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The Role of Diet, Prebiotic and Probiotic in the Development and Management of Inflammatory Bowel Diseases (IBD)

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1. Introduction

Inflammatory bowel disease (IBD) refers to a chronic inflammation condition of the intestinal tract concerning both small and large intestine. The major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic, relapsing and remitting diseases. The etiology of these diseases is quite complicated that involves genetic and environmental factors including diets, geographical and socioeconomic status and microbial factors. This chapter provides and discusses information about diet, prebiotic and probiotic and their role in the development and management of IBD.

Diet has important role in the development of IBD or protection against IBD. The nutritional components contribute in the balance of intestinal microflora either positively or negatively depending on the diet itself. Foods have been previously considered by consumers barely in term of taste and immediate nutritional needs. Instead of those two aspects, many consumers consider the foods ability to provide specific benefits beyond their nutritional as stringent reasons for choosing foods as their daily diet. Thus, functional foods have become an important and rapidly growing segment of the food markets, especially for the prevention and mangemnt of bowel-related diseases such as IBD. On the other hand, Prebiotic components and probiotic bacteria have also been used in the prevention and treatment of IBD, and they exhibit proven efficacy in many clinical studies. Prebiotic such as inulin and fructooligosaccharides (FOS) are commercially available in the markets, as well as probiotic supplemented food such as yogurt and fermented milk. Further information regarding this both food products will be discussed later in this chapter.

This chapter reviews the role of diet and its different elements namely, fibers, proteins, fatty acids (saturated and unsaturated fatty acids), and carbohydrates in the development and management of inflammatory bowel diseases (IBD). In addition, the chapter will discuss the link between life style and nutritional status with the enteric microbiota, and the balance between harmful bacteria and the beneficial bacteria (prebiotic components and probiotic bacteria). Moreover, the mechanisms of such relationship between the enteric microbiota

and diet will be discussed and explained. And the exact role of prebiotic and probiotic bacteria will be discussed thoroughly in the prevention, management and treatment of IBD along with the underlying mechanisms.

2. The healthy and unhealthy diet for intestine

Foods have a large impact on human digestive tract, particularly for those who have severe intestinal disorder such as constipation, inflammatory bowel disease, and colorectal cancer. Consumption of water, fiber containing food, prebiotic bacteria, probiotic bacteria, fruits and vegetables are thought to be beneficial for intestine, whereas specific red and processed meat are inconsistently exert detrimental effect to intestine. Prebotic and probiotic have been considered as healthy diet for the intestine. Water is required to keep foods and other substances move along more smoothly through the digestive tract as well as to make stools softer and easier to pass. In 117 patients with chronic functional constipation, a daily fiber intake of 25 g can increase the stools frequency and this effect was significantly enhanced by increasing water intake to 1.5-2.0 liters per day (Anti et al., 1998). In contrast, carbonated water improve dyspepsia, constipation and gallbladder emptying, however it decreases satiety in patients with functional dyspepsia and constipation (Cuomo et al., 2002). In early study, Lepkovsky et al. (1957) investigated the gastrointestinal regulation of water in rats fed with or without water. Rats fed without water ate less food than rats fed with water. However, the gastric contents (49% water) were similar within the both group, indicate close regulation of water in the gastric content. The authors suggested that diet without water resulted in decreasing appetite and food intake. Schoorlemmer and Evered (2002) revealed that a sensor located in the gastrointestinal tract or perhaps in the mesenteric veins, but not the hepatic portal vein or the liver mediated the inhibition of feeding during water deprivation. Therefore, water is considered as an important component that takes a part in maintaining the intestinal healthy.

Dietary fiber is an intrinsic substance of plants that are resistant to enzymatic digestion in the gastrointestinal track of human (Schneeman and Tietyen, 1994). It is usually differentiated into insoluble fiber (not dissolve in water) and soluble fiber (dissolve in water). Chemically, insoluble fiber consists of cellulose, hemicelluloses and lignin, while soluble fiber consists of pectin, gum and mucilage. Insoluble fiber enhances the movement of material through the digestive track and contributing bulk and moisture to the stool. Thus, it can be of benefit to those who suffer with constipation and irregular stools. Insoluble fiber is found in food such as whole grains, wheat bran and many vegetables. Soluble fiber absorbs water to form a gel-like material and can help lower blood cholesterol and glucose levels. Oat, peas, beans, nuts, some fruits and vegetables are good sources of soluble fiber. Consuming foods rich in fiber exert numerous benefits such as improved large bowel function, slowed digestion and absorption of carbohydrate and fat, and reduced risk for certain diseases (Schneeman and Tietyen, 1994). Average intake of dietary fiber in the United States is about 5 g/day. However, according to the American Dietetic Association, the recommended daily intake of fiber is 25-35 g (Slavin, 2008). Fiber should be increasingly consumed in certain time period rather than consumed promptly to achieve value of recommended daily intake, as it may cause stomach cramping and gas. In 2001, Bliss et al. revealed that dietary fiber may improve fecal incontinence. In their study, patients with fecal incontinence who are given dietary fiber as psylium or gum arabic showed significantly fewer incontinence stools than with placebo treatment.

Consumption of fruits and vegetables are believed to exert many beneficial effects to intestine, as they are sources of fiber. Chang et al. (2010) reported that consumption of kiwi fruit for 4 weeks be able to shorten colon transit time, increases defecation frequency, and improves bowel function in adults diagnosed with constipation. In another study with eight healthy volunteers, Shinohara et al. (2010) investigated the effect of apple intake on fecal microbiota in humans. They revealed that the number of bifidobacteria, *Lactobacillus* and *Streptococcus* in feces increase after the intake of 2 apples/day for 2 weeks. In contrast, the decreased numbers of *Clostridium perfringens*, *Enterobacteriaceae* and *Pseudomonas* was observed in the same groups. Their findings indicate that apple consumption improved intestinal environment and apple pectin was thought to be main component underlying this beneficial effect. In addition, Tamura et al. (2011) found that the occupation ratio of *Bacteroides* and *Clostridium* cluster IV were significantly higher in fecal flora of mice given Japanese apricot treatment compared to the control. The authors also suggested this Japanese apricot fiber possesses the fecal lipid excretion effects and feces bulking effects.

