

Understanding Prebiotics

Stephen Olmstead, MD, David Wolfson, ND, Dennis Meiss, PhD, Janet Ralston, BS

ABSTRACT: *The intestinal microbiota provides the human host with an array of health benefits. Microfloral organisms act as a functional barrier against colonization by pathogens, promote normal gastrointestinal function, contribute to energy production, and exert enteric and systemic immunomodulatory activity. Support for the health of intestinal flora can take the form of supplementation with living probiotic organisms or prebiotic substances that nourish beneficial endogenous species. Prebiotics are digestion-resistant carbohydrates that selectively stimulate the growth and activity of health-promoting microorganisms such as bifidobacteria and lactobacilli. Major prebiotics include inulin, inulin-type fructans, galactooligosaccharides, and lactulose. Prebiotics taken alone or with probiotics, as in a synbiotic supplement, contribute to the integrity of the gut barrier, help normalize colonic motility, improve nutrient bioavailability, enhance gastrointestinal and systemic immunity, and may favorably modulate blood sugar and lipid levels. Numerous studies in both animals and humans have demonstrated the health benefits of prebiotics. Prebiotic use in nutritional supplements and functional foods is rapidly gaining wide acceptance.*

substance that selectively promoted the growth of bifidobacteria (called *Lactobacillus bifidus* at that time).^{20,21} Human milk and colostrum were found to contain large amounts of “bifidus factor”.²² Multiple substances in human milk were found to be bifidogenic and were shown to stimulate the growth of bifidobacteria when administered to bottle-fed infants.^{22,23} Although early research focused on amino sugars,^{22,24} by the 1960s attention began to turn to oligosaccharides as the constituents in breast milk primarily responsible for its bifidogenic activity.²⁵ In the 1970s and '80s, Japanese investigators pioneered the use of digestion-resistant saccharides to favorably modify the intestinal microbiota using fructooligosaccharides, galactooligosaccharides, and lactulose.²⁶⁻²⁸ The 1980s and '90s saw a marked increase in the use of probiotics to favorably modify the intestinal microbiota and a concomitant growth in interest in using prebiotics to achieve the same goal. In contrast to the probiotic strategy for microflora modification by providing living microorganisms, the prebiotic strategy seeks to stimulate the growth and/or enhance the metabolic activity of the healthful bacteria already colonizing the intestines. Prebiotics offer the ability to enhance the healthful strains in a person's unique community of bacteria including beneficial strains not available as probiotics, such as *Eubacterium* species.²⁹ The readily apparent synergy of concomitantly using beneficial microorganisms and nutritive materials that support their growth led to the term “synbiotics” to describe foods or supplements that combine both probiotics and prebiotics.¹⁹

INTRODUCTION

The human gastrointestinal tract is the most densely populated ecosystem known, inhabited by 500-1000 largely unknown microbial species.¹ Most intestinal microorganisms reside in the terminal ileum and colon where they have evolved to metabolize food components undigested by their host as well as intestinal secretions, sloughed cells, microbial fermentation products, and metabolic end products secreted by the host into the bile.²⁻⁵ Weighing about 1.5 kilograms, the intestinal microbiota functions as a unique, vital organ with metabolic activity rivaling that of the liver.^{6,7} The gut microflora performs three major tasks: colonization resistance to pathogens, modulation of gastrointestinal and systemic immune responses, and nutritional support.^{6,8-10}

One strategy to support the intestinal microflora is to administer beneficial probiotic organisms. Another is to utilize prebiotics for restoring and favorably modulating microbiota organ metabolism.

A variety of situations may contribute to a disrupted intestinal microbiota including impaired microflora acquisition and development during infancy,^{11,12} aging,^{13,14} poor diet,^{2,13} antibiotic use,¹⁵ and stress.^{14,16} One strategy to support the intestinal microflora is to administer beneficial probiotic organisms. Another is to utilize prebiotics for restoring and favorably modulating microbiota organ metabolism.¹⁷

PREBIOTICS - Definition and History

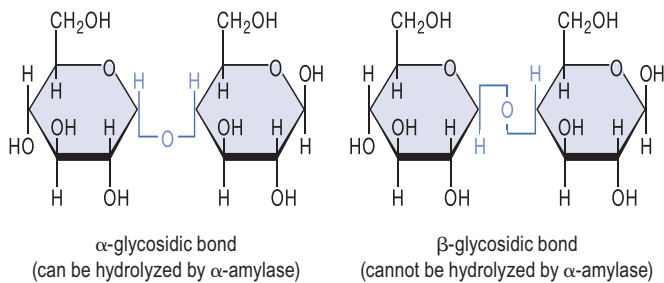
Prebiotics are defined as “selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host well-being and health.”¹⁸ The term “prebiotic” was coined in 1995 by Gibson and Roberfroid,¹⁹ although prebiotics were recognized as early as the 1950s when Györög and coworkers described “bifidus factor”, a bifidogenic

