

# Inulin and Oligofructose in Chronic Inflammatory Bowel Disease<sup>1–3</sup>

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## Abstract

Crohn's disease and ulcerative colitis, also called chronic inflammatory bowel diseases (IBD), affect up to 500 per 100,000 persons in the Western world. Recent studies in the etiology of IBD suggest that these diseases are caused by a combination of genetic, environmental, and immunological factors. Results from humans and especially animal models of colitis reported by our group and others have indicated that these diseases result from a lack of tolerance to resident intestinal bacteria in genetically susceptible hosts. Probiotic bacteria have health-promoting effects for the host when ingested and have also shown efficacy in ulcerative colitis and refractory pouchitis. In light of the efficacy of providing probiotic bacteria to patients with IBD, there has been interest in the prophylactic and therapeutic potential of inulin, oligofructose, and other prebiotics for patients with or at risk of IBD. Prebiotics are nondigestible dietary oligosaccharides that affect the host by selectively stimulating growth, activity, or both of selective intestinal (probiotic) bacteria. Prebiotics are easy to administer and, in contrast to probiotic therapy, do not require administration of large amounts of (live) bacteria and are therefore easier to administer. Studies using prebiotics, especially  $\beta$ -fructan oligosaccharides, for the treatment of chronic intestinal inflammation have shown benefit in animal models of colitis. Studies using these prebiotics alone or in combination with probiotics are emerging and have shown promise. These dietary therapies could lead to novel treatments for these chronic debilitating diseases. J. Nutr. 137: 2572S–2575S, 2007.

## Introduction

Crohn's disease and ulcerative colitis (UC),<sup>4</sup> collectively referred to as inflammatory bowel diseases (IBD), are chronic idiopathic inflammatory diseases of the gastrointestinal tract that affect up to 500 per 100,000 persons in the Western world. IBD is generally regarded as a Western world disease, and its frequency has increased considerably over the past few decades (1).

Quality of life is severely affected in IBD patients, mainly by the chronic relapses of disease.

## Clinical features

**Crohn's disease.** Although Crohn's disease and UC are both inflammatory disorders of the intestinal tract, they have distinct patterns of symptoms and therapeutic strategies. Crohn's disease was first described in 1932 by Crohn, Ginsberg, and Oppenheimer as "ileitis regionalis," to be distinguished from intestinal tuberculosis (2). Although Crohn's disease can occur at any location in the intestinal tract, the highest incidences are reported in the distal ileum, cecum, and right-sided colon. Clinical symptoms are diverse and involve nonbloody diarrhea, abdominal cramps, fever, weight loss, and perianal manifestations. Associated complications include fistulas to skin and internal organs, strictures, and perirectal abscess formation. Gross appearance shows a thickened intestinal wall with a narrowed lumen, which can lead to bowel obstruction. In more advanced stages of the disease, the mucosa has a nodular appearance, often referred to as cobblestones. Characteristic histopathologic features of Crohn's disease that do not occur in UC are transmural inflammation affecting all layers of the intestinal wall and mesenteric lymph nodes and chronic noncaseating granulomatous inflammation. The intestinal tract in Crohn's disease shows a discontinuous pattern: severely affected regions alternate with normal parts, the so-called skip-lesions. Current treatments for mild to moderate Crohn's disease include steroids, 5-aminosalicylic acid, and

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<sup>3</sup> In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all  $\beta$ -(2 $\rightarrow$ 1) linear fructans. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain or high-molecular-weight inulin will be used, respectively. Even though the oligomers obtained by partial hydrolysis of inulin or by enzymatic synthesis have a slightly different DP<sub>av</sub> (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Synergy will be used to identify the 30/70 mixture (wt:wt) of oligofructose and inulin HP otherwise named oligofructose-enriched inulin.

<sup>4</sup> Abbreviations used: DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; TG, transgenic; TNBS, trinitrobenzene sulfonate; UC, ulcerative colitis.

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antibiotics. More severe and recurrent Crohn's disease requires azathioprine/6-mercaptopurine (3,4), methotrexate (5), and/or anti-TNF (6,7) therapy as well as other biologic therapies. Surgical interventions are necessary to treat complications and drug-resistant patients.

**Ulcerative colitis.** UC was first described by Wilks in 1859 (6). UC is always restricted to the colon and involves the rectum. Major symptoms reflect colonic inflammation: diarrhea, rectal bleeding, and abdominal pain, often accompanied by fever and weight loss. The inflammation primarily involves the colonic mucosa, is uniform and continuous, and always progresses proximally. Pseudopolyps are commonly found during endoscopy. Initial microscopic findings include goblet cell depletion, crypt hyperplasia, and neutrophilic infiltration. Chronic UC can lead to dysplasia, with increased risk for colorectal cancer in later stages of disease. Laboratory findings show perinuclear staining for antineutrophil cytoplasmic antibodies in 70% of UC patients. Medical treatment of UC includes systemic and topical steroids and 5-aminosalicylic acid for mild to moderate UC. More severe and steroid-dependent disease requires azathioprine/6-mercaptopurine for maintenance of remission or even intravenous cyclosporine (7) and lately anti-TNF (8) for severe refractory disease. Because UC is restricted to the colon, surgical treatment by total colectomy will potentially cure the disease. Therapies directed against disease-inducing bacteria, such as probiotic and prebiotic therapies, are emerging and are discussed in this and other articles in this Supplement.