3. The kinds and nutritional status of diets and their role in the development of IBD

3.1 Sugar and refined carbohydrate

Many studies have been conducted to observe the role of sugar in the development of IBD. Martini and Brandes (1976) were among the earliest to reveal that intake of sugar and highly refined carbohydrate containing foods were higher in CD patients compared to the control. Mayberry et al. (1978) in UK observed the dietary breakfast on 100 CD patients and 100 controls, matched for age and sex. No significant difference was noted for the type of foods taken at breakfast, except for fruit and fruit juice, which were taken more often by control. Nevertheless, CD patients were observed to add significantly higher amount of sugar to their beverages and cereals compared to control. In later studies, a higher sugar intake in CD patients compared to control was eventually confirmed (Mayberry et al., 1980; Silkoff et al., 1980). Since then, numerous studies have confirmed the high level of sugar consumption noticed either in foods or beverages of CD patients (Jarnerot et al. 1983; Katschinski et al., 1988; Matsui et al., 1990, Reif et al., 1997).

Some debates have raised an issue on whether the increased sugar intake is a course or effect of the disease. However, the fact that increased sugar pattern has also been observed in new onset CD signifying that such pattern may contribute a role in the development of the disease. In a case controlled study, researchers used the odd ratio (OR) or relative risk (RR) as appropriate method for investigating the relationship between diet and disease. Persson et al. (1992) revealed that calculated RR of CD was increased for subjects who consume high amount of sucrose (>55 g/day) (RR= 2.6; 95% confidence interval (CI)= 1.4-5.0). Reif et al. (1997) found that a high sucrose intake was associated with the increase for IBD, with OR= 2.85 and 5.3 against population and clinic control, respectively. In addition, they found that lactose consumption exhibited no effect while fructose intake was negatively associated with risk of IBD. Sakamoto et al. (2005) used food frequency questionnaire (FFQ) to compare pre-illness diet in 108 CD and 126 UC patients with the diet of 211 controls in Japan. They found that high consumption of sugars and sweeteners (OR= 2.12; 95% CI= 1.08-4.17) and sweets (OR= 2.83; 95% CI= 1.38-5.83) were positively associated with CD risk. High intake of sweets was also observed to be positively associated with UC risk (OR= 2.86; 95% CI= 1.24-6.57).

3.2 Dietary fat

Dietary fat is suggested to be an important factor in the development of IBD. Hydrogenated fat such as margarine was found to contribute in the development of IBD. The causal relationship between margarine and IBD was previously proposed based on the association between the onsets of margarine consumption with the first report of ganulomatous ileitis (Geerling et al., 1999). Maconi et al. (2010) reported that moderate and high consumption on margarine (OR= 11.8 and OR= 21.37) was associated with UC.

An increase of fat consumption was observed in the pre-illness period of IBD, particularly of UC patients (Reif et al., 1997). The kind of fat observed in the study including animal fat, vegetable fat, saturated fat, monounsaturated fat, polyunsaturated fat and cholesterol, in which high intake of animal fat and cholesterol give high OR value of 4.09 and 4.57, respectively (Reif et al., 1997). Geerling et al. (2000) found in their study that high intake of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) were also associated with the development of UC. Similarly, Sakamoto et al. (2005) revealed that the intake of total fat, MUFA, and n-6 fatty acids was positively associated with CD risk, although they failed to found association with UC. An epidemiological study from Japan discovered that increasing incidence of CD (between 1966 and 1985) was in parallel increase with daily intake of animal protein, total fat and animal fat, particularly n-6 PUFA relative to n-3 PUFA (Shoda et al., 1996).

3.3 Dietary protein

Important source of protein such as meat, cheese, milk, eggs and fish are widely taken as dietary protein. Patients with CD and UC as well as ulcerative proctitis disorders exhibit higher protein intake compared to the control subject with other gastrointestinal disorders (Gee et al., 1985). Tragone et al. (1995) also found higher protein intake in UC but not CD patients compared to the control. On the other hand, Reif et al. (1997) failed to find the association between protein intake and the risk of IBD in their case control study. Shoda et al. (1996) who conducted an epidemiologic analysis of CD in Japan showed that increased incidence of CD was strongly correlated with increased dietary intake of animal protein (r= 0.908) and milk protein (r= 0.924). However, risk of CD is not correlated with fish protein (r= 0.055) and is inversely correlated with vegetable protein (r= -0.941). The study also suggests that the development of CD may be contributed by high intake of animal protein and n-6 PUFA with less n-3 PUFA. In recent study, Maconi et al. (2010) reported that high consumption of cheese was significantly associated (OR= 3.7; 95% CI= 1.14-12.01) with CD.

Allergy to milk protein was also proposed to be associated with the etiology of UC. Truelove et al. (1961) reported in earlier time that milk exclusion from the diet of patients led to clinical improvement, but an exacerbation of UC was observed when milk was re-added into the diet. Taylor and Truelove (1961) supported the theory with their discovery on raised circulating antibodies to cow's milk protein. Decades later, Glassman et al. (1990) reported a relationship between hypersensitivity to cow's milk during infancy and subsequent development of UC. Several studies investigated perinatal risk factor on the development of IBD found that the lack of breastfeeding is also an independent risk factor associated with development of CD (Koletzko et al., 1989; Thompson et al., 2000) and UC (Corrao et al., 1998) later in childhood. However, Koletzko et al. (1991) revealed that the association between breastfeeding and the increase risk of IBD remains obscure (Koletzko et al., 1991). Although discrepancies appear in many study, the relationship between protein intake and the development of IBD seems to be evidenced.