MAJOR PREBIOTICS AND THEIR CHARACTERISTICS

Prebiotics can be classified as a type of digestion-resistant carbohydrate or dietary fiber.^{30,31} Like all fibers, prebiotics resist breakdown by human digestive secretions and arrive relatively unchanged in the lower regions of the intestinal tract where they can be utilized as an energy source by the resident microflora. What distinguishes prebiotics from other fibers is that prebiotics by definition selectively stimulate the growth of only beneficial microfloral organisms such as lactobacilli and bifidobacteria.¹⁷ A number of important dietary fibers like cellulose and pectin fail to meet this definition.^{30,32,33} Prebiotic properties have been ascribed to many types of carbohydrates, but they have been best documented for digestion-resistant oligosaccharides (DGOs).^{17,19}

DGOs include inulin-type fructans, galactooligosaccharides, lactulose, isomaltoligosaccharides, xylooligosaccharides, soy-oligosaccharides, gentiooligosaccharides, and nigeroligosaccharides.^{17,18,34} They may be found naturally occurring in foods or milk or they may be synthesized. Most DGOs are composed of 3 to 10 sugar moieties, although the number of linked sugar molecules (degree of polymerization) varies.³⁴ Chicory inulin may have up to 60 linked fructose molecules while lactulose, a synthetic prebiotic, consists of only galactose linked with fructose.^{34,35} DGOs do not have uniform chain length, but are a mix of oligosaccharides with variable degrees of polymerization. They generally have glycosidic bonds in the β -configuration and resist hydrolysis by human salivary and pancreatic digestive enzymes which are specific for α -glycosidic bonds³⁰ (see Figure 1). Ingested DGOs reach the colon largely intact where they are fermented by specific colonic microbial strains possessing a wide assortment of carbohydrateolytic enzymes.^{34,36} The rate of fermentation is strongly

Figure 1 Bond Structure Between Sugar Moieties



influenced by the constituent monomeric sugars, the degree of polymerization, type of linkage between monomeric units, and the general complexity of the molecule.³⁴ Of the many forms of DGOs, only inulin-type fructans, galactooligosaccharides, and lactulose fully meet the criteria established for classification as prebiotics.^{17,37}

Inulin-type Fructans

The prebiotic effects of inulin-type fructans are well-established.³⁵ Inulin-type fructans are linear DGOs composed of fructose moieties linked by β -(2 \rightarrow 1) bonds. Inulin is arbitrarily defined as a mixture of oligosaccharides with chain lengths of 2-60 fructose molecules,³⁸ with or without an initial glucose (see Figure 2). Inulin has a mean degree of polymerization of 12. A related DGO, oligofructose, is defined as having a chain length no greater than 9 fructose molecules.¹⁸ Oligofructose occurs naturally but can also be derived from the enzymatic hydrolysis of inulin or from microbial sources via enzymatic synthesis. Fructooligosaccharides are chemically similar to oligofructose, but their derivation is typically synthetic. Inulin-type fructans are storage carbohydrates commonly found in wheat, onions, asparagus, bananas, garlic, artichokes, and leeks.³⁹ The average daily dietary consumption of inulin-type fructans has been estimated to be between 3 and 11 grams for Europeans³⁹ and between 1 and 4 grams in the United States.⁴⁰ The major commercial source of inulin-type fructans is chicory root (*Cichorium intybus*),³⁵ a member of the *Asteraceae* family. Naturally extracted, commercial preparations of inulin-type fructans normally contain small amounts of glucose, fructose, and sucrose.³⁵

Although prebiotic properties have been ascribed to many materials, they have been best documented for digestion-resistant oligosaccharides and the disaccharide lactulose.

Inulin-type fructans have their greatest effect on intestinal *Bifidobacterium* populations. Clinical studies consistently show that inulin and oligofructose feeding significantly increase intestinal bifidobacteria populations.¹⁷ The increase typically reaches its maximal value within 1 week of beginning prebiotic consumption³⁵ and generally persists as long as inulin-type fructans are consumed. The optimal prebiotic dose of inulin-type fructans is highly individualized and ranges between 4 and 15 grams daily,⁴¹ although some individuals will experience an increase in bifidobacterial populations with doses as low as 1 gram daily. The volume of the increase in bifidobacteria numbers is related to the size of the person's intestinal *Bifidobacterium* population prior to consuming prebiotics: the lower the baseline population, the greater the increase in bifidobacteria.⁴¹ Inulin and oligofructose result in similar increases in bifidobacteria numbers. In addition to sustained increases in *Bifidobacterium* populations, inulin-type fructans augment the numbers of *Lactobacillus* and the important butyrate-producing *Eubacterium* and *Roseburia* species.^{42,43} While inulin-type fructans are the most widely known prebiotics, their benefits are largely yet to be appreciated in clinical practice.

Galactooligosaccharides

Galactooligosaccharides are digestion-resistant oligosaccharides naturally found in both human and cow's milk.¹⁷ They can also be derived from specific microbial fermentation of lactose or synthesized using the enzyme β -galactosidase and lactose syrup. Galactooligosaccharides consist of a glucose moiety bound to a chain of β -glycosidically linked galactose molecules of 2 to 8 monomers in length (see Figure 2). Galactooligosaccharides selectively augment *Bifidobacterium* and *Lactobacillus* numbers within the human intestinal microbiota. Prebiotic applications of galactooligosaccharides are of great interest because of their natural occurrence in human milk. Administration of galactooligosaccharides to formula-fed infants has been shown to engender an intestinal flora similar to that of breast-fed infants.⁴⁴ Bifidobacteria populations are enhanced, pathogen numbers decrease, short-chain fatty acid production increases, fecal pH decreases, and stool characteristics such as frequency and consistency are improved. Galactooligosaccharides appear to offer well-documented prebiotic support, especially in infants, and are only now in the early stages of clinical acceptance.

