Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health?

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The colonic microflora is important to health. The growth and metabolism of the many individual bacterial species inhabiting the large bowel depend primarily on the substrates available to them, most of which come from the diet.[1 2] This has led to attempts to modify the structure and metabolic activities of the community through diet—using probiotics and prebiotics. Probiotics are live microbial food supplements. The best known are the lactic acid bacteria and bifidobacteria, which are widely used in yoghurts and other dairy products (fig 1). These organisms are non-pathogenic and non-toxigenic, retain viability during storage, and survive passage through the stomach and small bowel. Prebiotics are non-digestible food ingredients which selectively stimulate the growth or activities, or both, of lactobacilli or bifidobacteria in the colon, thereby improving health.

The probiotic concept

Since probiotics do not permanently colonise the host, they need to be ingested regularly for any health promoting properties to persist. Most studies on probiosis have been observational rather than mechanistic, and thus the processes responsible for many probiotic phenomena are seldom explained. Some probiotics are members of the normal colonic microflora and are not viewed as being overtly pathogenic. However, these organisms have occasionally caused infections in people whose health is compromised in other ways.[3 4]

Fig 1 A selection of "bio" yoghurts available in supermarkets

Summary points

- Microflora of the large intestine complete digestion through fermentation, protect against pathogenic bacteria and stimulate development of the immune system
- Probiotics and prebiotics in the diet can modify the composition and some metabolic activities of the microflora
- Probiotics are generally the live micro-organisms in foods such as yoghurts; they survive passage through the gut and temporarily bring the benefits of the normal gut flora
- Probiotics have been used to treat or prevent diarrhoea and to improve symptoms in lactose intolerance
- Prebiotics are non-digestible oligosaccharides that can stimulate selectively the growth of probiotic-like bacteria normally present in the gut
- Many claims for the potential health benefits of prebiotics remain unproved

Commercial probiotic preparations are usually mixtures of lactobacilli and bifidobacteria, although yeasts such as saccharomyces have also been used (box). Bifidobacteria are of particular interest. These are anaerobic pleomorphic rods or club shaped organisms (fig 2) which normally have an important role in breaking down dietary carbohydrate and interact directly with the host metabolism.[5] Bifidobacteria also synthesise and excrete water soluble vitamins, but there are considerable differences in species and strains.[6] These organisms predominate in the colons of breastfed babies; they account for up to 95% of all culturable bacteria and protect against infection.[7] Bifidobacteria do not occur in such high numbers in adults.

Adherence

Attachment of probiotics to the gut epithelium is an important determinant of their ability to modify host immune reactivity, but this is not a universal property

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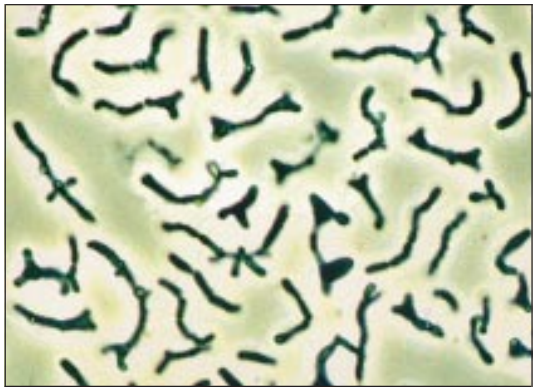

Fig 2 Gram stained preparation of *Bifidobacterium adolescentis* showing club shaped cells and other pleomorphic forms

Bacteria and yeasts used as probiotics

Bifidobacterium longum	*Enterococcus faecium*
B breve	*Lactobacillus rhamnosus*
B infantis	*L acidophilus*
B bifidum	*L casei*
B adolescentis	*L bulgaricus*
Lactococcus cremoris	*L gasseri*
L lactis	*Saccharomyces boulardii*
Streptococcus thermophilus	*S cerevisiae*

of lactobacilli or bifidobacteria and is not essential for successful probiosis.[8] Adherence of *Lactobacillus acidophilus* and some bifidobacteria to human enterocyte-like CACO-2 cells prevents binding of enterotoxigenic and enteropathogenic *Escherichia coli*, as well as *Salmonella typhimurium* and *Yersinia pseudotuberculosis*.[9 10] *Bifidobacterium infantis* and some strains of *B breve* and *B longum* attach strongly, although other *B breve* and *B longum* isolates are poorly adherent. Thus, there are species and strain variations in this probiotic attribute.