3.4 Other dietary components

Many dietary components either as whole foods or micronutrients have been examined for their risk in the development of IBD. Persson et al. (1992) found that consumption of fast food at least twice a weak associated with the increased relative risk of either CD (RR= 3.4; 95% CI= 1.3-9.3) or UC (RR= 3.9; 95% CI= 1.4-10.6). Reif et al. (1997) reported a positive association between retinol and the risk of IBD, while high intake of fluids, magnesium, vitamin C and fruits was negatively associated with the risk of IBD. In other study, a positive correlation was found between the intake of vitamin E (OR= 3.23; 95% CI= 1.45-717) and CD risk, whereas the intake of vitamin C (OR= 0.45; 95% CI= 0.21-0.99) was negatively related to UC risk (Sakamoto et al., 2005). A higher consumption of vitamin B_6 was observed in UC patients compared to the control (Geerling et al., 2000).

D'Souza et al. (2008) used the FFQ in a control case study to investigate the impact of dietary patterns in pediatric CD risk. They found that a characterized diet by meat, fatty food and dessert was positively associated with CD risk (OR= 4.7; 95% CI= 1.6-14.2). On the other hand, a diet characterized by fruits, vegetables, olive oil, fish, grains and nut was inversely associated with CD risk (OR= 0.2; 95% CI= 0.1-0.5). In other recent study, Maconi et al. (2010) evaluated the association between specific dietary pattern and IBD risk on adult. The dietary patterns were termed as refined (pasta, sweets, red and processed meat, butter and margarine), prudent (white meat, tuna fish, fish, eggs and potatoes) and healthy (bread, cheese, fruit and vegetables as well as olive oil). They observed that a "refine" pattern was associated with an increased risk of UC and CD. In contrast, the "prudent" diet was significantly associated with a decreased risk of UC and CD whiles the "healthy" pattern exhibited non significant association with increased risk of CD, and it was not consistently associated with UC. Although a meaningful conclusion cannot be drawn, these studies imply that specific dietary patterns has distinct role in the development of IBD either in children or adults.

4. Mechanisms underlying the association of diet with IBD

Diet is thought to play an important role in the development and treatment of IBD. However, the association between nutrition and IBD is complicated and involves several aspects such as nutritional support for malnourished patients, primary therapy for active disease and maintenance of remission, and nutrients risk factors involved in the etiology of IBD (Hartman et al., 2009). Malnutrition is commonly observed in patients with IBD, particularly CD (O'Sullivan et al., 2006; Razack and Seidner, 2007). Enteral nutrition has been applied as an adjunct therapy to correct or prevent malnutrition in CD patients in both adults and children (Dupont et al., 2008; Day et al., 2008; El-Matary, 2009). Enteral nutrition has also been considered to induce and maintain remission in CD (Tsujikawa et al., 2003; Griffiths, 2005; Smith, 2008). Nevertheless, mechanisms underlying the action of enteral nutrition are yet to be fully understood, although several mechanisms have been proposed by many researchers. These mechanisms include improvement of nutritional status (Beatti et al., 1994), down regulation of pro-inflammatory cytokines (de Jong et al., 2007), modification of gut flora (Leach, 2008), anti-inflammatory effects (Fell, 2005), promoting epithelial healing (Fell et al., 2000), decreased gut permeability (Guzy et al., 2009) and decreased antigenic load to the gut (Beatti et al., 1994).

The association between diet and IBD is likely to be determined by major components found in the foods. The ability of foods containing fiber in preventing the development of IBD is determined by the end products resulted from the fermentation of fiber in the gut. Fiber is

metabolized by gastrointestinal bacteria to produce lactate, gas and short chain fatty acids (SCFA) such as acetate, propionate and butyrate. The most important SCFA is butyrate since it has anti-inflammatory effects by inhibiting NFκβ and thus preventing transcription of pro-inflammatory cytokines. Butyrate is also known to reduce colonic permeability by promoting activation of peroxisome proliferator activated receptor γ (PPAR-γ) (Venkatraman et al., 2003). In addition, N-3 PUFA, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been associated with the prevention of IBD. These PUFA influence the inflammatory response through several mechanisms such as antagonizing the production of inflammatory eicosanoid mediators from arachidonic acid, suppress production of some inflammatory cytokines and downregulate the expression of a number of genes involved in inflammation (Gil, 2002).

5. The link among diet, prebiotic and enteric microbiota mainly probiotic bacteria

The human gastrointestinal tract that typically refers to stomach and intestine is colonized by an intricate community of microorganisms. The stomach is a home of typically 10^3 colony forming units (CFU)/g content (Gibson and Beaumont, 1996). The large intestine is the main colonization site of more than 500 indigenous microbial species which can reach up to 10^{12} CFU/g lumen contents (Conway, 1995; Gibson and Beaumont, 1996). A wide range of compounds that have both positive and negative effects on gut physiology is produced through fermentation process by predominantly strict anaerobe gut microflora. For instance, short-chain fatty acids (SCFA), mainly butyrate supplies energy metabolism for the large gut mucosa and colonic cell growth. This SCFA is the end fermentation products of complex carbohydrate and protein that usually present in human diet. In contrast, H_2S produced by sulfate-reducing bacteria is highly toxic and may induce ulcerative colitis (Gibson and Beaumont, 1996). From the host's perspective, the key function of gut microflora is to prevent colonization by potentially harmful microorganisms. The imbalanced gut microflora has been linked to the development of certain disorders such as gastroenteritis, colon cancer and inflammatory bowel disease (Gibson and Macfarlane, 1994). The composition of gut microflora is considered to be fairly stable over long periods. However, numerous factors such as competition for nutrients, metabolic interaction among bacteria, various host condition and individual dietary preferences may influence alteration of the pattern (Berg, 1981; Hill, 1986; Rowland and Tanaka, 1993). Therefore, it is of the foremost interest to manipulate the gut microflora composition toward an increased number of beneficial bacteria that provide health promising properties to the gut.

