design such as various formulations and doses of ω3-PUFA, heterogeneity of food intake for a whole day, duration of study, and compliance of patients. Whether ω3-PUFA has clinical benefits in IBD remains less evident; therefore, current guidelines do not recommend ω3-PUFA supplementation for the prevention and maintenance of remission in IBD patients.[30] Clinical decisions regarding ω3-PUFA supplementation in treating IBD patients should be taken into consideration considering the available evidences. Although the current state of knowledge is insufficient to support a clear recommendation for the usual use of ω3-PUFA in IBD patients, emerging studies suggest its potential benefits.

FIBER

Fermentable fiber resistant to digestion and absorption in the small bowel is mostly in soluble form and can the colon and metabolize into short-chain fatty acids (SCFAs) by colonic microbiome.[76] SCFAs have been recognized as energy substrates of colon cells, contributing to their homeostasis, and they trig-

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ger the anti-inflammatory properties in immune cells such as macrophages and dendritic cell by stimulating the differentiation of regulatory T cells.[77,78] Moreover, SCFAs enhance intestinal epithelial barrier function by reinforcing the integrity of epithelial tight junction.[79] Bacterial by-products derived from dietary fiber remodel the composition of the gut microbiome, which improves intestinal dysbiosis.[80] Thus, SCFAs have been investigated for their anti-inflammatory activity. IBD patients have significantly lower levels of SCFAs, including butyrate and acetate, than do healthy subjects.[81] Butyrate, which is a major type of SCFAs, is an important protective factor against colorectal cancer and might play a protective role against the development of IBD.[81,82]

Increased SCFA production from fiber supplementation reduces intestinal inflammation in patients with active CD.[83] An RCT of 105 UC patients with remission status was conducted, and it compared the dietary fiber obtained from *Plantago ovata* seeds, mesalamine, and dietary fiber plus mesalamine in the maintenance of remission for 12 months.[84] There was no difference in relapse rates between the dietary fiber and mesalamine groups (40% vs. 35%), with even the lowest relapse rates being observed in both groups (30%). This study concluded that dietary fiber might be as effective as mesalamine in maintaining remission in UC.

Because there is still insufficient clinical evidence that supports the efficacy of dietary fiber for the maintenance of remission in IBD, current guidelines do not recommend high-fiber diet supplementation.[30] Although dietary fiber supplementation may enhance anti-inflammatory effects, recent guidelines and systematic review have demonstrated that evidences for the efficacy of fiber in IBD are only limited.[85] It might be explained by 2 reasons even if speculated without the complete understanding of the action mechanism.[85,86] One reason is that efficacy of dietary fiber localizes only to the colon because SCFAs, by-product obtained from fiber fermentation, were mostly formed in the colon where the abundant gut microbiota exist. Thus, dietary fiber may be less efficient in CD patients with small bowel involvement. This reason is supported by the result of the previous studies with fiber intervention stating that UC patients had better positive effects in dietary fiber supplementation than CD patients.[84,87] It was well-established that all UC patients have only large bowel with continuous involvement starting with proctitis, but approximately greater than one-quadrant of CD patients have their disease localized in the small intestine only. Another reason is that the compositional changes of high dietary fiber supplementation do not necessarily mean functional changes available to attenuate intestinal inflammation.[86] In IBD patients with actively inflamed intestinal mucosa, alteration of metabolic activities and composition of the gut microbiota might be unable to utilize the fermentation effects of dietary fiber.[88,89] Previous study demonstrated that the benefits of a high-fiber diet could be determined according to the presence of bacteria that are able to digest fiber such as *Prevotella* in the gut microbiota.[90] It implies that the benefit of dietary fiber may more effectively play a role in inflammation relapse than that of existing treatment modality.[91]

