



# Prebiotics in Gastroenteritis

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## *Introduction*

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The gastrointestinal (GI) tract is home to more than 3 pounds of microorganisms, among which are beneficial species, including *Bifidobacterium* and *Lactobacillus*.<sup>1,2,3</sup> These organisms contribute to the nutritional status of the host, regulation of intestinal angiogenesis, and the development of immunity in infants and children, as well as protection from pathogens.<sup>4</sup> The balanced organization of this ecosystem of microorganisms has led to the concept of normobiosis, in which microorganisms with potential health benefits outnumber potentially harmful ones.<sup>5</sup> On the contrary, dysbiosis refers to a disruption in this balance, where one or more potentially harmful microorganisms are predominant, thus increasing the possibility of disease.<sup>5</sup>

Disruption of the GI microbiota can lead to malabsorption and consequently diarrhea, and in children and adults with diarrheal disease, the duodenal microflora has been shown to be abnormal compared to their healthy counterparts.<sup>1,6,7</sup> In turn, imbalances in the gut microbiota may be corrected and host health improved.<sup>5,8</sup> By altering the gut microbiota and promoting the growth of specific beneficial bacterial species, including bifidobacteria, studies have shown that the duration of diarrhea may be limited and symptoms may be improved.<sup>9,10</sup>

Two approaches have recently been employed to manipulate the gut microbiota—the use of prebiotics and probiotics. As you may know, probiotics are live microorganisms that are ingested to promote health.<sup>11</sup> Here, we focus on prebiotics, which are nondigestible (by the host) food ingredients that selectively stimulate the growth and/or activity of specific bacteria already residing in the digestive system in ways that are beneficial to health.<sup>12,13</sup>

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## Prebiotics vs Probiotics<sup>11,12</sup>

### **Prebiotics**

- Nondigestible (by host) food ingredients that selectively stimulate the growth and/or activity of certain health-promoting bacteria already residing in the digestive system, thus improving host health

### **Probiotics**

- Probiotics are live microorganisms that are ingested to promote intestinal microbial balance, therefore improving host health

## *A Closer Look at Prebiotics*

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Prebiotics were first identified and named by Marcel Roberfroid and Glenn Gibson in 1995.<sup>12,14</sup> They are usually in the form of oligosaccharides, such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), which can occur naturally or are added as dietary supplements to foods, beverages, and infant formula.<sup>13,15</sup> The complex polysaccharides present in edible fruits and vegetables that constitute dietary fiber can also be considered prebiotics. Foods containing fiber include wheat, onion, chicory, garlic, leeks, artichokes, and bananas.<sup>2,15</sup>

Prebiotic oligosaccharides usually contain fructose chains with a terminal glucose, and typically consist of 10 or fewer sugar molecules.<sup>15</sup> Vandeplass et al further distinguishes oligosaccharides as “short-chain” prebiotics, such as FOS, which contain 2 to 8 links per saccharide molecule and are fermented quickly in the colon ascendens, providing nourishment to the bacteria in that area. Longer-chain prebiotics, such as inulin, contain 9 to 64 links per saccharide molecule and tend to be fermented more slowly.<sup>14</sup> These prebiotics can nourish bacteria predominantly located in the colon transversum, descendens, and sigmoid.<sup>14</sup>

However, not all dietary carbohydrates are considered prebiotics. According to Roberfroid et al, the following criteria must be met in order for a carbohydrate to be considered a prebiotic: resistance to gastric acidity, hydrolysis by mammalian enzymes, and GI absorption (nondigestibility), in addition to the ability to be fermented by intestinal microflora, and the ability to selectively stimulate the growth and/or activity of microorganisms that contribute to health and well-being.<sup>13</sup> Oligosaccharides that meet these eligibility criteria and are considered prebiotics include inulin, FOS, GOS, and lactulose.<sup>13,16</sup> Isomalto-oligosaccharides, lactosucrose, and xylo-oligosaccharides have some data that make them promising prebiotics candidates.

## *Evidence for Alterations in Gut Microbiota in Gastroenteritis*

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There are studies suggesting that prebiotics may play an important role in preventing or treating diarrhea. As previously mentioned, the microflora of infants with acute and persistent diarrheal disease has been shown to be abnormal compared to healthy infants.<sup>6,7</sup> Househam et al examined the duodenal microflora of infants between the ages of 6 weeks and 1 year with a history of diarrhea for less than 48 hours when they were admitted to the hospital for rehydration. Out of 17 infants, 53% had coliforms (particularly *E. coli*) and bacteroides present in significant numbers in the duodenal fluid.<sup>6</sup> This indicates that in the majority of infants experiencing diarrhea, the duodenal microflora was abnormal.<sup>6</sup> A similar observational study also found that the duodenal microflora in infants with diarrheal disease differed markedly from that found in healthy infants.<sup>7</sup> These and other studies have contributed to our understanding about how aberrations in the gut microflora can lead to gastroenteritis, and has led research to develop treatment and therapies that can help restore balance to the GI tract.