Lactulose

Lactulose is synthetic galacto-fructose made by the isomerization of lactose.^{17,45} Although technically a disaccharide, lactulose is generally grouped together with the DGOs. Lactulose is not usually present in nature although very small amounts may be found in heat-treated milk products as a result of non-catalyzed isomerization. Use of lactulose as a prebiotic dates to the late 1950s when it was found to be bifidogenic and for a time was dubbed "the bifidus factor".⁴⁶ The β -(1 \rightarrow 4) bond in lactulose cannot be split by human intestinal enzymes and is preferentially metabolized by colonic lactic acid bacteria with lactate and short-chain fatty acids as major end products. Human studies reveal prebiotic effects at daily doses of 3 grams with significant increases in *Bifidobacterium* and *Lactobacillus* numbers and reductions in *Clostridium perfringens*, *Bacteroides*, *Enterobacteriaceae*, and *Streptococcus* populations.^{17,47,48}

PREBIOTICS – Health Benefits

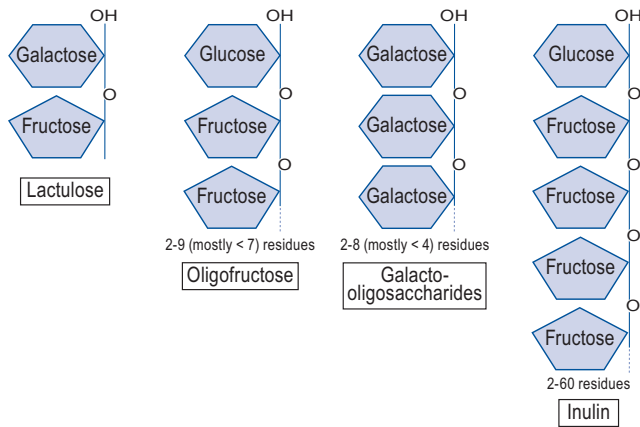
Promotion of Normal Colon Transit Time

Constipation is an exceedingly common clinical problem affecting large segments of the population including the elderly, pregnant and nursing women, people on weight loss diets, and people with disrupted daily schedules such as variable shift workers and business travelers.^{49,50} Prebiotics increase fecal bulk and optimize stool consistency primarily by increasing fecal microbial mass.³⁴ This increase in fecal bulk stimulates passage through the colon, shortening transit time. Colonic water resorption is reduced, stool becomes softer and heavier, and stool frequency increases. Together these factors alleviate constipation and improve colon evacuation. In a study of constipated elderly adults, 20 grams per day of inulin-type fructans had a significantly better laxative effect than lactose.⁵¹ A mixture of inulin-type fructans and galactooligosaccharides has been repeatedly shown to improve the stool frequency and consistency of bottle-fed infants similar to that of breast-fed infants.⁵² Administration of isomaltooligosaccharides has been shown to increase stool frequency and wet stool output in constipated elderly men,⁵³ xylooligosaccharides have been shown to reduce severe constipation in pregnant woman,⁵⁴ and lactulose administration has a long clinical history of alleviating constipation.⁴⁵

Production of Short-Chain Fatty Acids

Prebiotics are primarily energy sources for healthful intestinal bacteria that ferment them into short-chain fatty acids.³⁴ Many of the benefits of prebiotics derive from increased bacterial production of short-chain fatty acids. Much of the increase in short-chain fatty acids comes about through metabolic cross-feeding in which prebiotics are fermented by certain species, such as *Bifidobacterium*, into end

Figure 2 Simplified Structure of Some Prebiotics



products that are in turn metabolized by other microorganisms resulting in an increased quantity and diversity of short-chain fatty acids.^{55,56} Acetate is usually the dominant short-chain fatty acid in the colon followed by approximately equal concentrations of propionate and butyrate.^{57,58}

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Short-chain fatty acids play essential roles in the growth and physiology of intestinal tissue as well as in systemic metabolism.^{32,59} Acetate is an important energy source for the body and is metabolized by skeletal muscle,⁶⁰ the heart,⁶¹ and the brain.⁶² Gut microflora fermentation is the primary source of blood acetate.⁶³ Propionate stimulates proliferation of normal crypt cells in human cecal biopsy specimens, while having an anti-proliferative effect on HT-29 adenocarcinoma cell lines.⁶⁴ Propionate has been shown to reduce hepatic glucose output and cholesterol biosynthesis, but there are conflicting data on whether it can reduce serum glucose or cholesterol levels.^{65,66} Butyrate is accepted as the most important short-chain fatty acid produced by the intestinal microflora. It is the preferred energy source for colonocytes and its metabolism accounts for 70% of colonic oxygen consumption.³² Butyrate modulates colonocyte differentiation and proliferation, and regulates gene expression and transcriptional proteins. Of great importance to human health, butyrate upregulates glutathione S-transferase and catalase expression in colon cells, thereby enhancing cellular detoxification and antioxidant defenses^{67,68} while reducing cell cycle progression and possibly suppressing DNA repair mechanisms in cancer cells.^{69,70} Additionally, receptors for butyrate, as well as for acetate and propionate, have recently been identified on leucocytes, suggesting a role of short-chain fatty acids in enhancing immune function. Enhanced butyrate production may explain why dietary fiber intake is associated with a reduced risk of colon cancer. Although one *in vitro* study has suggested that under conditions of prolonged inflammation, as in ulcerative colitis, accumulation of intestinal butyrate may overload DNA repair and apoptotic mechanisms and facilitate mutations that may contribute to tumorigenesis,⁷¹ much more research needs to be done to determine whether this effect takes place in human physiological systems, especially given extensive data on the clinical benefits of butyrate in patients with ulcerative colitis.^{72,73} Absorption of sodium and water are closely linked with short-chain fatty acid transport, giving short-chain fatty acids a pivotal role in the critical colonic function of water reabsorption. Reduced colonic short-chain fatty acid concentrations are associated with diarrhea. Short-chain fatty acids are also essential for optimal absorption of other cations including calcium and magnesium.