The groups of beneficial bacteria that help maintain health and treat disease is broadly known as probiotic. Several definitions of probiotic have been suggested for over the years. Fuller (1989) defined probiotic as a live microbial food supplements which have beneficial effects on the host by improving its intestinal microbial balance. A probiotic bacterium should fulfill certain criteria to be described as useful. These include acid and bile stability, adherence to intestinal cells, persistence for some time in the gut, ability to produce antimicrobial substances, antagonism against pathogenic bacteria, ability to modulate the immune response, being of human origin and having generally regarded as safe (GRAS) status (Dunne et al., 2001). In human, probiotic has been associated with lactobacilli (e.g. *Lactobacillus acidophilus*, *L. delbruekii* and *L. casei*) and bifidobacteria (e.g. *Bifidobacterium bifidum*, *B. adolescentis*, *B. infantis* and *B. longum*). Other known bacteria include streptococci

(e.g. *Streptococcus lactis* and *S. salivarius* ss. thermophilus), nonpathogenic *E. coli* and *Saccharomyces boulardii* (Gibson and Roberfroid, 1995; Shanahan, 2001).

A practical approach in increasing the number and activities of probiotic is through dietary supplementation, particularly with intake of the so called prebiotic. Gibson and Roberfroid (1995) defined a prebiotic as 'a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health'. They revealed that food constituents can be categorized as prebiotic if meet the following requirements: 1) Resistant to hydrolysis and absorption in the upper part of gastrointestinal tract; 2) Act as selective substrate for one or a limited number of beneficial bacteria commensal to the colon; 3) Able to alter the colonic flora in favor to healthier composition; and 4) Induce luminal or systemic properties that are beneficial to the host health. Fructooligosaccharides (FOS), inulin, lactulose and galactooligosaccharides are commercially available prebiotic of proven efficacy. Inulin and FOS can be found in human breast milk and in food such as banana, asparagus, leeks, onion, garlic, wheat, chicory and tomatoes (Niness, 1999). Galactooligosaccharides (GOS), a mixture of oligosaccharides derived from lactose is frequently used as supplement in food and infant formula milk (Niness, 1999; Roberfroid, 2007). In their in vitro study, Wang and Gibson (1993) demonstrated that FOS and inulin are selectively fermented by most strains of bifidobacteria. The prebiotic effects of inulin and oligofructose in vivo have also been shown in many studies (Buddington et al., 1996; Kleesen et al., 1997). Moreover, the ability of these oligosaccharides in increasing the numbers of gut probiotic, particularly bifidobacteria has been shown in many human feeding studies. Breast milk is rich in human oligosaccharides and therefore the number of bifidobacteria in the gut microflora of breast-fed infants is higher than that in formula-fed infants (Gibson and Roberfroid, 1995; Harmsen et al., 2000). The predominance of bifidobacteria in breast-fed infants is usually associated with lower risk of intestinal infection. However, Moro et al. (2002) reported that after 28 days of feeding, the number of fecal bifidobacteria and lactobacilli in infant fed with a cow milk supplemented with FOS and GOS were significantly increased compared to the placebo group.

The link between prebiotic and probiotic has been pronounced to enhance the efficacy of the both agents in maintaining the health of intestine. Synbiotics have been defined as 'a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal track, by selectively stimulating the growth and/or by activating the metabolism of one a limited number of health promoting bacteria, and thus improving host welfare' (Gibson and Roberfroid, 1995). There are only few studies carried out to investigate the efficacy of synbiotics in human. Bouhnik et al. (1996) investigated the effect of symbiotic containing *Bifidobacterium* spp. and inulin fermented milk in healthy people. The authors reported that intake of *Bifidobacterium* spp. significantly increased fecal bifidobacteria, but no extra numbers of that particular probiotic was observed merely due to the addition of inulin. However, 2 weeks after trials, the volunteers who received symbiotic product had significantly higher number of *Bifidobacterium* spp. compared to those receiving probiotic alone. In addition, it was found that the trend whereby *Bifidobacterium* spp population decreases in the gut microflora of eldery may be reversed by the consumption of inulin (Kleessen et al., 1997).

