

Nutritional advantages of probiotics and prebiotics

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The potential ‘nutritional advantages’ of probiotics and prebiotics consist of preventive, and sometimes curative, effects against certain diseases. The evidence supporting such advantages, which requires randomised controlled trials and consistency of results from study to study, is rapidly increasing. This article summarizes the effects against diseases of intestinal origin. There is a high level of evidence for positive effects of some prebiotics to alleviate constipation and treat hepatic encephalopathy. Interesting aspects, but with a lower level of evidence at the present time, include prevention of colon cancer, intestinal infection, and recurrence of inflammatory bowel disease. There is a high level of evidence for positive effects of some probiotics in the alleviation of lactose intolerance, antibiotic-associated intestinal disorders and gastroenteritis. Evidence is rapidly growing regarding the prevention of recurrence of inflammatory bowel diseases. Positive trials have suggested preventive effects against intestinal colonization with specific gut pathogens including *Clostridium difficile* and *Helicobacter pylori*.

Probiotics: Prebiotics: Disease prevention by food

Introduction

Probiotics have been defined as viable microbial food supplements which beneficially influence the health of the host (Schrezenmeir & De Vrese, 2001). Prebiotics are food ingredients that are largely undegraded in the small bowel and can beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria (Schrezenmeir & De Vrese, 2001). In farm animals, probiotics and prebiotics may enhance growth and prevent early mortality, especially from infections (Huber, 1997; Mulder *et al.* 1997). In humans, their potential ‘nutritional advantages’ consist of preventative curative effects against diseases including intestinal dysfunctions, gastro-intestinal infections, inflammatory bowel disease and possibly colon cancer. The evidence supporting nutritional advantages of probiotics and prebiotics is rapidly increasing. Many studies now follow a pharmacological approach, and the rules of evidence-based medicine. The demonstration of a high or reasonable level of evidence requires randomized-controlled trials (RCT), and consistency of results from study to study. The effects of probiotics and prebiotics on mineral absorption, lipid metabolism, and cancer risk are discussed in other articles in the same issue of this journal, and the present article

summarizes the effects against intestinal diseases (or diseases of intestinal origin).

Do the nutritional advantages of prebiotics and probiotics differ?

Although prebiotics and probiotics probably share common mechanisms of action (especially modulation of the endogenous flora), they differ in their composition and metabolism. The fate of prebiotics in the gastrointestinal tract is better known than that of probiotics. Prebiotics, like other low digestible carbohydrates, exert an osmotic effect in the gastrointestinal tract as long as they are not fermented; when they are fermented by the endogenous flora, i.e. at the place where they exhibit their prebiotic effect, they also increase intestinal gas production (Roberfroid & Slavin, 2000). Prebiotics have therefore the theoretical risk to increase diarrhoea in some situations (because of the osmotic effect) and to be poorly tolerated in patients with irritable bowel syndrome. The tolerance of low doses of prebiotics is nevertheless usually excellent (Marteau & Flourie, 2001). Probiotics do not have this theoretical drawback, and have often been effective to prevent or alleviate various clinical situations with diarrhoea.

Note: For the definition of the terms inulin and oligofructose please refer to the introductory paper (p. S139) and its footnote.

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Prebiotics

Demonstrated effects

Alleviation of constipation. Low digestible carbohydrates with a low molecular weight exhibit a positive effect on intestinal transit in constipated patients. This is probably due not only to their osmotic effect but also to other mechanisms, which may include modulation of the indigenous microflora (Clausen & Mortensen, 1997).

Treatment of hepatic encephalopathy. Several RCT have shown that lactulose and lactitol are superior to placebo to treat hepatic encephalopathy (Clausen & Mortensen, 1997; Dhiman *et al.* 2000). The mechanisms involved include: bacterial incorporation of nitrogen and acidification of the colonic environment which in turn reduces the breakdown of nitrogen-containing compounds to ammonia and other potential cerebral toxins (Weber, 1996).

Other potential applications (lower level of evidence at the present time)

Pre-clinical studies have suggested that prebiotics may have promising properties in inflammatory bowel disease (Szilagyi, 1998), prevention of cholesterol gallstones (Rotstein *et al.* 1981), and prevention of infections of intestinal origin (Dai & Walker, 1999). Well controlled studies in patients are needed.

Protective effects against colon cancer have also been suggested. There is some experimental evidence that secondary bile salts are involved in colonic carcinogenesis, and that non digestible oligosaccharides can decrease the faecal concentration, probably through colonic pH reduction. Several animal studies have supported the hypothesis and even suggested that other mechanisms could be involved (Pool-Zobel *et al.* 2002). Roncucci *et al.* (1993) reported that lactulose decreased the recurrence rate of colonic adenomas. Two hundred and fifty-five patients with colon adenomas were randomized after removal of the adenomas to receive vitamins, lactulose (20 g/d) or no treatment. Colonoscopy was performed thereafter every 6 months. After a mean follow-up of 18 months, the percentages of recurrence of adenomas were 5.7% in the vitamin group, 14.7% in the lactulose group, and 35.9% in the untreated patients. Unfortunately, this study was not blinded and has not yet been confirmed.

