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Inulin and Oligofructose: Health Benefits and Claims–A Critical Review

Studies with Inulin-Type Fructans on Intestinal Infections, Permeability, and Inflammation[1–3]

Francisco Guarner*

Digestive System Research Unit, University Hospital Vall d'Hebron, CIBEREHD, Barcelona, Spain

Abstract

Symbiosis between host and gut bacteria can be optimized by prebiotics. Inulin-type fructans have been shown to improve the microbial balance of the intestinal ecosystem by stimulating the growth of bifidobacteria and lactobacilli. These changes have been associated with several health benefits, including the prevention of gastrointestinal and systemic infections in animal models and human studies. Inulin-type fructans induce changes of the intestinal mucosa characterized by higher villi, deeper crypts, increased number of goblet cells, and a thicker mucus layer on the colonic epithelium. Bacterial antagonism and competition of bifidobacteria and lactobacilli with pathogens, as well as the trophic effects on the intestinal epithelium, may explain the protective role of inulin against enteric infections. In contrast, studies with rats fed a low-calcium diet suggested a negative effect of prebiotics on intestinal barrier function. However, the adverse effect was clearly ascribed to the strong reduction of dietary calcium, as it could be reversed by oral administration of calcium. The adverse effect of a low-calcium diet on intestinal permeability has not been observed in humans. Inulin and oligofructose are now being tested in human studies aimed at prevention of bacterial translocation in critical health conditions. Mixtures of probiotics and prebiotics including inulin or oligofructose significantly reduced the rate of postoperative infections in liver transplant patients. Finally, inulin and oligofructose have proven useful to prevent mucosal inflammatory disorders in animal models and in patients with inflammatory bowel disease. J. Nutr. 137: 2568S–2571S, 2007.

Introduction

The human gut is the natural habitat for a large, diverse, and dynamic population of microorganisms that, over millennia, have adapted to live on the mucosal surfaces or in the lumen (1). The interaction between gut bacteria and their host is a symbiotic relationship mutually beneficial for both partners. The host provides a nutrient-rich habitat, and the bacteria confer important benefits to the host (2). Functions of the microbiota include nutrition (fermentation of nondigestible substrates that results in production of SCFA, absorption of ions, production of amino acids and vitamins), protection (the barrier effect that prevents invasion by alien microbes), and important trophic effects on the intestinal epithelium and the immune system (development and homeostasis of local and systemic immunity) (1,3).

The symbiosis between host and gut bacteria can be improved by prebiotics. Inulin and oligofructose are food ingredients that resist digestion by intestinal and pancreatic enzymes in the human gastrointestinal tract and are selectively fermented by bacteria living in the intestinal ecosystem. Numerous studies have shown that both inulin and oligofructose selectively stimulate the growth of bifidobacteria and lactobacilli in the human gut and that this effect is associated with a number of health benefits (4). Thus, inulin-type fructans are properly defined as prebiotics, as they fulfill the required criteria (5).

A healthy or "balanced" microbiota has been considered to be one that is predominantly saccharolytic and comprises significant numbers of bifidobacteria and lactobacilli (6). The genera *Bifidobacterium* and *Lactobacillus* do not contain any known pathogens. Review of the medical literature (7) and a consensus report by experts (8) indicate that these genera are safe. The risk of infection by these bacteria is in the "negligible" range, taking into account that exposure to them is universal and persistent, as they are common colonizers of the human body (digestive tract, oral and vaginal cavities). This lack of pathogenicity extends across all age groups, including preterm infants (9,10).

The epithelial surface of the intestine is heavily colonized by bacterial communities, which grow in biofilms on the mucosa.

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[3] In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all β–(2←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_{av} (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.

* To whom correspondence should be addressed. E-mail: fguarner@vhebron.net.

These bacteria are likely to be important in modulating the "barrier effect" (1), i.e., resistance to colonization by exogenous microbes and prevention of invasion by pathogens. Interestingly, animal and human studies have shown that consumption of inulin and oligofructose increases the number of bifidobacteria and lactobacilli in the mucosa-associated communities of the colon (**Table 1**) (11,12). Thus, inulin and oligofructose, by increasing the number of "friendly" bacteria on the mucosal surface, may improve the gut mucosal barrier and prevent gastrointestinal infections with enteric pathogens as well as systemic infections from translocation of gut bacteria. The current article reviews experimental and human studies that have tested this hypothesis.