6. The role of prebiotic and probiotic bacteria in the prevention of IBD

The inflammatory bowel disease is of complicated etiology, wherein genetic factors, immunity system and environmental factors as well as the interaction among them are supposed to play a pivotal role in the development of these disease states. The convincing evidence for interaction of these factors has been exposed in experimental animal models of either CD or UC (Elson et al., 1995; Strober et al., 1998; Blumberg et al., 1999). The environment factors such as the composition and metabolic activity of the gastrointestinal microbiota are likely to be the most important aspect. Its relationship with the host is so specific, thus alteration in the balance of microorganisms might initiate the pathogenesis of IBD. Some of intestinal bacterial resident are considered harmful as they are involved in toxin production, mucosal invasion or activation of inflammatory responses. These bacteria include *Mycobacterium paratubercolusis*, *Listeria monocytogenes*, adherent *E. coli* and measles virus. The equilibrium between protective and harmful bacteria inside the gastrointestinal tract exists in healthy people. However, this equilibrium is broken in IBD people (termed as dysbiosis), resulting in chronic intestinal inflammation (Tamboli et al., 2004). Major modification in gastrointestinal microbiota in IBD patient includes increased numbers of coliforms, bacteroids and *E.coli*, as well as decreased numbers of lactic acid bacteria (Kennedy et al., 2000; Borruel et al., 2002). Distribution of lesions in this intestinal inflammation disorder is found greatest in areas with the highest numbers of luminal bacteria (Shanahan, 2000). The consumption of probiotic has been known to exert many beneficial effects. Probiotics facilitate host defense against infection through competitive metabolic interactions, production of antimicrobials, and inhibition of adherence or translocation of pathogen. In a view point of IBD, Shanahan (2000) revealed that anti-inflammatory effects of probiotic require signal with gastrointestinal epithelium and mucosal regulatory T cells or dendritic cells.

Many studies revealed that oral administration of probiotic in tandem with prebiotic promote the prevention of IBD. Prebiotic is growth substrates specifically directed toward indigenous beneficial bacteria in colon, thus amplify the probiotic effects in preventing IBD. Although there is no recommended daily dose of prebiotic, but Roberfroid et al. (1998) suggested that a minimum daily dose of 4 g of inulin or FOS would be sufficient to increase the numbers of bifidobacteria in the intestine. In people with IBD, intake of prebiotic is required to prevent the disease recurrence, since prebiotic served as substrate for probiotic to produce SCFAs particularly butyrate that exert protective effects to the gut. For instances, Videla et al. (1994) reported that prebiotic inulin increases colonic butyrate and reduces inflammation and disease severity in animal models of colitis. Germinated barley foodstuff (GBF) rich in fiber also alleviate the symptomatology in both animal models of UC and patients with UC (Bamba et al., 2002). GFB is efficiently increases luminal butyrate production by stimulating the growth of protective bacteria (Kanauchi et al., 2002, Kanauchi et al., 2003). Therefore, the prebiotic and probiotic are likely work synergistically in the prevention of IBD.

7. The role of prebiotic and probiotic in the management and treatment of IBD

Prebiotic and probiotic have been widely involved in the management and treatment of IBD. Many studies on the use of prebiotic in the management of IBD are presented in Table 1. Fernandez-Banares et al. (1999) shown that a diet with Plantago ovate seeds was as effective as mesalazine in maintenance of remission in inactive UC patients in a randomized

controlled trial. Oral administration of GBF has been known to reduce clinical activity and prolonged remission time in UC patients (Kanauchi et al., 2002; Kanauchi et al., 2003; Hanai et al., 2004). In a recent study, Casellas et al. (2007) investigated the effect of oligofructose-enriched inulin in patients with active UC. They revealed that at day 7, an early significant reduction of fecal calprotectin was observed in patients who had taken oligofructose-enriched inulin, but not in placebo group. Fecal calprotectin has been used as an objective and quantitative marker of intestinal inflammation and its levels correlated significantly with histologic and endoscopic assessment of disease activity in UC (Roseth et al., 1997; Konikoff and Denson, 2006). Inulin has also been assayed in a placebo controlled clinical trial in patients with relapsing pouchitis (Welters et al., 2002). Dietary supplementation with inulin (24 g/day for 3 weeks) resulted in an increase of butyrate level, lower in pH, decreased numbers of *Bacteroides fragilis* and diminished level of secondary bile acids in feces. The authors further revealed that inulin was associated with reduction of endoscopic and histological scores of mucosal inflammation in the ileal reservoir. Nevertheless, more clinical trials are required to further validate the efficacy of dietary fiber as prebiotic in the management of IBD.

Prebiotic	Disease	Number of patients	Duration	Outcome Results	Reference
Inulin (24 g/day)	Pouchitis	20 adults	2.2 months	Reduction of inflammation of the mucosa of the ileal reservoir.	Welters et al. (2002)
Plantago ovata seed	UC	105 adults	12 months	Maintain remission as effective as mesalamine, Increased in fecal butyrate.	Fernandez-Banarez et al. (1999)
Synbiotic 2000 *	CD	30 adults	24 months	Fail to prevent postoperative recurrence.	Chermesh et al. (2007)
Synergy 1 (inulin and oligofructose) 6 g/day and *Bifidobacterium longum*	UC	18 adults	1 months	Reduction of β-defensins 2, 3, and 4, TNFα and Interleukin 1α.	Furrie et al. (2005)
Germinated barley foodstuff (30 g/day)	UC	10 adults	1 months	Reduction of clinical activity index scores and increase in stool butyrate concentrations.	Mitsuyama et al. (1998)

*: Synbiotic 2000 is combination of probiotic (Lactobacillus raffinolactis, L. paracasei, L. plantarum, Pediococcus pentosaceus) and prebiotic (2.5 g β-glucan, 2.5 g inulin, 2.5 g pectin and 2.5 g resistant starch).

Table 1. Studies of probiotics in the management of inflammatory bowel disease (IBD)

Many clinical studies have confirmed the efficacy of probiotic in the management and treatment of IBD (Table 2). In 1999, Venturi et al. reported the efficacy of VSL#3 (at 6 g/day) as maintenance treatment in patients with ulcerative colitis in remission and intolerance to 5-aminosalicylic acid (5-ASA). They observed that 75% of patients given VSL#3 remained in remission without any side effects throughout the 12 months period. VSL#3 is comprised of lyophilized viable cell of 4 strains of *Lactobacillus* (*L. casei, L. achidophilus, L. plantarum* and *L. bulgaricus*), 3 strains of *Bifidobacterium* (*B. longum, B. breve* and *B. infantis*) and 1 strain of *Streptococcus thermophilus*. In addition, the mixture of probiotic is found to be able to upregulate the intestinal mucosal alkaline sphingomyelinase and reduce the inflammation risk in UC patients (Soo et al., 2008). A non-patoghenic *E. coli*, Nissle 1917, also exhibits similar efficacy with mesalazine (the standard treatment) in the maintenance of UC (Rembacken et al., 1999; Kruis et al., 2004). In other study, the ability of *Saccharomyces boulardii* to induce the remission in 71% of patients with mild to moderate UC was reported (Guslandi et al., 2003).

