

Use of prebiotics for inflammatory bowel disease

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L'emploi des prébiotiques dans les maladies inflammatoires de l'intestin

The relevance of diet in both the pathogenesis and the therapy of inflammatory bowel disease is an evolving science. Disturbance of intestinal microflora (dysbiosis) is putatively a key element in the environmental component causing inflammatory bowel disease. Prebiotics are among the dietary components used in an attempt to counteract dysbiosis. Such predominantly carbohydrate dietary components exert effects on the luminal environment by physicochemical changes through pH alteration, by production of short chain fatty acids and by selectively promoting putatively 'health-beneficial' bacteria. The present review elaborates on some of the background rationale and mechanisms on the use of prebiotics. Additionally, published animal and human trials are discussed.

La pertinence du régime tant dans la pathogénèse que dans le traitement des maladies inflammatoires de l'intestin est une science évolutive. Des perturbations de la microflore intestinale (la dysbiose) sont présumément des éléments essentiels des composants environnementaux responsables des maladies inflammatoires de l'intestin. Les prébiotiques font partie des composants diététiques utilisés pour tenter de contrer la dysbiose. De tels composants diététiques à prédominance de glucides exercent des effets sur le milieu luminal par des modifications physicochimiques à cause de l'altération du pH, de la production d'acides gras à courte chaîne, ainsi que par la promotion sélective de bactéries présumément « bénéfiques pour la santé ». La présente analyse s'étend sur une partie de l'histoire et des mécanismes de l'usage des prébiotiques. De plus, on examine des essais publiés sur des animaux et sur des humains.

Key Words: *Inflammatory bowel disease; Prebiotics*

The role of diet in inflammatory bowel disease (IBD) has been difficult to elucidate, but may be relevant to both pathogenesis and treatment. Current emphasis on dietary therapy examines the role of anti-inflammatory molecules or food additives that promote putatively beneficial bacteria. These nutrients include prebiotics, defined by Gibson and Roberfroid (1) as "a nondigestible 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". While the use of live bacteria (probiotics) for therapy or maintenance in IBD has been frequently discussed (2-4), less attention has focused on the use of prebiotics (5). The present review will summarize studies, both animal and human, of the use of prebiotics.

Pathogenesis of IBD

Ulcerative colitis (UC) and Crohn's disease (CD) affect approximately one in 1000 people in industrialized countries. Although not very lethal, they do cause a significant reduction in the quality of life of patients (6). The cause(s) of these diseases remain unknown; however, significant progress in deciphering the pathogenesis has been made in the past 20 to 30 years. For example, it has become clear that the interaction of genetic predisposition (7), dysregulation of inflammatory response with failure of tolerance to ordinary antigenic stimuli (8,9) and environmental triggers are all instrumental in disease causation (10,11). Research in all areas continues and at this time it is difficult to assign a specific explanation for features of

abnormal mucin (12-17) (genetic or environmental effects of bacteria) and altered permeability (18-21) (genetic or effect of bacteria). A leading contender of environmental triggers is the effect of commensal bacteria (22-24). Combined with the loss of tolerance to such ordinary bacteria (25), there is a hyperimmune response leading to a cell-mediated cytokine cascade through a T helper 1 response in CD and a predominantly humoral or T helper 2 response in UC (26,27).

Changes in microbial flora by prebiotics

Bacterial microflora can be appreciated on two levels. Relatively free-floating (attached to particles) bacteria (described as planktonic) exist in the lumen. Bacteria attached to mucosa may be of different species and are associated with crosstalk with the host (28). A total increase in bacteria is observed in CD and UC, with a specific increase in aerobic populations and a decrease in bifidobacteria (in CD) (29) and lactobacilli (in UC) (30). In IBD, an increased presence of *Escherichia coli* has been observed attached to mucosal epithelium in both CD and UC (31-33). In addition, *Bacteroides* are reported to be a major microorganism found in IBD (34-37).

Acquisition of specific and permanent microflora in the lower intestine begins very soon after birth and remains quite stable in healthy individuals until later in life. Protective bifidobacteria start to diminish in late middle age and *Clostridium* species begin to increase progressively around the same time (38). These bacterial changes are thought to be related to altered health and may promote diseases associated with aging (eg, colorectal cancer).