Experimental studies

In mice inoculated orally with the pathogen yeast *Candida albicans*, dietary inulin or oligofructose significantly reduced the numbers of viable pathogen recovered from the intestine 7 d after inoculation (13). The improved clearance of the pathogen from the intestinal lumen was not a result of translocation because both incidence and density of pathogen recovery in mesenteric lymph nodes were very low, and no difference was found between control and prebiotic-fed mice. In another set of experiments, mortality from *Listeria monocytogenes* infection was significantly prevented in mice fed inulin and oligofructose (13). Likewise, mice fed the diet with inulin had lower mortality after challenge with *Salmonella typhimurium* compared with control mice (13). The findings were consistent with an enhancement of defense mechanisms probably related to changes induced by the prebiotic in the composition and metabolic activity of gut bacteria. These experiments show how intervention on enteric immunity can be transferred systematically.

The effects of inulin-type fructans on intestinal mucosal morphometry (height of villi, depth of the crypts, number of goblet cells) and thickness of the epithelial mucus layer were investigated by comparing germ-free rats and rats with a human fecal flora (11). The colonic epithelial mucus layer was thicker and the number of goblet cells was greater in human fecal flora-associated rats than in germ-free rats, and these features were enhanced by the diet containing inulin and oligofructose. Moreover, the prebiotic diet resulted in higher villi and deeper crypts in bacteria-associated but not in germ-free rats, suggesting that bacterial metabolism of the inulin-type fructans was an essential requirement for the trophic effect on mucosal architecture. An important finding of this study was the observation that inulin-type fructans stimulated the number of bifidobacteria in the mucosa-associated flora, as assessed by molecular techniques based on fluorescent in situ hybridization with 16S rRNA-targeted probes. Taken together, these changes suggested a role of these prebiotics in improving stability of the gut mucosal barrier (11).

TABLE 1 Effect of inulin-oligofructose on mucosa-associated flora*

	Proximal colon		Distal colon	
	Control	Prebiotic	Control	Prebiotic
Total anaerobes	8.5 ± 0.2	8.6 ± 0.2	8.7 ± 0.1	8.6 ± 0.1
Facultative anaerobes	6.4 ± 0.4	5.9 ± 0.4	6.4 ± 0.3	5.9 ± 0.4
Bifidobacteria	5.3 ± 0.4	6.3 ± 0.3*	5.2 ± 0.3	6.4 ± 0.3*
Eubacteria	4.5 ± 0.3	6.0 ± 0.4*	4.6 ± 0.3	6.1 ± 0.3*
Clostridia	5.1 ± 0.3	4.9 ± 0.3	5.0 ± 0.3	4.9 ± 0.3
Lactobacilli	3.0 ± 0.1	3.7 ± 0.2*	3.1 ± 0.1	3.6 ± 0.2*
Bacteroides	8.1 ± 0.3	8.3 ± 0.2	8.3 ± 0.2	8.5 ± 0.2
Enterobacteria	6.2 ± 0.4	5.6 ± 0.4	6.4 ± 0.3	5.9 ± 0.4

* Volunteers were fed either a prebiotic mixture (7.5 g/d oligofructose plus 7.5 g/d of inulin) for 2 wk or not given anything (12). Mucosal bacterial communities in biopsies from proximal and distal colon were characterized to species level and quantified. Data are logarithm counts of colony-forming units per gram of tissue, expressed as mean and standard error (*$P < 0.05$ vs. Control).

Further studies with this rat model by the same group of investigators tested the efficacy of the prebiotic diet in preventing colonization by the pathogenic species *Salmonella typhimurium* (14). Fifteen days after oral inoculation, high numbers of the pathogen were detected in mesenteric lymph nodes as well as in Peyer's patches and the mucus layer of the ileum. However, the survival of *Salmonella* in the intestinal lumen was inhibited in rats fed an inulin-oligofructose diet as compared with controls, and pathogen densities in the Peyer's patches were significantly lower. Translocation of *S. typhimurium* to mesenteric lymph nodes was partly reduced by the prebiotic diet, but changes did not reach statistical significance. A loss of adhesion sites for *Salmonella typhimurium* could explain these effects because increased numbers of mucosa-associated bifidobacteria were found in the ileum of rats fed an inulin-oligofructose diet (14). These data suggested that modulation of gut mucosal biofilms with inulin-type fructans to favor the growth and activity of health-promoting bacteria could be a way to reinforce the mucosal barrier function and protect the intestinal epithelium.