There are only few controlled clinical studies using probiotic in CD and the results were somehow inconsistent. Malin et al. (1996) reported that intake of *Lactobacillus rhamnosus* GG (2×10^{10} CFU/day, for 10 days) in pediatric CD stimulates the gut IgA levels, which could promote the gut immune response. Furthermore, using the same probiotic strain and dose, Gupta et al. (2000) reported an improved clinical scores and intestinal permeability in an open-labeled pilot study with four children with CD. In contrast, Prantera et al. (2002) reported the ineffectivity of *Lactobacillus rhamnosus* GG in preventing post operative disease recurrence or reducing severity of recurrent lesion in patients with CD. In addition, *Lactobacillus johnsonii* La1 was also unable to prevent endoscopic recurrence in the 12 week period following ileo-caecal resection (Van Gossum et al., 2005). Chermesh et al. (2007) showed that post operative recurrence of CD patients was not prevented by Synbiotic 2000, a combination of 4 probiotic lactic acid bacteria (*Lactobacillus raffinolactis, L. paracasei, L. plantarum, Pediococcus pentosaceus*) and 4 prebiotic fermentable fibers (beta-glucans, inulin, pectin, resistant starch). However, combination treatment of antibiotic rifaximin and probiotic VSL#3 resulted in a significantly lower incidence of severe endoscopic recurrence compared with mesalazine treatment (Campieri et al., 2000). Combination of VSL#3 and *Saccharomyces boulardii* was also observed to give a therapeutic effect in patients with CD.

Gionchetti et al. (2000) investigated the efficacy of VSL#3 (at 6 g/day) oral administration in the maintenance of remission in chronic pouchities in the double blind controlled study. They found that 15% patients in the VSL#3 group had relapses, compared with 100% patients in the placebo group ($P<0.001$) over a nine month trial period. The mechanism of VSL#3's impressive effect has not been established. However, Gionchetti et al. (1999) have previously found that the intake of VSL#3 increases faecal concentration of lactobacilli, bifidobacteria and streptococci, as well as increases tissue levels of IL-10 in patients with chronic pouchitis. Since the efficacy disappears after stopping therapy, the efficacy of VSL#3 therapy was thought to be due to the ongoing presence of these factors. In contrast, Kuisma et al. (2003) showed that *Lactobacillus rhamnosus* GG was ineffective to prevent relapses in patients with chronic pouchitis in a placebo controlled trial. In an open-labeled study, combined *Lactobacillus rhamnosus* LGG and prebiotic fructooligosaccharide, when administered as adjuvant to antibiotic therapy, induce remission in patients with pouchitis (Friedman and Goerge, 2000).

Probiotic Strains and dose	Disease	Patients number and condition	Duration	Outcome Results	Reference
VSL#3 *	UC, in remission	20 adults (12 male, 8 female), intolerance to 5-ASA	12 months	75% patients remained in remission during study period, no side effects	Venturi et al. (1999)
Eschericia coli Nissle 1917 (1×10^{11}cfu/day)	UC, active	116 adult adults, treated with prednisolon + gentamicin plus either probiotic of mesalazine	3 months	Prebiotic induce remission as effective as mesalazine (standard treatment)	Rembacken et al. (1999)
Eschericia coli Nissle 1917 (1×10^{11} cfu/day)	UC, in remission	116 adult adults	12 months	Prebiotic shown equivalent efficacy with mesalazine in the maintenance of remission	Rembacken et al. (1999)
VSL#3	UC, active	30 adults	6 weeks	VSL#3 resulted in combined induction of remission/response rate of 70%, with no adverse effects	Bibiloni et al. (2005)
Saccharomyces boulardii	UC, in remission	25 adults, unsuitable for steroid therapy	1 months	71% patients remained in remission	Guslandi et al. (2003)
Yakult ** (1×10^{10} cfu/day)	UC	21 adults (11 male, 10 female)	12 months	73% patients treated with probiotic remained in remission, while only 10% placebo	Ishikawa et al. (2003)
Saccharomyces boulardii	CD, in remission	32 adults (20 male, 12 female)	6 months	Probiotic plus mesalamine reduced relapsing incindence compared to mesalamine alone	Guslandi et al. (2000)
Lactobacillus rhamnosus GG (2×10^{10} cfu/day)	CD	4 children	6 months	Improve gut barrier function, pediatric crohn's disease activity index (PCDAI) were 73% lower than baseline	Gupta et al. (2000)
Lactobacillus GG (1×10^{10} cfu/day)	CD	14 adults	10 days	Increase the IgA immune response, thus promote the gut immunological barrier	Malin et al. (1996)
VSL#3 (1.8×10^{12} cfu/day)	Pouchitis	40 adults	9 months	Reduced risk of relapse recurring, only 15% patient in probiotic group relapsed compared with 100% in placebo group	Gionchetti et al. (2000)
Cultura *** (5×10^{10} cfu/day)	Pouchits	10 adults	1 months	50% endoscopic improvement, but no histological improvement	Laake et al. (2003)
VSL#3 (1.8×10^{12} cfu/day)	Pouchitis	36 adults	12 months	Induced remission in 85% patients	Mimura et al. (2004)

*: VSL#3 (VSL Pharmaceuticals Inc., Fort Lauderdale, Florida, USA) contain 4 strains of Lactobacillus (L. casei, L. achidophilus, L. plantarum and L. bulgaricus), 3 strains of Bifidobacterium (B. longum, B. breve and B. infantis) and 1 strain of Streptococcus thermophilus.
**: Yakult (Yakult Honsha Co. Ltd., Tokyo, Japan) contain Bifidobacterium breve, B. bifidum and Lactobacillus acidhophilus.
***: Cultura® (TINE Dairies BA, Oslo, Norway) contain 1×1010 live Lactobacillus acidophilus and Bifidobacterium lactis per 100 g.

