Prebiotics and Probiotics: A Critical Analysis

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**PREBIOTICS**

Prebiotics are nondigestible but fermentable oligosaccharides (food ingredients) that are specifically designed to change the composition and activity of gastrointestinal microflora (microbiota) with prospect to promote the health of the host. Two particular fructo-oligosaccharides (FOS) fully meet this definition: (1) oligofructose and (2) inulin. However, others also included in this group are galacto-oligosaccharides (GOS) and lactulose. Mannan oligosaccharides (MOS) have also been included but these would more correctly qualify as immunosaccharides.

Short-chain prebiotics (2–8 links per saccharide molecule) like oligofructose, ferment more quickly in the right side of the colon whereas long-chain prebiotics (9–64 links per saccharide molecule) like inulin are fermented more slowly providing nourishment to the bacteria in the left side of the colon. Recommended daily dietary intake of prebiotic fiber per day is 4–8 grams for general digestive health, while it is 15 grams and more for active digestive disorders. Percentage of prebiotic fiber content by weight in different dietary sources has been given in Table 1.

Those wishing to ensure sufficient prebiotic intake should carefully consider the prebiotic as well as the nutritive/caloric load, which comes along with its ingestion. Prebiotic oligosaccharides are increasingly being added to foods for their health benefits. Effects of prebiotics include:

- Effect on calcium and other mineral absorption
- Immune system effectiveness
- Bowel pH regulation
- Reduction of colorectal cancer risk
- Inflammatory bowel disorders
- Hypertension
- Effect on intestinal integrity.

**TABLE 1 | Percentage of prebiotic fiber content by weight in different dietary sources**

<table>
<thead>
<tr>
<th>Dietary source</th>
<th>Fiber content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw chicory root</td>
<td>64.6</td>
</tr>
<tr>
<td>Raw Jerusalem artichokes</td>
<td>31.5</td>
</tr>
<tr>
<td>Raw dandelion green</td>
<td>24.3</td>
</tr>
<tr>
<td>Raw garlic</td>
<td>17.5</td>
</tr>
<tr>
<td>Raw asparagus</td>
<td>11.7</td>
</tr>
<tr>
<td>Raw onions</td>
<td>8.6</td>
</tr>
<tr>
<td>Raw wheat bran</td>
<td>5</td>
</tr>
<tr>
<td>Whole wheat flour</td>
<td>4.8</td>
</tr>
<tr>
<td>Raw banana</td>
<td>1</td>
</tr>
</tbody>
</table>

Most of these effects possibly emanate from increased production of short-chain fatty acids by the stimulated colonic bacteria.

Prebiotics may cause unpleasant side effects like gas, bloating and increased bowel movements.

**PROBIOTICS**

Probiotic means “for life” and is defined as microorganisms that on ingestion may help improve microbial balance and the health of the host.

The origin of probiotics fermented foods and cultured milk predates recorded history. However, it was not until 1908 that Metchnikoff made observations that human health and longevity are associated with the ingestion of lactic acid producing bacteria. His observation stemmed from the fact that Bulgarian peasants who lived longer consumed large quantities of sour milk containing what is now known as *Lactobacillus bulgaricus*. The concept of probiotics evolved on such observations.

Human gastrointestinal tract contains 10 times more bacteria than there are eukaryotic cells in the body. These probiotic bacteria have: (1) protective, (2) immunomodulatory and (3) metabolic functions.

1. Gut bacteria form a protective layer, competitively inhibit the bad bacteria, synthesize mucus, tighten intercellular junction, thus protecting the intestinal mucosa.
2. They help in boosting host immunity by inhibiting proinflammatory mediators, stimulating release of anti-inflammatory cytokines and releasing bacteriocins.
3. The metabolic functions are digesting carbohydrates to produce short-chain fatty acids, synthesizing vitamin K, aiding in absorption of minerals and converting primary bile acids to secondary bile acids.