Enhancement of Mineral Absorption

Several animal studies have demonstrated that inulin-type fructans,⁷⁴ galactooligosaccharides,⁷⁵ isomaltooligosaccharides,⁷⁶ lactitol,⁷⁷ and lactulose⁷⁸ substantially enhance mineral absorption, especially calcium and magnesium. The combination of inulin and oligofructose has been shown to increase calcium and magnesium absorption more effectively than either oligosaccharide alone. In addition to augmenting calcium and magnesium absorption, inulin-type fructans have been shown to protect animals from developing symptoms associated with magnesium deficiency and to correct osteopenia. While not all human studies have demonstrated an effect, a number of clinical trials involving adolescents, postmenopausal women, and adult men have confirmed an enhancement of mineral absorption mediated by inulin-type fructans.⁷⁹ Increased colonic mineral absorption results from fermentation of inulin-type fructans which leads to higher concentrations of short-chain fatty acids, a lower colon pH, and enhanced mineral solubility and bioavailability. Studies show that only modest consumption (8 to 10 grams/day) of prebiotics such as inulin-type fructans and lactulose can significantly increase calcium absorption in adolescent girls and boys as well as in postmenopausal women.^{80,81,82} Improved magnesium absorption has also been observed in postmenopausal women following supplementation with 8 grams/day of fructooligosaccharides.⁸³ In addition to increasing mineral absorption, research suggests inulin-type fructans enhance calcium accretion and improve bone mineralization and density in young adults.⁸¹ A recent review of studies examining the effects of prebiotics on mineral absorption suggests that design flaws may have accounted for the lack of positive results observed in some of the studies.⁷⁹

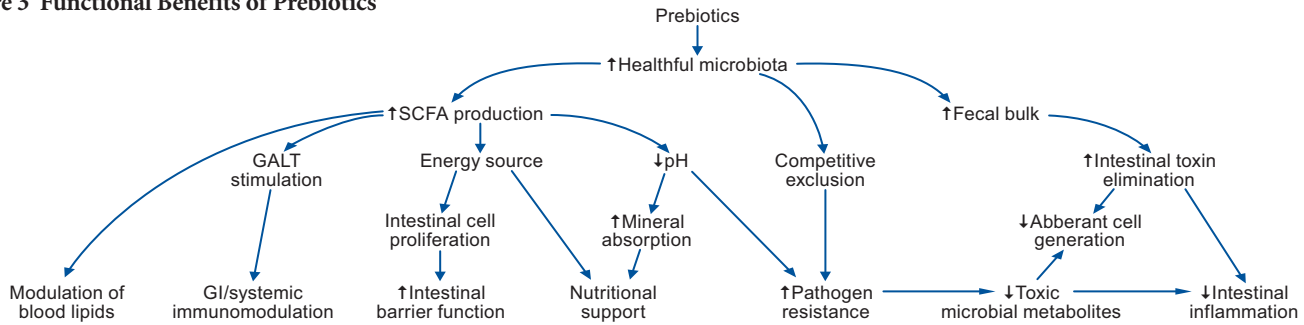
Favorable Modulation of Lipid Levels

Most of the results on the effects of prebiotics and lipid metabolism are derived from research with inulin-type fructans. Inulin-type fructans modulate the digestion, absorption, and metabolism of lipids resulting in reductions of serum lipid levels as well as favorable redistributions of lipids among the various lipoproteins. Animal studies show inulin-type fructans decrease both fasting and postprandial plasma triglyceride levels mostly due to a decrease in the concentration of plasma VLDL-triglyceride in the post-absorptive state.⁸⁴ Oligofructose has also been shown to prevent hypertriglyceridemia induced by both fructose⁸⁵ and high-fat⁸⁶ feeding in rats. The principal hypotriglyceridemic mechanism of action appears to be a decrease in liver lipogenesis through increased production of short-chain fatty acids in the large bowel. Short-chain fatty acid production leads to increased portal concentrations of propionate relative to acetate which inhibits lipogenesis in hepatocytes.^{34,87} Reduced lipogenic enzyme activity may also result from a prebiotic-mediated decrease in postprandial glucose and insulin concentrations that has been observed in some studies.³⁴ The effect of prebiotics on cholesterol levels is less consistent in animals and reductions are usually mild.^{84,88} In human studies, inulin is more effective than oligofructose in reducing triglyceride and cholesterol levels and the effects are more pronounced in diabetic and hyperlipidemic subjects. Administration of 7 to 20 grams/day of inulin-type fructans has been shown to reduce blood triglyceride and cholesterol levels by as much as 27% and 20%, respectively, in studies involving normal, diabetic, and hyperlipidemic human subjects.^{89,90,91} While the exact mechanism underlying inulin's hypocholesterolemic effect is not clear, evidence suggests it may result from propionate-induced inhibition of hepatic cholesterol synthesis.⁹¹ Galactooligosaccharides and xylooligosaccharides have also been shown to decrease serum cholesterol and triglycerides, respectively, in animal models.^{75,91}