Even though reduction in the intake of fiber could result in dysbiosis by altering the gut microbiota, IBD patients who have intestinal stricture or stenosis are often advised to restrict fiber from their diet for low-residue diet as the management of active flare status.[92,93] This clinical practice might be originating from preconceived frameworks that a low-fiber diet contributes to decreased risk of bowel obstruction by keeping low volume and frequency of stool. However, there is insufficient credible evidence for this recommendation. CD patients who consume low-residue diet might improve their disease activity index.[87] Previous prospective trial in patients with active CD found that there was no significant difference between the low-residue diet and unrestricted diet group in several clinical outcomes, including complication, hospitalization, surgery, postoperative recurrence, and nutritional parameters.[94] Moreover, low-fiber diet leads to adverse clinical outcomes of IBD, and high-fiber diet may improve bowel function and quality of life; additionally, fiber supplementation could contribute to favorable outcomes in the maintenance of remission.[95-97] Therefore, fiber restriction is recommended in patients with a high risk of obstruction due to intestinal narrowing or strictures only for short-term, and prolonged fiber restriction should not be considered.[30] The efficacy of fiber in IBD is entirely not yet understood, and current progressive trials have demonstrated that fiber supplementation could have significant benefits on the relief of symptoms and maintenance of remission. This accumulated evidence would support the assumption that fiber supplementation plays an important role in IBD management.

VITAMIN D

IBD patients have greater vitamin D deficiency than the general population.[98] The prevalence of vitamin D deficiency ranges from 16% to 90%, and CD seems to be more prevalent than

UC.[99,100] Vitamin D, which has an impact on bone density reduction, is of significant practical interest. The pathogenesis of bone density reduction in IBD is multifactorial including recurrent and chronic steroid use, insufficient intake of dietary calcium and vitamin D, and low BMI. Several pro-inflammatory cytokines derived from inflammatory reaction itself such as TNF-α can lead to osteopenia.[101] Hence, decreased bone density, presenting as osteopenia or osteoporosis in IBD patients, could be considered as an extraintestinal manifestation and drug-induced complication. Recent retrospective study showed that clinical factors associated with vitamin D deficiency in IBD patients are small bowel involvement or resection in CD and higher disease activity index in UC and identified that CD patients receiving anti-TNF-α treatment had significantly higher vitamin D level than those not receiving anti-TNF-α treatment.[102]

Moreover, vitamin D is involved in anti-inflammatory process and suppresses inflammatory cascade and reduces injury in the epithelial cell by increasing its resistance against irritants in the intestinal mucosa.[1,103] Additionally, vitamin D enhances the repair in the intestinal mucosal barrier and leads to a more rich and diverse composition of the gut microbiome.[104,105] A previous women cohort study provided the evidence of this protective role of vitamin D by identifying that the incidence of CD development significantly decreased in those with highest vitamin D level.[106] 25-Hydroxy vitamin D (25(OH)D) is one form of vitamin D that is absorbed from diet in the small intestine and synthesized in the skin as mediated by light exposure. 25(OH)D is recognized as both a major circulating metabolite of vitamin D and stored form in adipose tissue and liver and used to indicate vitamin D status.[107] The beneficial effects of vitamin D on IBD have been documented. A previous study reported that IBD patients with serum 25(OH)D <20 ng/mL had higher risk of surgery and hospitalization than those with serum 25(OH)D ≥20 ng/mL.[108] Furthermore, the normalization of 25(OH)D in IBD patients with an initial level <30 ng/mL could reduce the risk of IBD-related surgery.[108] Recent meta-analysis study involving 18 RCTs with a total of 908 IBD patients showed that vitamin D supplementation reduced the relapse rate more significantly than the control, but there were no significant differences between low- and high-dose vitamin D treatment.[109] In a recent study with 40,000 IU cholecalciferol supplementation weekly for 8 weeks, patients with active UC had significant improvement in inflammatory markers, including reduction of fecal calprotectin and CRP and increase of albumin and abundance of fecal microbiota, whereas those with inactive UC or non-IBD controls did not change.[110] One study demonstrated that IBD patients with vitamin D deficiency immediately discontinued the anti-TNF-α therapy due to loss of response, implying that vitamin D supplementation should be considered in maintaining the response to IBD therapy.[111] Another study of IBD patient receiving anti-TNF-α reported that those with normal levels of vitamin D at the beginning of anti-TNF-α therapy had a 2.64 increased odds ratio of successful remission in 3 months compared with those with low levels of vitamin D.[112] In a study of 2,809 IBD patients with a median of 11-year follow-up, those with vitamin D deficiency more frequently have colorectal cancer than those without vitamin D deficiency, and 1 ng/mL increase in serum 25(OH) D level could lead to 8% reduction in the occurrence of colorectal cancer.[113]