### Commensal intestinal bacteria and IBD

Although the exact pathogenesis of IBD is still relatively unknown, progress has been made in recent years to obtain a better understanding. Recent studies in the etiology of IBD suggest that these diseases are caused by a combination of genetic, environmental, and immunological factors (9).

The role of intestinal bacteria in the pathogenesis of IBD is well recognized (10), particularly in Crohn's disease. This chronic intestinal inflammation typically occurs at sites with the highest concentrations of intestinal bacteria, such as the colon and terminal ileum. Antibiotics and fecal diversion are effective treatments for Crohn's disease (11), whereas reestablishing continuity of the bypassed distal bowel or infusion of intestinal contents into the excluded ileum leads to disease recurrence (12). The role of intestinal bacteria in the initiation and perpetuation of chronic intestinal inflammation is most convincingly demonstrated in several rodent models of chronic intestinal inflammation in which genetically susceptible hosts

develop spontaneous colitis in the presence of commensal intestinal organisms, also called specific pathogen-free conditions. Most importantly, no disease occurs in the germ-free state (13).

HLA-B27 transgenic (TG) rats develop colitis in the presence of normal intestinal bacteria starting at 8 wk after birth (14), whereas non-TG rats, antibiotic-treated TG rats, and germ-free TG rats remain disease-free (15,16). Exacerbation of colitis correlates with increased densities of luminal *Bacteroides* spp. (17). *Bacteroides* spp. are among the most prevalent anaerobic organisms in the distal intestine (9). Early postoperative recurrence of Crohn's disease after surgical resection is associated with increased *Bacteroides* spp. (18). Most importantly, *B. vulgatus* preferentially induces colitis in TG rats after monoassociation for 4 wk, whereas monoassociation with *E. coli* does not cause disease (19). These findings indicate that not all bacteria are equal in their capacity to induce colitis.

### Probiotics and IBD

Several studies have shown that IBD patients have reduced numbers of colonic protective bacteria compared with non-IBD controls (20,21). A probiotic cocktail including 4 strains of lactobacilli, 3 strains of bifidobacteria, and 1 *Streptococcus salivarius* (VSL#3) maintains remission of refractory pouchitis after transient antibiotic therapy (22). The same probiotics showed efficacy in an open-labeled study to treat mild to moderate UC (23). Several probiotic preparations, including VSL#3, are also effective in experimental colitis (24). Dieleman et al. recently showed that oral *Lactobacillus rhamnosus* GG (*L. GG*) treatment significantly reduces colitis relapse after antibiotic treatment in specific pathogen-free TG rats, whereas another probiotic strain, *L. plantarum* 299v, has no effect (25).

Probiotics exert protection by several mechanisms, either as live organisms or through their secreted proteins, cell wall components, or DNA (26). These mechanisms include decreasing growth and epithelial binding by disease-inducing bacteria, improved epithelial function by production of short-chain fatty acids, and decreased intestinal permeability as well as immunoregulatory activities (24).

### Prebiotics and IBD

Prebiotics are nondigestible food and plant ingredients, mostly oligosaccharides, that beneficially affect the host by selectively stimulating growth, activity, or both of selective intestinal (probiotic) bacteria (27). Chicory-derived inulin and its hydrolysis product oligofructose are inulin-type  $\beta$ -fructans that are linked by  $\beta$ -(2-1) linkages that differ in a high (10-60)

**TABLE 1** Probiotic, prebiotic, and synbiotic treatment in experimental colitis

| Author (date)                      | Treatment  | Animal model                 | Result                     |
|------------------------------------|--|------------------------------|----------------------------|
| Prebiotic treatment                |  |                              |                            |
| Videla et al. (2001) (32)          | Dietary inulin   | DSS-induced colitis in rats  | Improvement distal colitis |
| Holma et al. (2002) (36)           | Galacto-oligosaccharides   | TNBS-induced colitis in rats | No reduction of colitis    |
| Moreau et al. (2003) (35)          | Oligofructose  | DSS-induced colitis in rats  | No reduction of colitis    |
| Hoentjen et al. (2005) (29)        | Oligofructose-enriched inulin  | HLA-B27 transgenic rat       | Reduction of colitis       |
| Daddaoua et al. (2006) (34)        | Goat milk oligosaccharides   | Hapten-induced colitis       | Colitis reduction          |
| Lara-Villoslada et al. (2006) (33) | Goat milk oligosaccharides   | DSS-induced colitis in rats  | Colitis reduction          |
| Synbiotic treatment                |  |                              |                            |
| Schultz et al. (2004) (30)         | SIM: inulin and the probiotic microorganisms <i>L. acidophilus</i> La-5 and <i>Bifidobacterium lactis</i> Bb | HLA-B27 transgenic rat       | Colitis reduction          |