Improved Gut Mucosal Barrier & Immune Function

The gastrointestinal tract is one of the most important components of the body's defensive system. In addition to providing non-specific

Figure 3 Functional Benefits of Prebiotics



protection in the form of a physical barrier against toxins and pathogenic organisms, the intestinal tract also provides specific protection in the form of gut-associated lymphoid tissue, or GALT. GALT represents the largest immune organ in the body and consists of a highly complex network of aggregated and non-aggregated immune cells.⁹² Research indicates prebiotics modulate both intestinal and systemic immunity largely through their association with gut microflora. Prebiotic support of health-promoting intestinal microorganisms leads to increased competition with pathogens for colonization sites, upregulated GALT expression of secretory IgA and immune-stimulating cytokines, and enhanced production of short-chain fatty acids and other antimicrobial substances that create an inhospitable environment for pathogen growth.^{93,94} Prebiotics have been shown to further enhance the integrity of the intestinal mucosa by increasing villous height, augmenting mucin release, and enhancing healthy mucosal biofilm composition.⁹⁵ The morphological and functional enhancements prebiotics bring to the gut all improve colonization resistance and reduce the risk of pathogen translocation. Prebiotics such as inulin, inulin-type fructans, galactooligosaccharides, and lactulose have been shown to enhance colonization resistance against a variety of enteropathogenic organisms, including *Clostridium difficile*,⁹⁶ *Clostridium perfringens*,⁹⁷ *E. Coli*,^{97,98} and other coliforms.⁹⁹

Prebiotic augmentation of both gastrointestinal and systemic immunity can enhance pathogen resistance in the intestinal tract and may reduce the risk of infections throughout the body.

Research indicates some prebiotic-like substances may also be able to directly stimulate immune cells. Yeast beta-glucans have been shown to activate receptors on phagocytes, NK cells, and certain classes of T- and B-lymphocytes⁹² and a novel class of oligosaccharides known as nigeroligosaccharides has been found to augment splenocyte proliferation and production of immune-potentiating cytokines such as interleukin-12 and interferon- γ .¹⁰⁰ Short-chain fatty acids resulting from prebiotic fermentation may play an additional role in immune cell activation. As described earlier, leukocytic receptors for short-chain fatty acids have been identified suggesting that immune cells located within the GALT may be stimulated by enhanced production of these fatty acids following prebiotic supplementation.⁹²

Prebiotic augmentation of both gastrointestinal and systemic immunity may help reduce the risk of cancers and infections throughout the body. In animal models, the administration of inulin-type fructans has been shown to lower the incidence of chemically-induced aberrant crypt foci in the distal colon, diminish levels of *Candida albicans* in the small intestine, and reduce mortality from systemic infection with *Listeria monocytogenes* and *Salmonella typhimurium*.¹⁷ Human studies examining the effects of prebiotics on systemic immunity are sparse, but in one trial involving elderly residents of a nursing facility, supplementation with 8 grams/day of fructooligosaccharides for 3 weeks resulted in a significantly increased percentage of peripheral T lymphocytes and CD4 and CD8

lymphocyte subsets.¹⁰¹ Paradoxically, a decrease in phagocytic activity of granulocytes and monocytes was also observed, along with a diminution of pro-inflammatory IL-6 mRNA expression. The authors speculate these effects may have resulted from a reduced intestinal pathogen load leading to an attenuated inflammatory response. This is a plausible explanation as anti-inflammatory effects of prebiotics have been noted in both animals and humans. Administration of short-chain fructooligosaccharides was shown to reduce multiple chemical mediators of inflammation such as myeloperoxidase, inducible nitric oxide synthase, and leukotriene B4 in rats with experimentally-induced colitis.¹⁰² In an open trial examining the effects of prebiotics on a small group of patients with Crohn's disease, supplementation with fructooligosaccharides for 3 weeks brought about a significant reduction in disease activity concomitant with a marked increase in mucosal bifidobacteria and a shift in dendritic cell function away from pro-inflammatory and towards immunoregulatory activity.¹⁰³ And in a study involving infants, a formula containing a mixture of galactooligosaccharides and fructooligosaccharides was shown to significantly reduce the incidence of atopic dermatitis compared to the same formula without the prebiotics.¹⁰⁴