Nineteen strains of lactobacilli (each 5×10^6/ml) were fed to healthy volunteers in 100 ml of fermented oatmeal soup.[11] Biopsy specimens showed that the organisms colonised jejunal and rectal mucosas. Adherent lactobacilli were recovered from jejunal samples 11 days after the probiotic was stopped, while mucosal clostridia decreased up to 100-fold in some volunteers. In rectal tissue, anaerobes and enterobacteria were reduced.

Probiotics and gut infection

The colonic microflora normally presents a barrier to invading organisms, but pathogens often become established when the integrity of the microbiota is impaired through stress, illness, antibiotic treatment, changes in diet, or physiological alterations in the gut. Bifidobacteria are known to be involved in resisting the colonisation of pathogens in the large bowel.[12] Feeding *B breve* to children with enteritis eradicated *Campylobacter jejuni* from their stools, although less rapidly than in patients treated with erythromycin,[13] and supplementation of infant formula milk with *B bifidum* and *Streptococcus thermophilus* reduced rotavirus shedding and episodes of diarrhoea in children in hospital.[14]

Lactobacilli have been widely used in treating diarrhoeal diseases such as pseudomembranous colitis, but the results have been mixed.[15] Feeding freeze dried powders of *L acidophilus* NCDO 1748 had no effect on patients with pseudomembranous colitis,[16] but lactobacillus GG successfully eradicated *Clostridium difficile* in five patients with relapsing colitis.[17] Viable lactobacilli (approximately 10^{10}) were fed daily in skimmed milk. Diarrhoea was immediately relieved in four patients, and there were concomitant reductions in titres of *C difficile* toxin in stool. The other patient also improved after further antibiotic and probiotic treatment. Lactobacillus GG had previously been shown to colonise the gut and secrete an antimicrobial product that was active against *C difficile* and a range of other micro-organisms.[18]

However, not all lactobacilli are effective in combatting enteric pathogens. Twenty three healthy volunteers were given a commercial product containing *L acidophilus* and *L bulgaricus* and were then challenged with enterotoxigenic *Escherichia coli*.[19] They did not differ in respect of attack rate, incubation period, and duration of illness from control subjects given a placebo.

The yeast *Saccharomyces boulardii* has also been used in studies on prevention and treatment of diarrhoea associated with *C difficile* infection.[20] Of 180 patients in a double blind controlled study, 9.5% of those receiving the probiotic had diarrhoea compared with 22% of the controls given placebo. The authors concluded that prophylactic use of the probiotic reduced the incidence of diarrhoea associated with *C difficile* infection, although *Sacc boulardii* did not prevent acquisition of the pathogen.

Traveller's diarrhoea

Lactobacilli, bifidobacteria, enterococci, and streptococci have been used prophylactically to prevent traveller's diarrhoea caused by enterotoxigenic *E coli*. Neither *L acidophilus* nor *Enterococcus faecium* had any probiotic effect on groups of Austrian tourists,[21] and no differences were observed in healthy volunteers given either placebo or lactobacilli, then challenged experimentally with virulent enterotoxigenic *E coli*.[19] However, the incidence of diarrhoea was reduced from 71% to 43% in tourists going to Egypt who were given capsules containing *S thermophilus*, *L bulgaricus*, *L acidophilus*, and *B bifidum*.[22]