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TABLE 1
Animal studies of inflammatory bowel disease using prebiotics

Author (ref)	Model	Prebiotic	Outcome
Madsen et al (66)	Interleukin-10 knockout mice	Oral lactulose	Prevents spontaneous colitis
Madsen et al (67)	Interleukin-10 knockout mice	Breast milk	Prevents colitis
Videla et al (71)	DSS colitis rats	Oral 1% inulin 400 mg/day	Prevents colitis
Rumi et al (72)	DSS colitis rats	Lactulose 300 mg/kg to 1000 mg/kg	↓ short chain fatty acids ↓ inflammation
Araki et al (73)	DSS colitis rats	GBF	Prevents colitis ↑ acetic acid, ↑ butyric acid ↑ bifidobacteria and eubacteria ↓ aerobic bacteria and <i>Bacteroides</i>
Fukuda et al (74)	DSS colitis rats	GBF	↓ myeloperoxidase ↓ pH
Kanauchi et al (75)	DSS colitis rats	GBF GBF + 5-aminosalicylic acid	↓ clinical inflammation ↑ cecal short chain fatty acids (combination better)
Kanauchi et al (76)	DSS colitis mice	GBF	Prevents clinical histological colitis
Holma et al (78)	Trinitrobenzene sulfonic acid rats	48 mg/kg transgalactooligosaccharides	↑ bifidobacteria/no prevention of colitis
Cherbut et al (79)	Trinitrobenzene sulfonic acid rats	Intragastric fructooligosaccharides	Improved histology of colitis

DSS Dextran sulfate sodium; GBF Germinated barley foodstuff; ↓ Decrease; ↑ Increase

The changes observed with aging qualify for the definition of dysbiosis, “a breakdown in balance between putative species of protective versus harmful intestinal bacteria” (39). As such, this term has been applied to IBD as well (especially CD) (39). In addition to the changes described above, the significant increase in enterobacterial species in both active CD and CD in remission (40) may facilitate adhesion of adherent bacteria to mucosa and set up conditions leading to an increased immunological response.

Alteration of the microbial flora can be executed temporarily by either antibiotics or dietary manipulation. Antibiotics have been traditionally used in severe cases of IBD. The evidence favouring the use of antibiotics is limited and better supported for colon involvement with CD (41). Because antibiotics also have potentially undesirable side effects, an alternate means of controlling dysbiosis would be ideal. In this context, two strategies have been used. First, the use of direct live probiotics has been tested. These bacteria have species-specific features that limit effects of other ‘harmful’ commensal species. Some of the described effects attributed to probiotic species in experimental conditions include stimulation of epithelial cell proliferation (42), enhancement of barrier function (43,44), prevention of pathogen epithelial adhesion (45), limitation on pathogen colony expansion (46,47) and anticytokine effects (48-50). Secondly, favourable manipulation of the luminal environment can also be achieved with the use of specific dietary components. The paramount dietary substances for this purpose are prebiotics.

The first prebiotics were mainly carbohydrates (1). The gold standard is inulin (a polyfructose molecule up to 60 fructose units in chain length) which is derived from leeks, onions and chicory (51). Hydrolysis products of inulin include oligofructose, with an average chain length less than 10 fructose units (51-53). However, the definition now embraces other products such as disaccharides (lactulose) and some noncarbohydrate-containing amino acid moieties. Germinated barley foodstuff

(GBF), which is a residue in the beer-making industry containing glutamine and a mixture of cellulose, hemicellulose and lignin, is also considered to be a prebiotic candidate (54). Furthermore, some other compounds such as resistant starch and other soluble fibres share some of the properties of prebiotics (54-57).

Two major features of these nondigestible products are relevant to their impact on the colonic environment. Bacterial metabolism leads to physicochemical alterations that include decreased pH because of lactic acid and short chain fatty acid (SCFA) production (acetate propionate and butyrate) (57). The specific bacteria, species of lactic acid-producing bacteria (LAB), metabolize prebiotics preferentially. These include lactobacilli and bifidobacteria; however, other microorganisms are affected as well, and some strict anaerobes like *Bacteroides* and *Clostridium* species may decrease in number (58-60).

The health benefits of SCFAs are thought to be related to their ability to replenish the metabolism of colonocytes, especially in distal UC, in which metabolism may be compromised (61). There may be a stimulation of apoptosis (62), stimulation of protective mucin (63) and inhibition of cytokines (64). In addition to physicochemical properties, the preferential metabolism by specific LAB could replicate benefits attributed to probiotics. Most recently, inulin and oligofructose have been clearly shown to alter both planktonic and mucosal-associated microflora (28).