Influences on Glucose & Insulin Levels

Evidence suggests prebiotics can favorably influence serum glucose and insulin levels in a variety of ways. Inasmuch as they may replace starches and/or sugars in foods, DGOs and other prebiotics can reduce the amount of glucose available for absorption into the bloodstream. Prebiotics may also prevent excessive blood glucose elevations after a meal by delaying gastric emptying and/or shortening small intestine transit time.³⁴ Bacterial fermentation yielding short-chain fatty acids is another mechanism whereby prebiotics can modulate glycemia and insulinemia. Propionate has been shown to reduce hepatic gluconeogenesis and enhance hepatic glycolysis,¹⁰⁵ and fermentation end products, mainly butyrate, are believed to be responsible for increases in the glucose-regulating and satiety-inducing hormone glucagon-like peptide-1 (GLP-1) observed in prebiotic-fed animals.¹⁰⁶ Although animal studies have demonstrated significantly lower blood insulin and glucose concentrations with inulin-type fructans, studies in humans have yielded conflicting data. Consumption of 20 grams/day of inulin-type fructans by healthy volunteers did not modify fasting plasma glucose and insulin concentrations, but decreased basal hepatic glucose production after 4 weeks.⁶⁵ Another study examining the effects of 10 grams/day of inulin in healthy middle-aged men and women reported significantly decreased insulin concentrations after 4 weeks.¹⁰⁷ A study of non-insulin-dependent diabetic subjects administered 8 grams/day of inulin-type fructans reported significantly lower blood glucose levels after 4 weeks.⁹⁰ However, in a more recent study, 20 grams/day of short-chain fructooligosaccharides administered to a group of type 2 diabetics for 4 weeks had no effect on fasting plasma glucose or insulin levels or hepatic glucose output.¹⁰⁸ These differing results underscore the need for more research to clarify how variables such as type, dose, and duration of administration of prebiotics effect blood glucose and insulin levels in normal and diabetic persons.

Table 1 Suggested Use of Prebiotics

Desired Clinical Outcome	Suggested Use of Prebiotics Based Upon Human Clinical Data
Normalize bowel transit time	<ul style="list-style-type: none"> • 20 gm/day inulin (elderly)⁵¹ • 20 gm/day lactulose (healthy subjects)¹²³ • 4.2 gm/day xylooligosaccharides (pregnant women)⁵⁴
Improve mineral absorption	<ul style="list-style-type: none"> • 10 gm/day inulin-type fructans (postmenopausal women)⁸³ • 10 gm/day lactulose (postmenopausal women)⁸² • 8 gm/day inulin-type fructans (pubertal males and females)^{80,81}
Favorably influence blood lipids	<ul style="list-style-type: none"> • 7-20 gm/day inulin-type fructans (healthy, type-2 diabetic, hyperlipidemic subjects)^{89,90,91}
Increase pathogen resistance	<ul style="list-style-type: none"> • 15 gm/day inulin and inulin-type fructans (healthy subjects)¹²⁴ • 20 gm/day lactulose (healthy subjects)⁹⁹ • 1 gm/dL galactooligosaccharides/inulin-type fructans (9:1) (infants)¹²¹
Enhance systemic immunity	<ul style="list-style-type: none"> • 8 gm/day inulin-type fructans (elderly)¹⁰¹ • 8 gm/L galactooligosaccharides/inulin-type fructans (9:1) (infants)¹²²
Attenuate GI inflammation	<ul style="list-style-type: none"> • 15 gm/day inulin-type fructans (Crohn's disease patients)¹⁰³ • 12 gm/day inulin-type fructans (ulcerative colitis patients)¹²⁵

Carcinogenesis & Reduction in Colon Cancer Risk

Carcinogenic substances introduced into the intestinal tract from exogenous dietary sources, or produced endogenously by the gut microflora, represent an environmental insult thought to play a role in the initial stages of cancer. *In vitro* and animal studies have revealed the potential of prebiotics to enhance detoxification processes in colon cells, reduce toxic metabolite production in the gut, and protect against colonic tumor development. In animal models, inulin-type fructans, galactooligosaccharides, and xylooligosaccharides have been shown to suppress chemically induced colon cancer and precancerous colon lesions.¹⁰⁹⁻¹¹¹ This effect is potentiated by the presence of lactic acid bacteria and associated with microflora fermentation and production of butyrate. Health-promoting bacteria inhibit the growth of pathogenic bacteria and thus decrease the production of carcinogenic substances such as ammonia, and tumor-promoting bacterial enzymes such as beta-glucuronidase. At the same time, bacterial growth increases biomass and thus stool bulk and accelerates colonic transit time decreasing exposure of the colon to potential carcinogens. Prebiotics reduce both the incidence¹¹²⁻¹¹⁴ and multiplicity^{112,114} of aberrant crypt foci and colon tumors in animal models and research indicates synbiotics may have an even more pronounced preventive effect.¹¹⁵ In addition to reducing the risk of colon cancer, dietary supplementation with inulin and oligofructose reduces the incidence of chemically-induced mammary cancer, slows the growth of implanted tumors, decreases metastases of implanted cancers, and enhances the efficacy of cancer chemotherapy.¹¹⁶ Two recent human studies demonstrate the potential benefit of prebiotic feeding in chemoprevention. In a 3-month trial, administration of 10 grams/day of short-chain fructooligosaccharides to healthy individuals significantly reduced the level of toxic bile acids in fecal samples.¹¹⁷ In another trial, a synbiotic combination of 12 grams of oligofructose-enriched inulin, *Bifidobacterium lactis*, and *Lactobacillus rhamnosus* significantly reduced DNA damage to colon cells and the cytotoxicity of fecal water in a group of subjects with a history of adenomatous colon polyps (but not those with extant colon cancer).¹¹⁸ These preliminary results corroborate the extensive animal data and underscore the need for further clinical trials to examine the efficacy of prebiotics in preventing and/or treating colon cancer.