Table 2. Studies of probiotics in the management of inflammatory bowel disease (IBD)

8. The underlying mechanisms of the protective effects of probiotic bacteria

Many studies have been addressed to disentangle the mechanisms on how probiotic bacteria exert their beneficial effects on human health. Although not entirely understood, several mechanisms underlying the useful action of probiotic have been proposed by researchers. The mechanisms include production of inhibitory substances, competitive exclusion of microbial adherence or translocation, modulation of immune response and reinforcement of barrier function. These functions are likely interrelated in supporting the protective effect of probiotic. Furthermore, it should be emphasized that the action of probiotic is species and strains specific, thus, appropriate choice of microorganism is of particular attention to improve the efficacy of probiotic treatment.

8.1 Production of inhibitory substances

Probiotic bacteria produce various substances that perform as inhibitory agents to pathogenic bacteria. The inhibitory agents such as organic acids, hydrogen peroxide and bacteriocins are typically produced by probiotic. These compounds may reduce the number of viable cells as well as inhibit bacterial metabolism or toxin production (Rolfe, 2000). Several strains of Lactobacilli produce acetic, lactic and propionic acid that decrease the local pH thus inhibit the growth of many Gram-negative pathogenic bacteria. Some strains of Lactobacillus inhibit the growth of Salmonella enterotica merely by the production of lactic acid (Makras et al., 2006). The 2-component lantibiotics (lanthionine and methyllanthionine) are small microbial peptide bacteriocins produced by Gram positive bacteria such as Lactococcus lactis (Lawton et al., 2007). At nanomolar concentration, these peptides actively inhibit multidrug resistant pathogens by targeting the lipid II component of the bacterial cell wall (Morgan et al., 2005). Lactobacilli are also known to produce non-lanthione containing bacteriocins. A large group of bacteriocins with highly divergence sequences are produced by Lactobacillus strains including L. plantarum, L. sakei, L. acidophilus NCFM, and L. johnsonii NCC 533 (Makarova et al., 2006; Chaillou et al., 2005; Altermann et al., 2005; Pridmore et al., 2004). In addition, Collado et al. (2005) reported that several strains of human fecal Bifidobacteria produce bacteriocin like compounds that exert toxicity to both Gram-positive and negative bacteria.

8.2 Competitive exclusion of microbial adhesion or translocation

The adhesive properties of probiotic bacteria on epithelial cells enable the competitive inhibition of bacterial adhesion site, thus hampering colonization of pathogenic bacteria (He et al., 2001; Lee and Puong, 2002; Boudeau et al., 2003). Some probiotic have the ability to block the intestinal mucosal receptor, thus prevent adhesion of pathogenic bacteria. Several strains of Lactobacilli and Bifidobacteria are able to compete with many pathogenic bacteria such as Bacteroides vulgates, Enterobacter aerogene, Listeria monocytogenes, Staphylococcus aureus, Salmonella enterica, enterotoxigenic E. coli and enteropathogenic E. coli for intestinal epithelial cell binding (Collado et al., 2007; Candela et al., 2005; Roselli et al., 2006; Sherman et al., 2005). Displacement of pathogenic bacteria can also occur even if the pathogen have attached to intestinal epithelial cells prior to prebiotic treatment (Collado et al., 2007; Candela et al., 2005). Nevertheless, specific strains of probiotic or its combinations are required to inhibit or displace specific strains of pathogen (Collado et al., 2007).

8.3 Modulation of immune response

Probiotic bacteria play a key role in stimulating the immunity by increasing immunoglobulin A (IgA) production (Gewirtz et al., 2002). Bakker-Zierikzee et al. (2006) reported that fecal sIgA levels increase in infants fed with Bifidobacterium animalis enriched formula, and suggested that the use of probiotic may reinforce innate function. Interestingly, beside resulting in increased levels of fecal sIgA, spleen cells of mice treated with non viable LGG exhibited enhanced secretion of IL-6 which stimulate IgA antibody response at the mucosal surface (He et al., 2005). Moreover, probiotic protects the intestine from pathogen induced injury by modulating the balance of pro and anti-inflammatory cytokine production. Probiotic increase anti-inflammatory interleukin (IL)-10 and inhibited generation of inflammatory Th1 cells as well as decreases pro-inflammatory IL-12 (Hart et al., 2004). For instances, VSL#3 induces the production of IL-10 in human and murine dendritic cells (Drakes et al., 2004; Hart et al., 2004). Di Giancinto et al. (2005) reported that VSL#3 also stimulate IL-10 production in chemically induced IBD.