Prebiotics

To be effective, prebiotics should escape digestion in the upper gut, reach the large bowel, and be utilised selectively by a restricted group of micro-organisms that have clearly identified, health promoting properties. The food ingredients most likely to meet these criteria at present are oligosaccharides—including inulins and their derivatives, the fructo-oligosaccharides (table 1). These low molecular weight carbohydrates occur naturally in artichokes, onions, chicory, garlic, leeks, and, to a lesser extent, in cereals. Other oligosaccharides such as raffinose and stachyose are the major carbohydrates in beans and peas. These simple molecules can also be produced industrially, and a number of new potential prebiotics are being developed for this market (see below). The degree of polymerisation of these substances (table 1) refers to the number of individual monosaccharides in the molecule.

Table 1 Chemical composition and characteristics of candidate prebiotic carbohydrates

Oligosaccharide (example)	Chemical composition
Fructo-oligosaccharides (Raftilose P95)	95% oligosaccharides β (2-1) fructan; 60% glucose, fructose$_{(n)}$, 40% fructose$_{(n)}$ dp 2-8, average 4-5
Inulin	>99% oligosaccharides β (2-1) fructan; average dp 10-12
Pyrodextrins	Complex mixture of glucose-containing oligosaccharides
Transgalactosylated oligosaccharides (Oligomate 55)	Mainly 6' galactosyllactose, dp of oligosaccharide fraction 2-5 (primarily dp 3); 55% pure
Galacto-oligosaccharides	Oligogalactose (85%), small amounts of glucose, galactose, and lactose
Soya oligosaccharides	Stachyose (fructose, galactose, galactose, glucose) and raffinose (fructose, galactose, glucose), dp 3-4
Xylo-oligosaccharides	β (1-4) linked xylose; 70% pure, dp of oligosaccharide fraction 2-4
Isomalto-oligosaccharides	Mixture of α (1-6) linked glucose oligomers (isomaltose, panose, isomaltotriose)
Lactulose	Galactose and fructose-containing disaccharide

dp=degree of polymerisation.

Not all non-digestible oligosaccharides have prebiotic properties, and inulin, fructo-oligosaccharides, and (to a lesser degree) galacto-oligosaccharides dominate the published reports (table 2). Fructo-oligosaccharides have an energy value of 6 kJ/g; they have no genotoxic, carcinogenic, or toxicological effects; and they are mildly laxative, although flatulence is often a complaint when large doses are taken.[23] In controlled dietary studies with human volunteers, fructo-oligosaccharides (15 g/day) increased faecal bifidobacterial numbers 10-fold while reducing clostridia and enterobacteria counts, showing that species composition of the microbiota could be selectively manipulated through diet. In vitro, eight different bifidobacterial species that were grown on fructo-oligosaccharides produced inhibitory substances which were antagonistic, to various degrees, against salmonella, listeria, campylobacter, shigella, and vibrio.[24] Feeding fructo-oligosaccharides (8 g/day) to elderly people increased faecal bifidobacteria 10-fold,[25] while ingestion of soybean oligosaccharides (10 g/day) resulted in a smaller, though still appreciable increase in bifidobacteria.[26] Fructo-oligosaccharides do more than promote bifidobacterial growth, however, and several other intestinal bacteria are clearly involved in their metabolism.[27]

Galacto-oligosaccharides are present naturally in human and cow's milk and are also produced from lactose by β galactosidase. Feeding 2.5 g, 5 g, or 10 g of galacto-oligosaccharides to volunteers resulted in a dose related increase in faecal bifidobacterial excretion, although stool weight and frequency did not change noticeably.[28] At present, no clinical studies on the use of prebiotics to prevent diarrhoea have been reported.