In contrast to these observations, a series of publications by a single group of investigators have reported a potential risk of translocation of enteric pathogens after prebiotic consumption in rats on a low-calcium diet (15–17). These studies were based on the hypothesis that rapid fermentation of prebiotics would produce high concentrations of SCFA that could compromise the mucosal barrier function. Rats were put on a low-calcium diet, 20 (15) or 30 mmol/kg diet (16,17), whereas the recommended amount is 125 mmol/kg diet (18). After 2 wk on this regimen, oral inoculation of the pathogen *Salmonella enteritidis* was associated with increased fecal water cytotoxicity, as tested in vitro with a suspension of red blood cells, increased excretion of nitrates and nitrites in urine, and increased excretion of mucins in feces. All these 3 responses to *Salmonella* infection were enhanced by oligofructose or lactulose in rats fed the low-calcium diet (15–17) but not in rats with a normalized calcium intake (100 mmol/kg diet) (17). Previous work by this group of investigators had already shown that calcium intake plays a critical role in the resistance against *Salmonella enteritidis* (19,20). Moreover, they also reported a protective effect of the prebiotic lactulose in rats with a calcium-supplemented diet (21).The interpretation of these studies is difficult. Usually, cytotoxicity of fecal water is tested in vitro using intestinal epithelial cells rather than red blood cells, which may be too susceptible to changes in pH by SCFA, whereas intestinal epithelial cells normally use organic acids as an energy source. Likewise, translocation of gut bacteria is demonstrated by the detection of viable bacteria in mesenteric lymph nodes rather than by the urinary excretion of nitrites and nitrates, which measures the host response (for instance, the oxidative burst of white blood cells can be enhanced by probiotics) (22). Fecal mucin excretion is not a marker of mucosal irritation. Indeed, mucins are secreted in response to irritation as a repair mechanism, but other functions of mucins are lubrication to improve transit and nutrition of commensal bacteria (2). Fibers increase mucin secretion for lubrication purposes, and this is not associated with a deranged barrier function, but, on the contrary, deficiency of dietary fiber results in colonic mucosal fragility (23). In any case, studies with human volunteers on low (24) or normal (25,26) calcium intake did not show changes in barrier function,

as assessed by the EDTA test (24,25), or changes in fecal water cytotoxicity (24,26) associated with fructan consumption.

Clinical studies

A randomized, placebo-controlled study tested the efficacy of oligofructose-enriched inulin in the prevention of traveler's diarrhea in 2 parallel groups (27). The prevalence of diarrhea in subjects traveling to high- or medium-risk destinations was less in the treated group (11.2%) than in the placebo group (19.5%), but this was not statistically significant ($P = 0.08$). However, those subjects taking oligofructose-inulin experienced less severe attacks of diarrhea than the placebo group (28).

Saavedra and Tscherina (29) conducted a randomized, blinded clinical trial of infant cereal supplemented with oligofructose and found that children consuming the supplemented cereal had fewer symptoms associated with loose stools, fewer physician visits for diarrhea, and fewer missed days of daycare because of diarrhea than did children consuming nonsupplemented cereal. On the other hand, a large, randomized, blinded trial of prebiotic supplementation was unable to document any effect on the occurrence or severity of diarrhea in free-living Peruvian infants, aged 6 to 12 mo at entry and followed for 6 mo (30). A possible reason alleged for the lack of effect of the prebiotic in the Peruvian trial could be the widespread practice of breast-feeding among the population studied, because oligosaccharides in human milk may play a role in intestinal host defense against pathogens (30).

Antibiotic-associated diarrhea caused by the bacterium *Clostridium difficile* is a significant cause of morbidity and mortality for hospitalized patients, and a substantial proportion of patients experience relapse after successful treatment. A recent study tested the effect of oligofructose in 142 consecutive inpatients with *C. difficile* -associated diarrhea, randomly allocated to receive oligofructose or placebo for 30 d in addition to specific antibiotic treatment (31). As shown in **Figure 1**, relapse of diarrhea was more common in those taking placebo (34.3% in placebo vs. 8.3% in oligofructose, $P < 0.001$). Thus, oligofructose appears to be effective at preventing relapse of *C difficile*–associated diarrhea.

Rayes et al. (32) conducted a prospective randomized study in 95 liver transplant patients comparing the incidence of infections among 3 groups of patients on early enteral nutrition after surgery. The first group ($n = 32$) received selective digestive tract decontamination with antibiotics for 6 wk. The second group ($n = 31$) received the probiotic *Lactobacillus plantarum* plus 15 g of fermentable fibers including inulin for 12 d postoperatively. Finally, the third group ($n = 32$) received heat-killed *Lactobacillus plantarum* and the fermentable fibers. Interestingly, the number of postoperative infections was significantly higher in the antibiotic group (23 infections involving 15 patients) than in the other 2 groups (4 infections in 4 patients, and 17 infections in 11 patients, respectively), which did not receive prophylaxis with antibiotics. The presence of the live probiotic was associated with the best outcome. In a study with patients undergoing elective abdominal surgery, Anderson et al. (33) did not observe significant differences in postoperative infections between synbiotic- (15 g oligofructose plus a probiotic mix) and placebo-treated patients. However, the number of enteric microorganisms isolated from mesenteric lymph nodes was higher in placebo (8 of 56) than in synbiotic-treated (4 of 66) patients, suggesting a lower rate of bacterial translocation in the subjects receiving synbiotic before surgery.