The location and prevalence of probiotic bacteria vary in different parts of the gut. They are rare in esophagus, uncommon in the stomach, $10^2$–$10^4$ in the jejunum (primarily aerobes) while $10^{10}$–$10^{12}$ in the colon, where they are primarily anaerobic. The predominant human fecal flora is:

**Aerobic species**

- *Escherichia coli*
- *Enterococcus spp.*
- *Streptococcus spp.*
- *Bacillus spp.*
- *Citrobacter spp.*
- *Klebsiella spp.*

**Anaerobic species**

- *Anaerobic cocci*
- *Bacteroides spp.*
- *Eubacterium spp.*
- *Bifidobacterium spp.*
- *Lactobacillus spp.*
- *Fusobacterium spp.*
- *Clostridium spp.*

The proportion and composition of gut microbiota in each individual is as unique as his fingerprint.
Section 6

Gastroenterology

Probiotics may have a promising role in the following diseases:

- Inflammatory bowel disease
- Irritable bowel syndrome
- Antibiotic-associated diarrhea (AAD)
- Clostridium difficile infection
- Infectious diarrhea
- Miscellaneous digestive disorders
- Nondigestive disorders

Inflammatory Bowel Disease

In general, probiotic studies in Crohn’s disease and ulcerative colitis have small sample sizes, lack of controls and inconsistent results. The use of probiotics for the prevention of pouchitis is supported by multiple randomized placebo-controlled trials in adult patients showing efficacy with high doses of certain probiotics.

Probiotics have no proven role in inducing or maintaining remission in Crohn’s disease. With regards to ulcerative colitis, Escherichia coli, Nissle 1917 has been found to be equivalent to mesalamine in some studies in maintaining remission and may be a viable alternative to mesalamine.

Irritable Bowel Syndrome

A number of studies have evaluated the responses in irritable bowel syndrome to probiotic preparations. Although results between studies are difficult to compare because of differences in study design, probiotic dose, strain and duration of therapy, some studies do suggest symptom improvement. Nine randomized and two open studies in adults and only one available randomized pediatric study were reviewed. Ten of the 12 studies reported amelioration of symptoms such as bloating, abdominal pain and colonic transit. Many of the studies were fairly short and did not reflect improvement in the quality of life.

Antibiotic-Associated Diarrhea

Many of the studies evaluating the efficacy of probiotics in AAD are small and have significant methodological flaws. However, two meta-analyses suggest a reduction in AAD by approximately 60%. The probiotic agents showing efficacy in this condition were S. boulardii in adult patients and Lactobacillus GG in children. A recent meta-analysis of data from five randomized controlled trials showed S. boulardii to be moderately effective in preventing AAD in children and adults treated with antibiotics.

For every 10 patients treated, one will not develop AAD. Not all probiotics are equally effective in this condition as a combination of L. acidophilus and L. bulgaricus was ineffective in preventing diarrhea in children receiving amoxicillin therapy during a double-blind placebo-controlled trial. Furthermore, a study from the Mayo Clinic failed to show superiority of Lactobacillus GG over placebo in preventing diarrhea in 302 hospitalized adult patients receiving antibiotics.

Clostridium difficile Prevention and Treatment

A randomized placebo-controlled trial of S. boulardii plus standard antimicrobial therapy in adult patients with recurrent C. difficile infection showed a risk reduction of recurrence down to 34.6% as compared with 64.7% in the placebo group. Surawicz et al. demonstrated benefit from using S. boulardii when combined with high doses of oral vancomycin to prevent recurrent C. difficile disease. In general, the benefit of probiotic therapy in C. difficile diarrhea was mostly seen in a subgroup of patients characterized by severe disease. A small open-label trial of Lactobacillus GG in children also suggests this agent may be of benefit in prevention of relapsing C. difficile.

Infectious Diarrhea

Perhaps the most studied potentially beneficial effect of probiotics is in mild to moderate infectious diarrhea. Results have been summarized in several meta-analyses, all of which found an overall reduction in the duration of diarrhea by about 1 day. The probiotic agent showing consistent benefit was Lactobacillus GG. However, in children with more severe diarrhea, there was no demonstrable benefit. This phenomenon is further supported in a recent study from Bangladesh showing lack of efficacy of L. paracasei strain ST11 in severe diarrhea while being effective in ameliorating less severe, non-rotavirus diarrhea.