Prebiotics & Infant Microflora

The intestinal microflora of breast-fed infants differs significantly from that of formula-fed infants. Formula-fed infants often have an altered balance of microorganisms in their gastrointestinal tract characterized by lower numbers of bifidobacteria and higher numbers of bacteroides, clostridia, enterobacteria, and staphylococci.^{119,120} Formula-fed infants also have a higher risk of intestinal infections. Human breast-milk contains numerous antibodies and a very high concentration of oligosaccharides that contribute to the natural defense against infection and promote a bifidobacteria-dominant microflora in the infant. Efforts to replicate the immunoprotective and bifidogenic effects of human breast milk on the intestinal tract of bottle-fed infants have led to research examining the effects of incorporating prebiotics into infant formulas. Formulas containing a mixture of galactooligosaccharides and fructooligosaccharides in a ratio of 9:1, have been shown to promote a microflora in infants similar to that seen in breast-fed infants.^{104,119,121} Infants consuming this prebiotic mixture have significantly higher levels of fecal bifidobacteria, lower fecal pH, reduced levels of fecal pathogens, improved stool characteristics such as frequency and consistency, and short-chain fatty acid patterns more characteristic of breast-fed infants compared to infants fed a control formula. One recent study also shows this type of prebiotic supplementation can reduce the incidence of both intestinal and systemic infections during infancy.¹²² These data suggest that supplementing formula-fed infants with prebiotics can have significant beneficial effects on intestinal microbial ecology, immune development, and protection against infection.

Efforts to replicate the immunoprotective effects of human breast milk have led to research examining the effects of incorporating prebiotics into infant formulas.

PREBIOTICS - Frequently Asked Questions

Are the terms “fiber” and “prebiotics” synonymous?

No. Most prebiotics can be generally classified as dietary fiber however not all dietary fibers demonstrate prebiotic activity. The distinction arises because, while all fibers are fermented to a certain degree, not all are selectively fermented by beneficial intestinal organisms. Prebiotics therefore are unique dietary fibers that preferentially promote the growth and/or metabolic activity of species within the gastrointestinal microflora that contribute to health benefits. In recent years, the concept of a “prebiotic index” has been introduced in an effort to quantitate the effects of various digestion-resistant carbohydrates on the intestinal flora,^{18,33} but different authors have proposed different methods of calculating such an index and it may be some time before a consensus is reached on an acceptable methodology.

What is the difference between oligofructose and fructooligosaccharides?

Although often used interchangeably, the consensus is that the term oligofructose refers to molecules naturally produced by enzymatic hydrolysis of inulin while fructooligosaccharides refer to synthetic oligosaccharides produced on a commercial scale from sucrose. Although both molecules can be described as oligosaccharides with chains of approximately 2-9 fructose molecules, the semantic classification depends on whether the molecules derive from the enzymatic breakdown of inulin or the chemical modification of sucrose.

Do prebiotics need to be refrigerated?

No. Unlike probiotics, which are fragile, living organisms vulnerable to the damaging effects of heat, prebiotics are a specific type of soluble dietary fiber and do not require refrigeration.

Should I take prebiotics with a probiotic?

Prebiotics can be taken with probiotics, either separately or as part of the same product. When the two are incorporated into the same

product, the combination is termed a synbiotic. This term reflects the idea that delivery of probiotic organisms along with a supportive growth medium can bring about synergistic health benefits that surpass what might be achieved by taking either of the 2 ingredients alone. Data from several preclinical studies support the synbiotic concept. In one study, a combination of *Lactobacillus paracasei* and fructooligosaccharides, compared to *L. paracasei* alone, significantly increased numbers of bifidobacteria and lactobacilli while reducing enterococci in the fecal flora of weanling pigs.¹²⁶ In another study, a combination of *Bifidobacteria longum* and inulin more effectively inhibited carcinogenesis in rats than either of the 2 ingredients administered alone.¹¹⁵ While more research is needed to confirm the benefits of prebiotic-probiotic combinations, the preliminary data suggest that synbiotic preparations may offer advantages over non-synbiotic products.

Can I take prebiotics without a probiotic?

Yes. While some evidence suggests there may be advantages to taking prebiotics along with probiotics, as in a synbiotic product, prebiotics by themselves have a demonstrated track record of producing health benefits and need not be taken with a supplemental probiotic.

How do I know I need prebiotics?

Most people do not consume sufficient fiber in their diets and are thus probably not consuming enough fermentable substrates to support a healthy intestinal microflora. As the intestinal microbiota greatly influences the health of the gastrointestinal tract and promotes systemic health, adequate consumption of prebiotics should be an important consideration in any nutritional program. The need for prebiotics may or may not manifest itself with symptoms. Ongoing or unresolved gastrointestinal problems may be the first indication of an imbalanced gastrointestinal flora suggesting the need for supplemental prebiotics, probiotics or synbiotics. Systemic immune dysfunctions such as allergies or frequent upper respiratory tract infections may also reflect the need for support of the intestinal microbiota. Consultation with a healthcare professional can help clarify whether supplemental prebiotics are advisable for a particular situation.