Probiotics

Demonstrated effects

Improvement of lactose intolerance and other enzymatic effects. Lactose maldigestion is a frequent situation for many adults. Studies have demonstrated that digestion and tolerance are improved when lactose is ingested in yogurt containing live bacteria than when it is consumed in milk or heated yogurt (in which the bacteria have been killed during the heating process) (de Vrese *et al.* 2001). This effect is largely due to digestion of lactose in the gut lumen by lactase contained in yogurt bacteria and released in the small bowel when these bacteria are lysed by bile acids (Marteau *et al.* 1990). In clinical practice,

replacement of milk by yogurt or fermented dairy products decreases or suppresses the symptoms of lactose intolerance (de Vrese *et al.* 2001).

Preliminary trials have suggested that sucrase or lipase could be delivered in the small bowel in subjects or animals with enzyme deficiency using natural or genetically modified probiotic vectors (Harms *et al.* 1987; Drouault *et al.* 2001). However, this way of delivery needs to be studied in more robust detail.

Antibiotic associated diarrhoea. Diarrhoea occurs in up to 20% of patients who receive antibiotics, and results from microbial imbalance. Several randomized double-blind trials have demonstrated that *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and *Enterococcus faecium* SF68 are significantly more efficient than a placebo to decrease the risk of diarrhoea in healthy volunteers or patients receiving antibiotics (Marteau *et al.* 2001a; Szajewska *et al.* 2001; Armuzzi *et al.* 2001). The mechanism involved is unclear, and is in fact probably not unique. For example, oral administration of *S. boulardii* has been shown in humans or animals treated with antibiotics to decrease, in some cases, the colonization of the endogenous ecosystem by *C. difficile*, in other cases to decrease the toxin production by *C. difficile*, and in other experiments to protect the epithelial barrier function (Elmer *et al.* 1996; Czerucka *et al.* 2000). Other probiotic products may work as well but they have not (hitherto) been sufficiently well studied to reach a fair level of evidence.

Gastroenteritis. Gastroenteritis is a frequent disorder that heals, usually spontaneously, within a few days. Several RCT demonstrated a beneficial effect of *L. rhamnosus* GG in the treatment of infant diarrhoea, especially due to rotavirus infection (Guandalini *et al.* 2000; Marteau *et al.* 2001a). It was suggested in one study that heat inactivated *L. rhamnosus* was as effective as living *L. rhamnosus* on diarrhoea, however the effect of the living probiotic was more pronounced on rotavirus specific IgA response (Kaila *et al.* 1995). *E. faecium* SF 68 (Bioflorin[®], Giuliani, Switzerland) has also been shown to significantly shorten diarrhoea in four RCT. Other probiotics are probably also effective (Marteau *et al.* 2001a).

Saavedra *et al.* (1994) showed that the preventive feeding of *Bifidobacterium bifidum* and *S. thermophilus* to infants, admitted to hospital, significantly reduced the risk of diarrhoea and shedding of rotavirus. In a double-blind placebo controlled trial, fifty-five children admitted to a chronic medical care unit were randomized to receive a standard formula or the same plus *Bifidobacterium bifidum* and *S. thermophilus*. During follow up, diarrhoea occurred in 7% of the children receiving the probiotic versus 31% of the controls. The shedding of rotavirus was also reduced to 10% versus 39%.

Other potential applications (lower level of evidence at the present time)

Inflammatory bowel disease (IBD). Inflammatory bowel diseases (IBD) are disorders of unknown cause characterized by chronic or recurrent intestinal inflammation. They include ulcerative colitis, Crohn's disease,

Table 1. Results of randomized controlled trials which reported efficacy of probiotics in patients with inflammatory bowel disease

Situation (prevention)	Probiotic	Control	n	Duration	Relapse: probiotic group/control	P	Reference
Ulcerative colitis	<i>E. coli</i> Nissle 1917	5-ASA	120	4 months	16%/11.3%	NS	Kruis <i>et al.</i> (1997)
Ulcerative colitis	<i>E. coli</i> Nissle 1917	5-ASA	120	12 months	67%/73%	NS	Rembacken <i>et al.</i> (1999)
Ulcerative colitis	<i>S. boulardii</i> + 5-ASA	5-ASA	31	12 months	30%/35%	NS	Copaci <i>et al.</i> (2000)
Pouchitis (chronic)	VSL #3	placebo	40	9 months	15%/100%	<0.05	Gionchetti <i>et al.</i> (2000a)
Pouchitis	VSL #3	placebo	40	12 months	10%/40%	<0.05	Gionchetti <i>et al.</i> (2000b)
Crohn's disease (post-operative recurrence)	VSL #3	5-ASA	28	12 months	20%/40%	<0.05	Campieri <i>et al.</i> (2000)
Crohn's disease	<i>E. coli</i> Nissle 1917	placebo	28	12 months	30%/70%	<0.05	Malchow (1997)
Crohn's disease	<i>S. boulardii</i> + 5-ASA	5-ASA alone	28	6 months	6.3%/37.5%	<0.05	Guslandi <i>et al.</i> (2000)

