

REVIEW

Probiotics and prebiotics in the elderly

J M T Hamilton-Miller

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Probiotics (usually lactobacilli and bifidobacteria) and prebiotics (non-digestible oligosaccharides) have been shown to be useful in preventing certain disease conditions as well as possibly promoting specific aspects of health. In the present review, the evidence from clinical trials for benefits from probiotics and prebiotics to elderly populations is presented and discussed, specifically in respect of three common conditions found in the elderly. Both probiotics and prebiotics may be helpful in malnutrition, particularly in lactose intolerance and calcium absorption, and in constipation. Probiotics have been shown clearly to boost immunity in the elderly, but the clinical significance of this remains to be clarified. These results are encouraging, and further large scale studies seem justified to establish the place of probiotic and prebiotic supplements in elderly subjects.

probiotics did not become popular until the public embraced the idea of functional foods ("foods that provide physiological benefits or reduce the risk of chronic diseases, over and above their basic nutritional value") during the last decade of the 20th century. Metchnikoff's theory that gut flora contribute in some way to aging was supported in the 1950s, by the finding that germ-free animals live longer than their conventional counterparts.⁷

Today, probiotics are familiar to the public as the components of bioyoghurts and dietary supplements, are widely available, and extensively purchased. In 1997, Europeans spent the equivalent of almost \$900 million on probiotic yoghurts and milks, and this market is growing rapidly.⁸

Prebiotics are a more recent concept, first defined less than 10 years ago.⁹ They are chemical substances, usually oligosaccharides, that act as substrates specifically for the host's intrinsic probiotic bacteria, and thus encourage their growth. Prebiotics are selected as being non-digestible by the host and not metabolised by non-probiotic gut flora such as *Bacteroides* spp and *Escherichia coli*. Prebiotics are available naturally in breast milk and in certain vegetables (for example, Jerusalem artichokes and onions), and as synthetic oligosaccharides based on fructose or galactose, known as FOS and GOS respectively.¹⁰ The latter can be added to foods, or combined with a probiotic to make a *synbiotic*.

It is the purpose of this review to describe ways in which use of probiotics, and possibly prebiotics, might benefit elderly subjects in respect of three commonly occurring conditions—namely, constipation, undernutrition, and diminishing efficiency of the immune system.

AVAILABILITY OF PROBIOTICS AND PREBIOTICS

Probiotics

Products containing probiotic bacteria are readily available to the public, the most common being yoghurt. The standard type of yoghurt consists of milk (usually from the cow, but milk from the goat or sheep may also be used) fermented by bacteria that convert lactose into lactic acid (see table 1).

Lactic acid gives the yoghurt its characteristic sharp taste (usually modulated with sweeteners and flavouring) and also denatures and precipitates casein, resulting in a semisolid consistency. So-called "bioyoghurts" are produced in a

Abbreviations: FOS, synthetic oligosaccharide based on fructose; GOS, synthetic oligosaccharide based on glucose; LAB, lactic acid producing bacteria; NK, natural killer (cells)

Probiotics—a word derived from Latin and Greek meaning literally "for life"—has been defined in many ways since it was first coined 50 years ago.¹ The most recent consensus is "defined, live micro-organisms administered in adequate amounts which confer a beneficial physiological effect on the host".² While the concept that consuming large numbers of live bacteria can promote health and prevent and cure disease may at first seem strange, the usefulness of probiotics is rapidly becoming apparent.

Probiotics are usually bacterial components of the normal human intestinal flora, for example lactobacilli and bifidobacteria, that produce as end products of metabolism lactate and short chain fatty acids such as acetate and butyrate. Certain specific probiotic strains (for example, *Lactobacillus rhamnosus* GG, *L. plantarum* 299v, *L. casei* Shirota and *L. johnsonii* La1) have well defined and proven clinical effects for the treatment and/or prevention of diseases of intestinal and extraintestinal origin. These effects have been extensively reviewed recently.^{3,4}

Lactic acid producing bacteria (LAB) have been used, unwittingly, for centuries to preserve food (for example, sauerkraut), and most countries developed their own characteristic type of fermented milk.⁵ The first deliberate use of LAB for health reasons was by Metchnikoff early in the 20th century as a possible antidote to the aging process, proposed by him to be at least partly due to toxins produced by putrefactive intestinal bacteria (that is, not LAB). After some initial enthusiasm, interest waned,⁶ and

Correspondence to:
Professor J M T Hamilton-Miller, Department of Medical Microbiology, Royal Free and University College Medical School, Rowland Hill St, London NW3 2PF, UK;
j.hamilton-miller@rfc.ucl.ac.uk