The ability of probiotic in suppressing pro-inflammatory cytokine production has been accounted for their efficacy in the treatment of IBD. Pena et al. (2005) said that LGG inhibit lipopolisaccharide (LPP) and Helicobacter pylori-stimulated tumor necrosis factor (TNF) production by murine macrophage. The authors further explained that substances derived from LGG decrease TNF production in macrophages in LGG conditioned cell culture media. In addition, Lactobacillus casei strain Shirota (LcS) inhibits the regulation of LPS-induced IL-6 and the production of IFN-γ by peripheral blood mononuclear cells isolated from normal and chronic colitis mice (Matsumoto et al., 2005). In colonic biopsies of inflamed mucosa from UC patients, Bifidobacterium longum was found to reduce the secretion of pro-inflammatory TNF-α and IL-8 (Bai et al., 2006). Moreover, Sturm et al. (2005) reported that E. coli Nissle 1917 inhibits peripheral bold T-cell cycle progression and expansion, increase IL-10 and decrease the liberation of TNF, IFN-γ and IL-2.

8.4 Reinforcement of barrier function

The defensive mechanisms of the intestinal epithelium are manifested by the intestinal barrier function which requires effective tight junctional complexes between the epithelial cells. The intestinal disintegrates are likely occur when the tight junctional structure or its function are disrupted, resulting in an increased ability of pathogenic bacteria to attach to the gut mucosa. Many studies revealed that the processes involved in mucosal barrier formation are possibly modulated by probiotic, as well as shown the function of probiotic in upregulating expression of defensins, mucins or other proteins associated with tight junction such as claudins and occludins. Therefore, the ability of probiotic in inducing barrier formation is considered as an important mode underlying their efficacy in the prevention and treatment of IBD. Zyrek et al. (2007) have shown that in vitro E.coli Nissle 1917 restored the disrupted epithelial barrier in the polarized T84 cell infected by enteropthogenic E. coli strains E2348/68. They found that E.coli Nissle 1917 increases expression and distribution of zonula occludens-2 (ZO-2) protein and of distinct protein kinase C isotopes to the cell surfaces to exert that protective function. Probiotic VSL#3 increased mucin gene expression and excretion in intestinal epithelial cells (Caballero-Franco et al., 2007). VSL#3 and Lactobacillus fermentum maintain the intestinal barrier function by upregulating the human β-defensin-2 (Schlee et al., 2008). β-defensin is an inducible antimicrobial peptide synthesized by the intestinal epithelial cells to prevent

bacterial adherence and invasion (Wehkamp et al.,2004). In rats with ethanol induced colitis, LGG increases the production of Muc6 and basal mucosal PGE2, resulting in an increased thickness of the mucosal mucus layer of the stomach (Lam et al., 2007). In addition to bacteria, Garcia Vilela et al. (2008) reported that yeast Saccharomyces boulardii induces the improvement but not normalization in leaky gut of CD patients.

The prevention of cytokine-induced epithelial damage by enhancing intestinal epithelial cell survival is another mechanism contributing the clinical efficacy of probiotic. Probiotic exhibit cytoprotective function by reducing intestinal epithelial apoptosis (Yan and Polk., 2002; Lin et al., 2008). Apoptosis is a major factor in the colonic inflammatory response and the pathogenesis of IBD (Sartor, 2002). LGG is found to prevents cytokine-induced apoptosis either in human or mouse intestinal epithelial cells by activating antiapoptotic Akt in a phosphatidylinositol-3-kinase (PI3K)-dependent manner, as well as preventing proapoptotic p38/MAPK activation (Yan and Polk, 2002).

9. Conclusion

Inflammatory bowel disease is a complex disorder in which both genetic and environmental factors involved in the pathogenesis of IBD. Most pivotal etiological factor for IBD is the alteration of gastrointestinal microbial flora to a larger proportion of harmful rather than beneficial bacteria. The alteration is likely to be strongly affected by the type of diet intake. Fibers containing foods are considered as good substances that may enhance the number of beneficial bacteria in the gut, thus maintaining the health of the gut. The end products of fiber fermentation by bacteria in the gut exert many beneficial impacts on either bacteria or host. For instance, short chain fatty acids, particularly butyrate that provides energy to the host and involved in regulating the anti-inflammatory constituents, was found to protect the gut. Efforts to manipulate the bacterial composition of the gut toward a more salutary regiment are of emerging interest today. The most prominent effort is by introducing probiotic (such as lactobacilli and bifidobacteria) and prebiotic (such as inulin and fructooligosaccharide) into the intestine. Probiotics and prebiotics have been used as altervative to current drug treatment in large number of studies of gastrointestinal disorder, particularly IBD. Several evidences support the efficacy of probiotic and prebiotic in the prevention and treatment of UC, CD or pouchitis. However, many trials have given conflicting results; thus large clinical trials using standardized methodology are required to reconfirm the evidences. In addition, more research should be better focused on mechanisms underlying the protective effects of probiotic and prebiotic; thus can be translated into meaningful clinical trial outcome.

10. References

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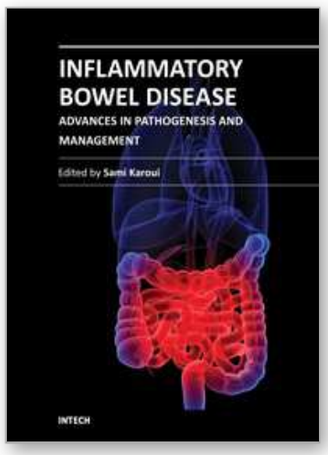

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This book is dedicated to inflammatory bowel disease, and the authors discuss the advances in the pathogenesis of inflammatory bowel disease, as well as several new parameters involved in the etiopathogeny of Crohn's disease and ulcerative colitis, such as intestinal barrier dysfunction and the roles of TH 17 cells and IL 17 in the immune response in inflammatory bowel disease. The book also focuses on several relevant clinical points, such as pregnancy during inflammatory bowel disease and the health-related quality of life as an end point of the different treatments of the diseases. Finally, advances in management of patients with inflammatory bowel disease are discussed, especially in a complete review of the recent literature.

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