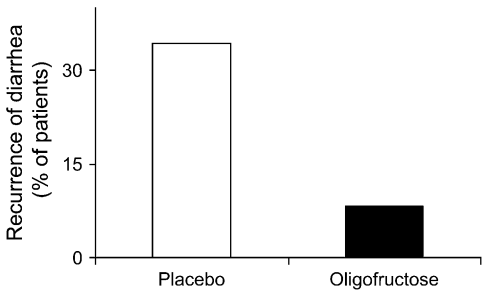

FIGURE 1 A total of 142 patients with *C. difficile*-associated diarrhea were randomly allocated to receive oligofructose (12 g/d) or placebo (sucrose, 12 g/d) for 30 d to test the efficacy of oligofructose to prevent relapse (31). Of these patients, 30 experienced a relapse of diarrhea a median of 18 d (range, 8–34 d) after the cessation of their initial episode: 24 patients in the placebo group and 6 patients in the oligofructose group ($P < 0.05$).

A randomized, double-blind, controlled clinical trial was carried out in burn patients who ingested 6 g/d oligofructose or placebo for 15 d (34). Gastrointestinal permeability was evaluated by the urinary excretion of orally administered sugars (sucrose and lactulose/mannitol ratio) before and after treatment. A permeability test was also performed in healthy controls. Urinary excretion of sucrose and the lactulose/mannitol ratio were 5- and 4.4-fold higher in burn patients than in controls. In burn patients, both markers declined progressively to normal levels from days 1 to 21, and no differences were observed between subjects receiving oligofructose or placebo. Thus, the normalization of gastrointestinal permeability was not affected by prebiotic intake. The fact that sucrose excretion was highly increased in burn patients indicates the existence of major defects of permeability in the upper gut, mainly at gastric level, because sucrose is rapidly hydrolyzed by small-bowel disaccharidases. It is therefore not surprising that prebiotic intake did not accelerate the recovery because stimulation of the growth of lactobacilli and bifidobacteria mainly occurs at lower gut levels.

Jain et al. (35) investigated whether the oral administration of a synbiotic preparation could alter gut barrier function in critically ill patients and thus reduce sepsis. A total of 90 patients admitted to an intensive care unit were randomized to receive either placebo or a synbiotic preparation (*Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb 12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose, 15 g/d). Gut barrier function was assessed by measurement of intestinal permeability (urinary lactulose/rhamnose ratio) and culture of nasogastric aspirate. All septic complications and mortality were recorded. After 1 wk of therapy, patients in the synbiotic group had a significantly lower incidence of potentially pathogenic bacteria (43% vs. 75%, $P < 0.05$) and multiple organisms (39% vs. 75%, $P < 0.01$) in their nasogastric aspirates than controls. There were no significant differences between the groups in terms of intestinal permeability, septic complications, or mortality. Thus, administration of synbiotic in critically ill patients favorably altered the microbial composition but had no effect on intestinal permeability and was not associated with measurable clinical benefit.

Finally, the use of inulin-type fructans is being tested in preliminary trials with ulcerative colitis (36) or Crohn's disease (37) patients. Short-term synbiotic treatment of active ulcerative colitis resulted in improvement of inflammatory markers. In Crohn's disease, oligofructose supplementation increased fecal bifidobacteria concentration and decreased disease activity in a small open-label trial (see Leenen et al. in this Supplement for more details on the results of these clinical trails).

Inulin-type fructans stimulate the growth of bifidobacteria and lactobacilli both in the gut lumen and at the colonic mucosal surface. In animals, inulin feeding is associated with higher villi, deeper crypts, increased number of goblet cells, and a thicker mucus layer on the colonic epithelium, suggesting a trophic effect of the prebiotic on the mucosal barrier.

In randomized controlled human trials, inulin and oligofructose were proven effective in mitigating the severity of diarrhea in children with diarrhea acquired in the community and in adults with traveler's diarrhea. In addition, oligofructose appears to be effective at preventing relapse of *C. difficile*–associated diarrhea. Some clinical studies in critical disease conditions suggest improvement of parameters related with barrier function and systemic infection by prebiotic intake, whereas other studies show no significant benefit. All these clinical studies have confirmed that inulin-type prebiotics are safe.

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