The role of probiotics in preventing nosocomial infectious diarrhea has shown contradicting evidence. A double-blinded randomized control trial using Lactobacillus GG in 81 children aged 1-36 months showed a significant reduction in the risk of rotavirus gastroenteritis (2.2% vs 6.7%). Seven children would need to be treated with the probiotic to prevent one patient from developing nosocomial rotavirus gastroenteritis. However, a larger double-blinded randomized study in 220 children did not show a statistically significant protective effect of the same probiotic for nosocomial rotaviral infection. Another randomized trial studying 55 infants admitted to a chronic care pediatric hospital showed a lower risk of developing nosocomial diarrhea when infants were fed probiotic-containing formula (7% vs 31%). This protective effect becomes far less significant if the incidence of diarrhea (episodes per patient-month) rather than the percentage of patients with diarrhea is taken into account. With regard to the prevention of community-acquired diarrhea, randomized controlled studies suggest a modest protective effect.

Miscellaneous Digestive Disorders

Necrotizing enterocolitis is a condition seen mostly in premature infants and can result in small bowel resection in severe cases. Review of the literature shows an inconsistent effect of probiotics in this condition. In three studies, the use of a combination probiotic therapy administered to premature infants reduced the incidence of necrotizing enterocolitis. Other investigators, however, were unable to demonstrate any benefit of Lactobacillus GG in necrotizing enterocolitis prevention. The role of probiotics in the treatment of hepatic encephalopathy was examined in a few pilot studies. Therapy with probiotics or prebiotics resulted in improvement of hepatic encephalopathy and lower blood ammonia levels. This effect may be related to colonization of the intestine with acid resistant, nonurease producing bacteria. Probiotics are generally not effective in eradicating Helicobacter pylori infection, but they can reduce side effects of recommended antimicrobial therapy.

Nondigestive Disorders

Allergic Disorders

Probiotics have been shown to reduce inflammatory cytokines and intestinal permeability in vitro. Such an effect would be beneficial in allergic disorders. Therefore, several studies have looked at the efficacy of probiotics in allergic conditions, such as eczema, allergic rhinitis and food allergies. The results of these studies are promising, but a definitive role is yet to be confirmed. When Lactobacillus GG or placebo was given to pregnant mothers with a strong family history of eczema, allergic rhinitis or asthma and to their infants for the first 6 months after delivery, the frequency of developing atopic dermatitis in the offspring was significantly reduced at 2 and 4 years. Another placebo-controlled study showed significant improvement in children with atopic dermatitis after a 6-week administration of L. rhamnosus 19070-2 and L. reuteri DSM 122460. Children with high immunoglobulin E levels and one or more positive skin tests were more responsive to probiotic therapy. Infants with atopic eczema and cow’s milk allergy responded more
effectively to hydrolyzed whey formula when *Lactobacillus GG* was added in a large controlled study. When *L. paracasei* 33 was given for 30 days to 80 children with perennial rhinoconjunctivitis, the quality of life questionnaire scores significantly improved relative to placebo.16

**Extraintestinal Mucosal Effects**

Probiotics, such as *Lactobacillus GG*, colonizing the gastrointestinal tract have been shown to influence distant mucosal sites such as respiratory and urogenital tracts. They have been shown to be of benefit in urinary tract infections, vulvovaginal candidiasis, otitis media and bacterial vaginosis.17 *Lactobacillus GG*, in the form of a milk preparation, was recently reported as having some modest but consistent benefits in terms of preventing and reducing the severity of respiratory tract infections at daycare centers.

**Safety**

In general, probiotics are considered safe. Some studies on immunocompromised patients with HIV18 and transplant19 population have been reassuring. However, there are multiple reports of bacteremia and fungemia20 with lactobacilli and saccharomyces organisms, especially in patients who are immunocompromised or have indwelling central venous catheters. Interestingly, some of these patients did not directly receive probiotics but were in the same hospital unit with patients who had probiotics. Contamination of the air, environmental surfaces and hands is suggested in these cases.21 Caution should be used especially when considering probiotics in patient populations with indwelling venous catheters. In addition, another potential concern is the fact that D-lactate can be produced by some lactic acid bacterial strains, which may result in neurological changes.

**CONCLUSION**

Probiotics hold promise for a variety of digestive and nondigestive disorders. In specific clinical circumstances, there is clear evidence of benefit such as acute viral gastrointestinal tract infections and AAD. The beneficial effect of the probiotic can be modest, and the anticipated advantage must be viewed along with associated cost and available alternatives. The evidence or lack thereof to support the use of probiotics in a variety of disorders has been summarized in Table 2.