Are there any undesirable effects associated with the use of prebiotics?

Prebiotics may cause some of the same types of side effects reported with increased fiber consumption, notably an increase in intestinal discomfort, bloating, and flatulence due to fermentation and gas production in the large bowel. In larger doses, they may also cause sufficient osmotic absorption of water in the colon to produce laxation and diarrhea. Generally, doses of 15 grams or more have been observed to cause gastrointestinal side effects, although mild flatulence and borborygmus has been reported with smaller doses. The gastrointestinal effects of prebiotics are usually dose-related, transitory, and vary significantly from one individual to the next.

How much prebiotic should I take?

The effects of prebiotics vary from one individual to another. The results of clinical trials suggest that while higher doses may be needed to achieve specific therapeutic effects, (see Table 1) an optimal and well-tolerated daily dose of 7-10 grams increases *Bifidobacterium* populations. However, bifidogenic effects have been observed at lower doses, and research suggests that the extent to which bifidobacteria numbers increase depends less on the dose and more on initial bifidobacteria levels in the intestinal tract.¹²⁷ Increases in bifidobacteria numbers typically become significant and reach maximal value within 1 week of beginning prebiotic consumption and usually persist as long as the prebiotics are consumed. Once prebiotic intake ceases, bifidobacteria numbers will likely decline after 1 to 2 weeks. Daily use of prebiotics is recommended to achieve optimum results.

Can infants be given prebiotics?

Yes, prebiotics can safely be given to infants. Normal human breast milk contains a multitude of prebiotic compounds. Prebiotics are becoming more common in infant formulas in an attempt to supply formula-fed babies with some of the prebiotic benefits normally provided by breastfeeding. Dose-response studies of formulas supplemented with inulin-type fructans and galactooligosaccharides suggest 0.4gm/dL to 0.8gm/dL stimulates intestinal bifidobacteria without causing undesirable side-effects.^{17,122}

Do inulin-type fructans feed pathogenic organisms?

Occasionally, concern is expressed within the nutritional and medical communities that inulin-type fructans, especially shorter-chain varieties, may encourage the growth of intestinal pathogens. These concerns probably stem from scattered references in the literature to growth of organisms such as *Klebsiella pneumoniae* or *Staphylococcus aureus* on growth media containing short-chain fructooligosaccharides.^{41,128} It must be noted, however, that such observations have been reported only in *in vitro* settings in which pure cultures of different bacterial species have been utilized. Under conditions of multispecies competition that more closely approximate the environment of the intestinal tract inulin-type fructans do not have a long-term growth-promoting effect on populations of pathogenic organisms. On the contrary, multispecies studies show that bacterial feeding with either short- or long-chain inulin-type fructans supports the growth of beneficial organisms while diminishing numbers of pathogens. One *in vitro* competition experiment showed that in an oligofructose medium where bifidobacteria were co-cultured with enterobacteria and clostridia species, despite an initial rise in numbers of all organisms, pathogen counts began to decline after approximately 14 hours as the pH of the growth medium fell.⁹⁷ Human clinical trials confirm such observations. In one study, feeding of oligofructose and inulin to groups of healthy test subjects led to significant increases in fecal bifidobacteria counts while numbers of fecal *Bacteroides*, *Clostridium* and Gram-positive cocci significantly declined.¹²⁴ In another study, 2 groups of infants were fed either a placebo formula containing maltodextrin or a test formula supplemented with a mixture of galactooligosaccharides and fructooligosaccharides. At the end of 28 days, fecal bifidobacteria counts were significantly higher while counts of pathogenic organisms, including staphylococci, *Pseudomonas*, streptococci, clostridia, and *Klebsiella*, were all significantly decreased in the oligosaccharide-fed group.¹²¹ A careful interpretation of the research data thus points to a beneficial prebiotic effect of fructan oligosaccharides and does not support the idea that either short- or long-chain inulin-type fructans encourage the growth of harmful organisms in a multispecies competitive environment such as that of the human intestinal tract.

CONCLUSION

Dietary fiber has been associated with a myriad of health benefits including lowering blood lipid and sugar levels and reducing the risk of heart disease and colon cancer. Fiber supplements have also been used to improve a variety of gastrointestinal disorders including hemorrhoids and constipation. A type of dietary fiber, prebiotics resist digestion and absorption in the small bowel and arrive largely intact in the colon where they are fermented by the intestinal microflora. What distinguishes prebiotics is that they selectively stimulate the growth and/or metabolic activity of only beneficial microbiota organisms. These organisms provide specific health benefits for the host that include normalization of colonic transit time, increased production of short-chain fatty acids, improved pathogen resistance, enhanced mineral absorption, favorable modulation of blood lipids, improved gut mucosal barrier and immune function, and possible regulation of blood glucose and insulin levels. A combination of prebiotics and probiotics, termed a synbiotic, may offer even greater health advantages than either substance taken alone.

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