Animal studies with prebiotics

Published studies to date on the use of prebiotics in IBD models have established proof of principle in animals (Table 1). Models used include the interleukin-10 knockout mouse that tends to reproduce a colitis resembling CD. Although the mice are normal at birth, by four weeks they develop a mild colitis which reaches a maximum severity by eight weeks (65). Madsen et al (66) have published at least two relevant studies with this model. In the first report, orally administered lactulose or *Lactobacillus reuteri* by rectal enema were able to attenuate

TABLE 2
Human studies of inflammatory bowel disease using prebiotics

Author (ref)	Patients (n)	Disease	Study type	Length	Active agent	Control	Outcome
Hallert et al (80)	29 remission	UC	RCT	4 months	Ispaghula husk	Placebo	Improved symptoms
Fernandez-Banares et al (81)	105 remission	UC	RCT open label	1 year	<i>Plantago ovata</i>	5-ASA	Equivalent effect
Mitsuyama et al (82)	10 active	UC	Pilot open label	4 weeks	GBF	–	Clinical endoscopic improvement
Kanauchi et al (83)	18 mild-moderate reactive	UC	Open label + standard therapy	4 weeks	GBF 20 g/day to 30 g/day	Standard therapy	Improvement ↑ bifido ↑ eubacteria
Kanauchi et al (84)	21 mild-moderate reactive	UC	Open label + standard therapy	24 weeks	GBF	–	Clinical score improved
Hussey et al (85)	10 active	CD	Open	6 weeks	Fructooligosaccharides + inulin	–	Weight gain PCDAI↓, ESR↓
Szilagyi et al (88)	10 remission	UC	Open control + standard therapy	3 weeks	Lactulose 10 g twice daily	–	Failure of adaptation
	10 remission	CD					
Welters et al (93)	20 active	IPAA	Double-blind RCT crossover	3 weeks	24 g inulin	Placebo	Inflammation improved ↓ <i>Bacteroides fragilis</i> ↓ 2° bile acids ↑ butyrate
Kuisma et al (94)	21 active	IPAA	Open retrospective diet questionnaire	–	Lactose	–	Inverse correlation with bacteria, sulfomucins

5-ASA 5-Aminosalicylic acid; CD Crohn's disease; ESR Erythrocyte sedimentation rate; GBF Germinated barley foodstuffs; IPAA Ileal-pouch-anal-anastomosis (pouchitis); PCDAI Pediatric Crohn's disease activity index; RCT Randomized controlled trial; UC Ulcerative colitis; ↓ Decrease; ↑ Increase

colitis. In the second study, breast milk from normal wild mice fed to interleukin-10-deficient mice also failed to develop colitis (67). While mouse-derived breast milk may be different from that of humans, the latter contains many components (68) including lactoferrin (which can inhibit bacterial pathogen growth [69]). However, fructooligosaccharides (FOS) in human milk are considered to be an important prebiotic element with bifidogenic properties (70). It is likely that similar processes could apply to mouse-derived breast milk. The use of dextran sulfate sodium produces a disease resembling UC after ingestion. At least six studies using this model of UC have shown response to a variety of prebiotics (inulin [71], lactulose [72] or GBF [73-76]), with clinical improvement, increased measurable SCFAs or markers of oxidative damage (like myeloperoxidase). In dextran sulfate sodium-challenged rats treated with GBF, both bifidobacteria and eubacteria were measurably increased and the total number of aerobes and bacteroides were decreased (73). In addition to these effects, the glutamine-containing portion of GBF may also exert independent effects. Rats exposed to glutamine alone, before another agent (trinitrobenzene sulfonic acid [TNBS]), showed resistance to inflammation (77).

Prebiotics, much like individual species of probiotics, may exert specific effects on the type of colitis induced. Using the TNBS (enema) model of Crohn's colitis, Holma et al (78) were unable to show prevention of colonic damage despite elevation of bifidobacteria using transgalactooligosaccharides (a manufactured prebiotic produced from lactose). The authors argued that perhaps TNBS was too severe a model of colitis. Nevertheless, Cherbut et al (79) using the same model showed that intragastric installation of FOS ameliorated colitis. Intracolonic installation of SCFAs at less than pharmacological

doses required the addition of LAB. The authors suggested that in this experiment FOS exerted benefits by supporting the growth of LAB in improving colitis.

Human studies with prebiotics

To our knowledge there are nine published papers on the use of prebiotics in some form in IBD (Table 2). Two studies are with fibre that represent candidate prebiotics in an expanding definition from the original. The first of these studies evaluated 29 patients with UC in remission. Over a four-month period Hallert et al (80) evaluated the effect of Ispaghula husks (*Plantago ovata*) against placebo while patients were maintained on standard therapy. There was a statistically significant quantity of symptomatic improvement in the intervention group (69% versus 24%).

The largest study is a randomized controlled trial in UC patients using fibre (*P ovata*). The study was conducted with 105 participants over 12 months and compared treatment failure rates between *P ovata* and 1.5 g per day mesalazine or a combination of both. The failure rate was 14 of 35 for fibre, 13 of 37 in the 5-aminosalicylic acid (5-ASA) group and 9 of 30 in the combination group. None of these differences were statistically or clinically significant, leading to the suggestion that fibre, while no better than 5-ASA, was of equivalent benefit for maintenance of remission. Patients treated with fibre had significantly increased measured butyrate in their stool (81).