VSL#3 (CSL, Milan, Italy) contains 300 billion viable lyophilized bacteria per gram of four strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*), three strains of bifidobacteria (*B. longum*, *B. breve*, *B. infantis*), and one strain of *Streptococcus salivarius* subsp. *thermophilus*.
5-ASA: 5-aminosalicylic acid.

and pouchitis. The mechanisms responsible for initiation and perpetuation of the inflammatory process remains unknown but the main theory is that IBD may result from abnormal host responses to some members of the intestinal flora, and/or from a defective mucosal barrier (Shanahan, 2001). Several RCT have recently demonstrated that certain probiotics could be of great clinical interest and need to be further studied (Table 1). For some, the level of evidence is close to that needed for physicians to prescribe them to patients. Trials are on going and knowledge is progressing quickly in this field (for a review see Marteau & Shanahan, in press).

Intestinal infections and colonisation by pathogenic bacteria. Protective effects of probiotics against intestinal infections have been demonstrated in animal models and seem to be an important mechanism for 'nutritional advantages', i.e. growth stimulation and decrease in mortality (Huber, 1997; Mulder *et al.* 1997). The mechanisms that may be implicated include the production of acids, hydrogen peroxide, or antimicrobial substances, competition for nutrients or adhesion receptors, antitoxin actions, and stimulation of the immune system.

Studies have suggested a beneficial role of *L. rhamnosus* GG, *S. boulardii* and *L. plantarum* LP299v during *Clostridium difficile* related infections (see references in Marteau *et al.* 2001a). Two RCT have tested the efficacy of *S. boulardii* to decrease the risk of recurrence of *C. difficile* infection (McFarland *et al.* 1994; Surawicz *et al.* 2000). In the first trial, 124 patients were randomized to receive either *S. boulardii* (1 g/d for 28 d) or a placebo, associated with the standard antibiotic treatment. The risk of clinical recurrence for the subjects with several episodes of *C. difficile* infection was significantly reduced in the *S. boulardii* group: 34.6% versus 64.7% ($P=0.04$). In the second study, a significant decrease in the risk of recurrence was observed in patients treated with a high dose of vancomycin plus *S. boulardii* versus a high dose of vancomycin plus placebo (Surawicz *et al.* 2000).

Helicobacter pylori is a good target for an efficient probiotic therapy. Colonization of the gastric mucosa is strongly associated with gastritis, duodenal and gastric ulcers, but also with lymphoma and carcinoma. Antagonistic actions of some *Lactobacillus* strains against *H.*

pylori *in vitro* have been reported (Coconnier *et al.* 1998). A significant reduction of the urease activity has been reported in patients treated with a supernatant of *L. johnsonii* LA1 (Nestlé, Switzerland) associated with omeprazole (Michetti *et al.* 1999). Two RCT have recently reported that the ingestion of a fermented dairy product containing this strain or a heat killed *Lactobacillus acidophilus* could help to decrease the gastric colonization by *H. pylori* (Canducci *et al.* 2000; Felley *et al.* 2001). Further confirmation and proof of effect is needed.

Traveller's diarrhoea. Acute diarrhoea occurs in about half of travellers to high risk-areas. Several RCT were performed using probiotics (see references in Marteau *et al.* 2001a), however, their methodology was often insufficient (e.g. drop outs, statistics, end-points) such that no clear conclusion could be drawn.

Irritable bowel syndrome (IBS). Several authors have tested the effects of various probiotics in subjects with IBS. At the present time, the level of proof is low and the majority of trials were negative. It seems however, an interesting track as at least two RCT have shown that some probiotics could influence the transit time of healthy humans (Bouglé *et al.* 1999; Marteau *et al.* 2001b).

Colon cancer. Regular consumption of some probiotics may decrease the faecal levels of enzymes, mutagens, and secondary bile salts which may be involved in colonic carcinogenesis (Wollowski *et al.* 2001). Some, but not all, epidemiological studies have also suggested that consumption of fermented dairy products may have some protective effect against large colon adenomas or cancer (Boutron *et al.* 1996). Clinical studies are currently ongoing in Europe to study the effects of probiotics in subjects with colon adenomas.

Concluding remarks

Prebiotics and probiotics are obviously interesting agents in the field of preventive nutrition, and they should therefore have an important development. Positive effects have now clearly been demonstrated in specific fields with certain products. However, unreasonable extrapolation of results to other clinical situations, products or doses should be avoided.

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