Antimutagenic activities

Probiotics and prebiotics seem to be antimutagenic in several ways. Gram positive and Gram negative bacteria bind mutagenic pyrolysates produced during cooking at a high temperature, and studies with lactic acid bacteria show that they can be living or dead, since the process occurs by adsorption of mutagen to carbohydrate polymers in the cell wall.[29] Lactobacilli also degrade carcinogens such as N-nitrosamines, which may be important if the process occurs at the mucosal surface.[30] Co-administration of lactulose and *B longum* to rats injected with the carcinogen azoxymethane reduced intestinal aberrant crypt foci, which are preneoplastic markers.[31] Purified bifidobacterial cell walls have antitumour activities in that the cell wall of *B infantis* induces activation of phagocytes to destroy growing tumour cells.[32] Bifidobacteria probiotics reduced colon carcinogenesis induced by 1,2-dimethylhydrazine in mice when used with fructo-oligosaccharides[33] and inhibited liver and mammary tumours in rats.[34] When Neosugar (4 g/day; fructo-oligosaccharides) was given to healthy volunteers in the form of chewable tablets, it increased the intestinal bifidobacteria and reduced appreciably the faecal activities of enzymes involved in producing genotoxic metabolites such as β glucuronidase and glycocholic acid hydroxylase,[35] indicating the potential of prebiotics and probiotics to reduce or prevent carcinogenesis.

Immunity

The colonic microbiota affects mucosal and systemic immunity in the host.[36] Intestinal epithelial cells, blood leucocytes, B and T lymphocytes, and accessory cells of the immune system are all implicated.[37] Bacterial products with immunomodulatory properties include endotoxic lipopolysaccharide, peptidoglycans, and lipoteichoic acids.[38] Lipoteichoic acids of Gram positive bacteria such as bifidobacteria possess high binding affinity for epithelial cell membranes and can also serve as carriers for other antigens, binding them to target tissues, where they provoke an immune reaction.[39] Yoghurt lactobacilli bind in vitro to peripheral

Table 2 Physiological importance and health benefits claimed for non-digestible oligosaccharides

Physiological effects	Health factors
Stimulated carbohydrate metabolism in colonic bacteria; increased bacterial cell mass, short chain fatty acids, and fermentation gases	Through short chain fatty acids, they provide energy sources for the colonic epithelium and control of differentiation. Flatulence may be a problem. Laxative effects
Selection of bifidobacterial and lactic acid bacterial growth in large bowel	Enhanced resistance to invading pathogens
Not hydrolysed by oral micro-organisms	Protection against caries
Not glycaemic	Potentially useful for diabetics
Non-specific stimulation of immune function	Resistance to infection
Modulation of carcinogen metabolism	Anticancer properties
Reduced hepatic synthesis of very low density lipoprotein cholesterol and serum triglycerides	Coronary heart disease
Increased absorption of Mg and Ca	Osteoporosis

blood CD4 and CD8 T lymphocytes but not to B cells, while lactobacilli which adhere to human intestinal epithelial cells are capable of activating macrophages.[40 41]

There are as yet no experimental data to support the immunostimulatory properties of non-digestible oligosaccharides in humans. However, probiotic organisms interact with the immune system at many levels, including cytokine production, mononuclear cell proliferation, macrophage phagocytosis and killing, modulation of autoimmunity, and immunity to bacterial and protozoan pathogens.[36 37 42 43]

In vitro, bifidobacteria induce formation of large amounts of IgA.[44] Of 120 strains tested belonging to a number of species (*B animalis*, *B longum*, *B breve*), three *B breve* strains and one *B longum* isolate induced appreciable synthesis of IgA. This was confirmed in vivo when mice given one of the *B breve* strains together with cholera toxin had augmented immune responses in lymphoid tissue associated with the gut. In mice, *B breve*, fed in fermented milk, induced macrophage-like cells in Peyer's patches to release a factor that stimulated mitosis in B cells and enhanced production of antibodies against food allergens and pathogens.[45]