**TABLE 2** Clinical trials of probiotic, prebiotic and synbiotic treatment in IBD

| Author (date)              | Study                                 | n  | Clinical situation     | Treatment   | Duration of treatment | Result                                      |
|----------------------------|---------------------------------------|----|------------------------|---|-----------------------|---|
| Prebiotic treatment        |                                       |    |                        |   |                       |   |
| Welters et al. (2002) (37) | Double-blind placebo-controlled trial | 20 | Chronic pouchitis      | Dietary inulin 24 g/d   | 6 wk                  | Effective in treatment of chronic pouchitis |
| Lindsay et al. (2006) (39) | Open-labeled trial                    | 10 | Active Crohn's disease | Synergy 15 g/d  | 3 wk                  | Reduction of disease activity               |
| Synbiotic treatment        |                                       |    |                        |   |                       |   |
| Furrie et al. (2005) (38)  | Double-blind placebo-controlled trial | 18 | Active UC              | Synbiotic: 2x1 011 <i>Bifidobacterium longum</i> + 6 g of Synergy twice daily | 1 mo                  | Reduction of intestinal inflammation        |

(inulin) and low (3–7) (oligofructose) number of fructose monomers. They naturally occur at high levels in plants such as chicory, leek, onion, garlic, and asparagus (28).

### Prebiotics and experimental colitis (Table 1)

Studies using prebiotics for the treatment of chronic intestinal inflammation are emerging and have been performed mostly in animal models. Feeding a chicory-derived long-chain inulin plus oligofructose mixture (Synergy) at 5 g/kg body weight reduces colitis in TG rats (29). (Note that a dose of 5 g/kg body weight given to HLA-B27 rats does not correspond with the dose given to human IBD patients). The HLA-B27 transgenic rat used in this research project is a model that is used to assess working mechanisms of prebiotic treatment in chronic colitis. This beneficial effect was seen in conjunction with an increase of intestinal bifidobacteria and lactobacilli. In addition, feeding this prebiotic combination to the colitis-susceptible rats not only reduced mucosal proinflammatory cytokines but also increased the immunoregulatory transforming growth factor- $\beta$ . Schultz et al. showed a beneficial effect with inulin plus probiotics in TG rats (30).

Lactulose and inulin have been shown to attenuate inflammation in IL-10 knockout mice and dextran sodium sulfate (DSS)-induced colitis, respectively (31,32).

In DSS-induced colitis, rats that were fed goat's milk oligosaccharides showed reduced clinical symptoms, and increased MUC-3 expression was observed compared with control rats (33). Goat's milk oligosaccharides also caused decreased colonic inflammation and fewer necrotic lesions in trinitrobenzene sulfonate (TNBS)-induced colitis in rats compared with untreated controls (34). However, not all studies using prebiotics have resulted in positive outcomes. Moreau et al. (35) found oligofructose to be ineffective in improving DSS-induced colitis in rats, and Holma et al. (36) reported a similar inefficacy of galacto-oligosaccharides in TNBS-colitis rats.

### Prebiotics and UC

Although there is a paucity of human studies using prebiotics, the few emerging studies showed that there is potential for this treatment modality (Table 2). Inulin was effective in the treatment of chronic pouchitis after colectomy for UC (37). A recent randomized, double-blinded controlled trial by Furrie et al. examined the use of prebiotics plus probiotics, also called synbiotics, in 18 patients with active UC (38). This therapy consisted of a combination of *B. longum* and a prebiotic mixture of inulin and oligofructose (Synergy). Sigmoidoscopy inflammation scores were reduced in the synbiotic-treated population compared with the placebo group. Intestinal TNF and IL-1 $\alpha$  levels were also reduced. Additionally, rectal biopsies demonstrated

reduced inflammation and more epithelial regeneration in the synbiotic-treatment group.

### Prebiotics and Crohn's disease

In a small, open-labeled trial of 10 active CD patients, 21 d of 15 g oligofructose and inulin (Synergy) oral intake resulted in a significant decrease of disease activity from baseline, an increase of intestinal bifidobacteria, and concurrent modifications of the innate immune system, such as increased expression of Toll-like receptors and increased IL-10 expression in mucosal dendritic cells (39) (Table 2).

The link between the intestinal microflora as part of the host-bacteria interaction for the pathogenesis of IBD is currently being heavily studied. Altering the composition of the microflora using probiotics and/or prebiotics holds promise as a therapeutic strategy for ameliorating chronic intestinal inflammation. Future developments in this field must include rigorous double-blind, placebo-controlled trials, using probiotics and/or prebiotics, along with a further understanding of their protective mechanisms. Because of their excellent safety profile and lack of serious side effects, there is little contraindication to the consumption of prebiotics, probiotics, and their combination (synbiotics) by IBD patients. Further understanding of the interactions between microbes and the gastrointestinal tract will help identify which strains of bacteria and/or which prebiotics may be effective in different types of chronic inflammatory disease.

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