## *Evidence That Prebiotics Exhibit Bifidogenic Effects*

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One possible treatment for diarrhea is the use of prebiotics. Thus, it has been imperative to investigate the potential of prebiotic consumption in restoring balance to altered microflora. There is evidence from both in vitro and in vivo studies that prebiotics, such as GOS, exhibit bifidogenic and non-bifidogenic effects important for disease recovery and prevention. In an in vitro study utilizing a human colon model, GOS was found to increase several *Bifidobacterium* and *Lactobacillus* species, and (13)C-labeled GOS components were incorporated into the 16S rRNA of several bifidobacteria and lactobacilli within 2 to 4 hours of adding GOS.<sup>16</sup> A separate study of the effects of prebiotic GOS consumption on the mucosal structure and function in the small intestine of mice showed that GOS was able to modify some characteristics of the intestinal mucosa. Specifically, mice receiving GOS were found to have higher sucrase-specific activity associated with the intestinal mucosa, and mucosal protein and mucin content increased compared to controls.<sup>17</sup> These studies showed that GOS is able to modify the GI tract prompting additional studies of the effect of prebiotic consumption in humans with gastroenteritis.

Studies in humans have also demonstrated the bifidogenic effects of prebiotic consumption. Davis et al demonstrated that feeding GOS to adults increased the abundance of bifidobacteria, suggesting that GOS could be used to specifically enrich bifidobacteria in the human gut.<sup>18</sup> In this study, healthy adult volunteers (n=18) were fed caramel chews with varying amounts of GOS (0 g, 2.5 g, 5.0 g, and 10.0 g) every day for 3 weeks. DNA isolated from weekly stool samples was analyzed by a technique called pyrosequencing. The results indicated that consumption of 5.0 g GOS/day led to several significant ( $P<.05$ ) changes in the family *Bifidobacteriaceae* and the genus *Bifidobacterium* compared to the control dose. Consumption of 10.0 g GOS/day resulted in additional changes in the

presence of several bacteria such as *Bifidobacterium*. From this single-blind, randomized study, Davis et al confirmed previous findings that GOS consumption induces significant ( $P<.05$ ) bifidogenic shifts in the fecal microbial community of healthy human adults. Additionally, pyrosequencing analysis confirmed that GOS exhibits a dose-dependent bifidogenic effect in the human gut, and showed for the first time that the changes attributed to GOS consumption are highly specific to a small number of bacterial groups, primarily bifidobacteria.

Similar results were observed in a randomized, double-blind clinical trial in which 43 healthy, full-term infants (2 to 8 weeks old) were fed a formula containing partially hydrolyzed whey protein with GOS/FOS.<sup>19</sup> The primary objective of the study was to compare the proportions of fecal bifidobacteria in infants fed formula with prebiotics (4 g/L GOS/FOS) to infants fed a formula without prebiotics and to infants exclusively breastfed. Holscher et al collected stool samples at baseline, 3 weeks, and 6 weeks for subsequent bacterial enumeration, SCFA quantification, and fecal pH measurement. The fecal samples of infants who consumed prebiotics had significantly higher numbers ( $P=.0083$ ) and proportions ( $P=.0219$ ) of bifidobacteria compared to the infants who consumed formula without prebiotics. Thus, feeding prebiotic-containing formula resulted in a modification of the established microbiota that more closely resembled that of the breastfed infant reference group. Taken together, these studies help demonstrate the health benefits of prebiotic consumption in the enrichment of bifidobacteria in the human gut.

## *Importance of Prebiotics in Gastroenteritis*

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Other studies suggest that prebiotics play an important role in the regulation and treatment of diarrhea. For example, in people traveling to a country where there is a risk for travelers' diarrhea (TD), consumption of a GOS mixture before and during their visit showed significant potential in preventing the incidence and symptoms of TD.<sup>9</sup> This placebo-controlled, randomized, double-blind study investigated the effects of GOS consumption on the incidence and symptoms of TD in healthy volunteers who would travel and stay in a country of low or high risk for TD for 14 days to 60 days. Travelers consumed 5.5 g of a GOS mixture once daily for 7 days prior to arriving at their destination and throughout their stay. Signs, symptoms, and duration of diarrhea were reported on a daily basis. The prebiotic GOS mixture significantly reduced the incidence and duration of diarrhea ( $P<.05$ ) compared to the placebo group, suggesting that prebiotic consumption before and during a visit to a foreign country where TD is a serious concern can effectively prevent the incidence and symptoms of TD, and thus allow for a better quality of life during the experience.

The effects of prebiotic consumption have also been shown to limit the duration of diarrhea in children.<sup>10</sup> In this randomized, placebo-controlled, single-blind study, adolescent patients experiencing diarrhea were treated with either a standard hypotonic oral rehydration solution (ORS) ( $n=60$ ) or super-hypotonic ORS containing prebiotics and zinc ( $n=59$ ). The parents were instructed to rehydrate their children orally with ORS and then administer ORS for dehydration prevention until diarrheal symptoms were no longer present. The resolution of diarrhea at 72 hours (the principal outcome measure) was observed in 72.9% ( $P=.01$ ) of the prebiotics plus zinc ORS group and 50.0% of the placebo group. Thus, according to Passariello et al, consuming a hypotonic ORS containing prebiotics and zinc is useful in the treatment of acute diarrhea in children.

## *Summary*

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The composition of the human GI tract microbiota may play an important role in health and disease, particularly in gastroenteritis. Clinical studies have demonstrated the health benefits and efficacy of prebiotic consumption, especially in the treatment of diarrhea. Manipulation of this composition may be done with the use of prebiotics, or nondigestible food ingredients that stimulate the growth and/or activity of certain bacteria, such as bifidobacteria, already residing in the digestive system in ways that are beneficial to health in adults, children, and infants alike.<sup>5,8,12,13,18,19</sup> Indeed, the consumption of prebiotics (GOS, FOS) has been shown to improve acute diarrhea in children and can help prevent the incidence and symptoms of TD in adults.<sup>9,10</sup> Therefore, prebiotics may play role in the restoration of the microbiota of the human GI tract, as well as maintaining overall health.

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