L acidophilus and *B bifidum*, given in capsule form to elderly people, effected appreciable changes in inflammatory and immunological responses.[46] They reduced colonic inflammatory infiltration considerably but did not affect the numbers of B lymphocytes and T lymphocytes. However, study subjects had a greater increase in B cells in peripheral blood than did controls. Lactobacillus GG was used to manage cow's milk allergy and atopic eczema in 31 infants aged 2-16 months.[47] It resulted in a considerable improvement in their condition and reduced faecal excretion of α_1 antitrypsin and tumour necrosis factor α through "an improvement in antigen elimination by the gut mucosal barrier."[47]

Conclusions

We are entreated to buy the "bio" yoghurts on sale in supermarkets with promises that they will boost our body's natural resistance, promote healthy digestion, and improve the balance of our gut microflora. This is to be achieved through their content of probiotic bacteria. Even more remarkable is the suggestion that some dietary carbohydrates can selectively stimulate growth of these organisms when they occur naturally in our gut and thus produce the same benefits. If true, this is one of the most important stories to emerge in nutrition and gut microbiology since the turn of the century.

Although there are now many published reports on the use of probiotics in humans, information on prebiotics is more limited. Consequently, many of the health claims made in relation to these substances are unsubstantiated. The ability to target specific organisms in the large intestine for defined, health promoting purposes will clearly be of great value and needs to be developed. However, there are considerable differences in bacterial carbohydrate utilisation patterns between strains as well as species,[48] and this is particularly important for the development of prebiotics. A few strains have been identified as having health promoting potential in vivo, but non-specific increases in total bifidobacterial or lactobacillus numbers in the large bowel through the introduction of "functional foods" will probably be of questionable benefit to health.

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Competing interests: JHC has been reimbursed for speaking at a conference sponsored by Ross Laboratories, which manufactures artificial feeds containing prebiotics. JHC and GTM received European Union funding for a project on non-digestible oligosaccarides in which Orafti, Belgium, which manufactures prebiotics, was a partner. JHC is a temporary consultant to Lamberts Healthcare, which sells prebiotics and probiotics.

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The World Bank and world health

Healthcare strategy

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The World Bank is accustomed to criticism, and since the second world war few organisations have generated as much outcry. Most analysts, however, accept that the bank has conducted a successful campaign to improve its image over the past decade. Indeed, I was surprised during my meetings with health workers outside the bank that it attracted far less criticism than I had expected. None the less, reservations remain about the bank's approach, and this article discusses some of the most controversial aspects of the bank's policies.

Summary points

Despite its recent change in image, the World Bank still has staunch critics

Structural adjustment, user charges, and DALYs (disability adjusted life years) are unpopular strategies that have attracted criticism for many years

Introducing evidence into policy making and ensuring sustainability of projects are key issues for the future

These issues and the bank's underuse of health outcome measures are stumbling blocks to wider acceptance of its policies

Structural adjustment

Critics of the World Bank argue that structural adjustment loans are a mechanism of forcing free market economics on countries through coercion. Countries with a debt crisis, whatever their other characteristics, agree to the bank's package of legal and economic reforms, and the bank agrees to lend them money. Argentina, Ecuador, and India have all either weakened their labour legislation or amended their land laws to qualify for an adjustment loan. India is reported to have changed 20 pieces of major legislation.[1]

Bank employees themselves have been sceptical about the wisdom and potential efficacy of such reforms, and the bank's critics have been scathing about the negative impact that adjustment loans have had on economies and on health indicators. The bank's hope is that adjustment should take no more than five years and require no more than five loans, but its figures reveal that, by 1995, not one out of 88 countries that had embarked on adjustment had stuck to the bank's timescale.[2]

The bank's view is that by achieving increased gross domestic product, domestic investment, and exports, and reduced inflation rates and "excessive" external borrowing, structural adjustment will lead to a reduction in poverty.[2] World debt, however, has risen from $0.5 trillion to $1.2 trillion between 1980 and 1992, with most countries that have pursued structural adjustment policies being in greater debt.[3] According to Unicef, a drop of 10-25% in average incomes in the

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