Although vitamin D deficiency in IBD is common, clinical manifestations associated with low bone mineral density develop silently and remain a subclinical symptom in most cases. Therefore, insufficient established data regarding the consequences and frequency because of heterogeneity in diagnostic criteria, measurement tool, and study population were observed. The available studies have an inconsistent design, which varies from 1,000 to 300,000 IU in vitamin D doses, oral or intramuscular route, or from 3 months to 5 years in administration duration.[114,115] Moreover, the widely accepted cutoff level of vitamin D deficiency remains unclear. The optimal dosage of supplementation needed to prevent vitamin D deficiency remains under discussion. There is a wide dosing range of recommended vitamin D supplementation among several guidelines, ranging from 400 IU to 10,000 IU daily.[116]

Vitamin D may be beneficial in the development and clinical course of IBD and occurrence of complications related to bone density. Currently, high-quality and large-sized RCT for appropriate vitamin D therapy in IBD patients is insufficient. Thus, no guideline has found explicit regimen including appropriate doses, supplementation route, and kind of substrate to maximize the benefits of vitamin D in IBD patients. Nevertheless, based on expert opinion, it is recommended that IBD patients should maintain a vitamin D level >75 nmol/L in the serum, which is assessed by regular checkup, for the improvement of disease-related prognosis.[99] Improvement of vitamin D status through intended supplementation is being increasingly recognized as an indispensable approach for the appropriate treatment of IBD patients.

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PROBIOTICS

Prebiotics are nondigestible ingredients in food that are beneficial in the composition of GI microbiota by fermentation.[117] Probiotics contain live microorganisms that provide beneficial effect on the host's health. Prebiotic supplementation modulates the endogenous microbiota by stimulating the growth of selective bacteria mediated by substrates such as galacto-oligosaccharides, whereas probiotic supplementation aims to provide exogenous bacteria in the luminal microflora. Health benefits obtained from prebiotic or probiotic consumption mean that a restrictive number of beneficial microbial species stimulate functional activity and are becoming more abundant.

Recently, intestinal microflora participates in the pathophysiology of IBD through the immunoregulatory function.[118] Alteration in the composition and function of the gut microbiota, namely dysbiosis, could lead to the stimulation of inflammatory response, dysfunction of the intestinal epithelium, and increased mucosa permeability.[119] Dysbiosis was defined as an imbalance in the intestine between the protective (e.g., *Lactobacillus* and *Bifidobacterium* species) and harmful (e.g., mucosa-associated *Escherichia coli*) gut microbiomes.[120] Probiotic supplementation to modulate dysbiosis might be a therapeutic option for managing the disease course in IBD patients. Little is known about prebiotic use in IBD due to insufficient studies. Most studies on prebiotics were conducted in a small study population and reported conflicting results.[121]

Probiotics seem to be able to alter the clinical course of IBD patients based on clinical practice and available studies. A previous study with positive effect for CD patients showed that those receiving mesalamine with *Saccharomyces boulardii*, known as a nonpathogenic yeast, had significantly lower relapse rate than those receiving mesalamine alone (6.25% vs. 37.5%), and this species may represent a useful modality in the maintenance of CD.[122] However, in the majority of studies, there is no strong evidence that confirmed the usefulness of probiotic strains in the management of CD. Meta-analysis studies showed that the beneficial effect of probiotics in CD remains uncertain in both the induction and maintenance of remission.[123] Another current meta-analysis study supported the assumption that the combination of *S. boulardii, Lactobacillus*, and VSL#3 probiotics in CD was marginally significant ($P=0.057$) with efficacy.[124] The efficacy obtained from probiotics is strain specific; hence, meta-analysis comparing studies using widely dissimilar probiotics might be difficult when drawing firm conclusions. Hence, further well-designed studies are required to clarify the efficacy of probiotics in CD.