Table 2: Summary of the quality of evidence for the use of probiotics in different diseases

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Comments</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouchitis</td>
<td>Efficacy clearly shown in adult studies with VSL no. 3</td>
<td>I</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>No clear efficacy (mostly <em>Lactobacillus GG</em> data)</td>
<td>I</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Efficacy suggested (equivalent to ASA preparations)</td>
<td>I</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Efficacy possible</td>
<td>I</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>Efficacy clearly shown but not all probiotics are effective (mainly <em>S. boulardii</em> and <em>Lactobacillus GG</em>)</td>
<td>I</td>
</tr>
<tr>
<td><em>C. difficile</em> diarrhea</td>
<td>Efficacy clearly shown but mainly in severe recurrent disease using <em>S. boulardii</em> and <em>Lactobacillus GG</em></td>
<td>I</td>
</tr>
<tr>
<td>Mild to moderate acute diarrhea</td>
<td>Efficacy clearly shown; treatment shortens duration of illness by 1 day (mostly lactobacilli, 10 billion per dose or more), prevention, modest effect with some conflicting reports</td>
<td>I</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>Efficacy possible</td>
<td>I</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Efficacy possible; small studies favoring efficacy in adults; large studies as well as pediatric studies are necessary</td>
<td>I</td>
</tr>
<tr>
<td><em>H. pylori</em> eradication</td>
<td>No efficacy supported</td>
<td>I</td>
</tr>
<tr>
<td>Allergy</td>
<td>Efficacy clearly shown in preventing atopic dermatitis</td>
<td>I</td>
</tr>
<tr>
<td>Cancer therapy and prevention of urogenital disorders, respiratory tract infections</td>
<td>Efficacy possible; inconsistent clinical data</td>
<td>II</td>
</tr>
</tbody>
</table>

The quality of the evidence was rated according to the following categories:

I Evidence obtained from at least one properly designed randomized controlled study

II-1 Evidence obtained from well-designed cohort or case-controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

II-3 Evidence obtained from multiple time series with or without intervention

III Evidence obtained from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

When prescribing probiotics, one must consider the probiotic formulation including live, dead, compounded preparations or their products, the effective dose to use and the type of disease targeted. In as much as not all probiotics are created equal, one cannot extrapolate specific actions or doses of a given probiotic and generalize these properties to other doses or strains of probiotic bacteria. It is also important for the prescribing clinician to realize that there is no governing agency overseeing quality control, and the actual number of viable organisms in commercial products may be quite different from what is being advertised. In summary, future large-scale clinical trials controlling dosing, viability and other critical variables will be crucial to provide the necessary scientific evidence required to determine efficacy of the ever-increasing use of probiotics.

**Fecal Microbiota Transplantation**

Fecal microbiota transplantation (FMT) is the process of transplantation of fecal bacteria from a healthy individual into a recipient patient for the treatment of *C. difficile* infection, which (latter) produces effects ranging from diarrhea to pseudomembranous colitis.

The procedure involves single to multiple infusion of bacterial fecal flora originating from a healthy donor. The procedure can be carried out via enema (simplest and most acceptable) through the colonoscope, or through a nasogastric or nasoduodenal tube. Most patients with *C. difficile* infection recover and have it eradicated after just one treatment. In over 370 published reports, there has been no reported infection transmission.

The hypothesis behind fecal bacteriotherapy rests on the concept of bacterial interference, i.e. using harmless bacteria to displace pathogenic organisms. Given that antibiotics are the original causes of *C. difficile* infection through their damage of the normal human flora and removal of protective Bacteroidetes and Firmicutes species,
further antibiotic therapy for cure should be avoided. The restoration of the colonic microbiota to its natural state by replacing missing Bacteroidetes and Firmicutes species, leading to eradication of *C. difficile* and resolution of clinical symptoms such as diarrhea, cramping and urgency is the aim of FMT. Although once considered to be “last resort therapy” by some medical professionals the recent position statement by specialists in infectious diseases and other societies is moving toward acceptance of FMT as standard/first-line therapy for severe or relapsing *C. difficile* infection. The earlier the infusion is initiated, the less likely the patient’s condition will deteriorate, thereby preventing the higher mortality rate associated with severely affected patients.

REFERENCES