There are three published open-label studies (82-84) comprising a total of 49 patients treated with GBF for mild to moderately active UC in Japan. The first pilot study by Mitsuyama et al (82) showed clinical improvement with GBF 30 g/day for four weeks. A follow-up study also for four weeks with 20 g to 30 g GBF per day using slightly larger numbers also showed clinical

improvement and confirmed that bifidobacteria and eubacteria were increased in the stool (83). A more recent study by the same group extended treatment for 24 weeks and again showed clinical improvement (84). In all of these studies, patients were continued on standard 5-ASA or corticosteroid therapy and these were continued throughout the observation period.

There is only one study to date which attempts to address the possible impact of prebiotics as therapy for CD (85). The study involved nasogastric feeding of 10 children with active CD for a period of six weeks using a whey protein peptide-based formula containing a mixture of FOS and inulin. Results showed the children gained weight and the pediatric CD activity index improved. Unfortunately, the role of added prebiotics is not clear because similar results can be obtained without their addition (86,87).

A second study is somewhat different. A small study (88) was published comparing 15 healthy controls with 20 patients with colonic IBD (9 UC, 9 CD, and two indeterminate colitis). The three-week intervention trial used 10 g of lactulose given twice daily and used the measurable instrument of colonic adaptation to the high-dose lactulose challenge to compare outcome in controls versus patients. Colonic adaptation is defined as diminished breath hydrogen and improved symptoms of sugar intolerance on repeat challenge after continued low-dose consumption of the specified sugar. The concept was based on the work of Flourie et al (89) and the hypothesis of Liao et al (90). The results showed that while controls achieved significant reductions in measured breath hydrogen and symptoms, the combined group and, especially, the separated CD patients failed to adapt. These results were interpreted in one of two ways. First, for IBD, the amount of lactulose may have been given for too brief an amount of time because both CD and UC are thought to be deficient in LAB (29,30). As such, a longer time of feeding may have to be given in patients rather than in healthy subjects to demonstrate adaptation. Secondly, an interesting possibility was that because both UC and CD can be associated with mucosal permeability defects, disaccharides that failed to reach the colon may be detected in the bloodstream (91). This short-circuiting may have relevance to lactose in lactose maldigesters with IBD. Lactose, a potential prebiotic, also has not been demonstrated to have an impact in disease development when predisease diet history is considered (92). Perhaps disaccharides are not ideal prebiotics in patients with established IBD. They may be more beneficial in preventing early IBD.

There are two papers published with the use of prebiotics for pouchitis. The first by Welters et al (93) reported the only double-blind placebo-controlled study. The study consisted of

20 patients and compared placebo with 24 g of inulin per day in a crossover design. Although the study was only three weeks long, inulin lowered luminal pH, increased butyrate concentrations and lowered secondary bile acid concentrations and *Bacteroides fragilis*. In addition, there was evidence of histological improvement.

The second study by Kuisma et al (94) differs from others in that it was not an intervention study. Thirty-two patients with a history of chronic pouchitis were included and a seven-day prospective food diary was obtained. The results of the diet questionnaire were compared with endoscopic and histological results from biopsies of pouches. As well, bacterial cultures were obtained. They found that both villous atrophy and colonic metaplasia correlated with fecal anaerobic bacteria. A low intake of lactose was associated with a predominance of sulfomucin (a characteristic of colonic mucosa). In addition, there was also an inverse association with lactose intake and fecal aerobes. The authors concluded that the relationship between lactose intake and findings of mucin and fecal bacteria supports a possible prebiotic effect of lactose.

CONCLUSIONS

Conclusions drawn from the present review on the use of prebiotics for IBD include the following. In general, proof of principle has been established that prebiotics work. Improvement of colitis is either due to their physicochemical properties, stimulation of predominantly LAB species or both. While there is an expectation that prebiotics have a wider spectrum of effect on existing microflora despite original definitions there does exist some variation in effect (eg, failure of transgalactooligosaccharides versus FOS).

We are in the early stages of applying basic research with prebiotics to human benefits. The studies reported herein require confirmation; however, to date, the use of fibre for remission in UC and the therapeutic benefit of GBF in mild-to-moderate UC appear to offer some optimism. Similarly, the adjunctive use of inulin for pouchitis may have benefits to maintain remission.

Note: While awaiting publication of this manuscript, Furrie et al (95) published a small randomized controlled trial combining inulin/oligofructose with the probiotic *Bifidobacterium longum*. In the short term, remission was induced in the active combination group demonstrating usefulness of both agents together on UC.

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