Probiotic supplementation for therapeutic manipulation of the gut microbiota has proven more valuable in the management of UC. The current meta-analysis study investigated the effect of probiotic supplementation on inflammatory marker in IBD.[125] Probiotics had significant effects on serum CRP reduction ($P=0.002$) and TNF-α ($P<0.001$), whereas it had no significant effects on IL-10 ($P=0.24$) and IL-6 ($P=0.88$). Two recent meta-analysis studies reported that probiotics may be as effective as mesalamine in preventing relapses in UC and VSL#3 in particular may be effective in the induction of remission in patients with active UC.[120,123] VSL#3 contains a total of 4×10^{10} colony-forming units consisting of 8 lactic acid bacteria including 4 strains of *Lactobacilli* (*Lactobacillus paracasei, L. plantarum, L. acidophilus,* and *L. delbrueckii*), 3 strains of *Bifidobacteria* (*Bifidobacterium longum, B. infantis*, and *B. breve*), and 1 strain of *Streptococcus thermophilus*. In a large study comparing the efficacy between *E. coli Nissle 1917* and mesalazine 1,500 mg in maintaining remission for 12 months, the probiotic preparation of *E. coli Nissle 1917* showed equivalent efficacy and safety.[126] *E. coli Nissle 1917* is a nonpathogenic *E. coli* that colonizes the intestine and inhibits the growth of enteropathogenic and other enteric bacteria.[125]

The most guaranteed effects of probiotics in IBD have been the prevention and treatment of pouchitis after ileal pouch-anal anastomosis (IPAA) for UC.[127] A previous international multicenter study in patients with recurrent refractory pouchitis reported that maintenance of remission was 85% in the high-dose VSL#3 group of 6 g once daily and 6% in placebo.[128] The prophylactic effect of probiotic therapy to pouchitis was shown in a study of patients receiving either VSL#3 or placebo for 12 months.[129] A total of 10% of patients (2/20) treated with probiotics and 40% of patients (8/20) treated with placebo had the onset of acute pouchitis, where probiotic therapy could be effective in the prevention of pouchitis. Probiotic strains such as *L. rhamnosus GG* are also beneficial in preventing pouchitis.[130]

The ESPEN guidelines published in 2018 recommend probiotic therapy using *E. coli Nissle 1917* or VSL#3 for the induction and maintenance of remission in patients with mild-to-moderate UC but not in active CD.[30] VSL#3 was also recommended in antibiotic-unresponsive pouchitis and primary and secondary prevention of pouchitis in patients with IPAA. Probiotics containing other bacterial strains were not necessarily considered.

The specific strain, duration, frequency, and dose of probiot-

ic therapy should be established to achieve optimal efficacy. Additionally, when considering highly various interactions between the host and gut microbiota, individual strategies that modulate dysbiosis present a challenge. Hence, further studies are required to evaluate the efficacy of probiotics and supply tailored therapies in IBD patients.

CONCLUSIONS

It is clear that nutritional approaches play a valuable role in managing IBD patients; hence, such approaches need to be developed to significantly evaluate the effectiveness of dietary interventions used to treat IBD. Malnutrition in IBD patients has been insufficiently recognized, resulting in the underestimation and suboptimal treatment of malnutrition to date. Nutritional interventions not only correct nutritional deficiencies but also improve symptoms and clinical courses of the disease. The multidisciplinary team, comprising dietarians, IBD nurse specialists, and gastroenterologists, may play a vital role in the nutritional approach for IBD patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

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