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Table 1 Examples of availability of probiotics in various forms

Type of probiotic	Example	Biological effects	Comments
Yoghurt			
Classical type	<i>Lactobacillus delbrueckii</i> var <i>bulgaricus</i> ; <i>Streptococcus salivarius</i> var <i>thermophilus</i>	Biological effects shown (but limited); very palatable	Products often pasteurised; component bacteria cannot colonise gut; short shelf life; bacterial numbers not stated
"Bio" type	<i>Lactobacillus acidophilus</i> ; bifidobacteria may also be present	Wide range of biological effects; component bacteria colonise gut; very palatable	Short shelf life; bacterial numbers not stated; component bacteria often not adequately identified
Probiotic drinks			
Milks, fruit juices	<i>Lactobacillus casei</i> ; <i>Lactobacillus plantarum</i> ; <i>Lactobacillus reuteri</i>	Component probiotic strains have proven beneficial effects; accurate labelling, helpful package inserts; very palatable	Short shelf life
Supplements			
Capsules, tablets, powders	Various: mainly <i>Lactobacillus acidophilus</i> , often with bifidobacteria	Some brands contain probiotics with proven beneficial effects; long shelf life	Quality assurance issues: many brands contain contaminants, lower than claimed numbers and/or strains with no proven beneficial effects; some tablets or capsules may be difficult to swallow

similar way, but fermentation is carried out with different probiotic strains, usually *L acidophilus*.

Drinks containing probiotic bacteria include fermented milks and fortified fruit juices.

There are many brands of yoghurts and probiotic drinks available in supermarkets and other retail outlets.

A third source of probiotics is supplements consisting of freeze dried bacteria in capsule, tablet, or powder form. Such goods may be bought in health food shops and some pharmacies.

The constituents and relative merits of these types of probiotic products are summarised in table 1.

When choosing a probiotic product, an important caveat is that many contain unknown or variable numbers of bacteria, and most have strains with no proven record of probiotic activity. There are many thousands of strains of lactobacilli, all of which differ; while many of them may indeed show beneficial activity, very few have actually been proven to do so.

Prebiotics

Some probiotic preparations also contain prebiotics such as FOS or GOS, but the amounts present are probably too small to have a significant effect. Although several synthetic prebiotic oligosaccharide compounds are available commercially, in the UK they have not yet been incorporated into generally available foods. The best sources of prebiotics at present thus remain vegetables such as artichokes, onions, and chicory.

PROBIOTICS, PREBIOTICS, AND MALNUTRITION

Malnutrition is remarkably common. It has been estimated that approximately 30% of the world's population suffer this condition in some degree,¹¹ and it is by no means confined to developing countries. Two studies in the past 10 years showed that nearly 50% of patients admitted to hospitals in Europe and the USA were either malnourished or considered at risk.¹²⁻¹³

This condition is well recognised among the elderly. According to a standard text, 7% of those living at home and apparently well come into this category,¹⁴ and the incidence doubles in subjects aged >80. Being housebound or ill are additional risk factors.

It is postulated that undernourishment leads to damage to the gut epithelium, causing decreased gut mediated immunity, reduced absorption of essential dietary components, and loss of appetite. A leaky gut allows intestinal flora to enter the circulation (a phenomenon known as translocation); this may predispose to septicaemia and infections at remote sites.

Probiotics are helpful in normalising the nutritional status of children, and the use of yoghurt has been suggested by the World Health Organisation for nutritional recovery.¹⁵ Probiotic species proved to show a positive effect include *L acidophilus*, yoghurt organisms (*L delbrueckii* var *bulgaricus* and *Streptococcus salivarius* var *thermophilus*), *L plantarum* 299v, and *Bifidobacterium lactis* Bb12.¹¹⁻¹⁸ It would be interesting and instructive to determine whether such probiotic species can also help to correct malnutrition in the elderly.

Lactose intolerance is a common condition, and the associated symptoms seem to get worse with age.¹⁹⁻²⁰ These can be largely avoided by not consuming milk, but this strategy may severely limit intake of necessary dietary elements such as calcium. The condition is due to low levels of β -galactosidase (lactase) in the intestinal mucosal cells. It is commonly observed that fermented milk products such as yoghurts are better tolerated than unprocessed milk,³ and it is suggested that this is due at least in part to the β -galactosidase activities of the bacteria (*L delbrueckii* var *bulgaricus* and *S salivarius* var *thermophilus*) used to ferment the yoghurt. This enzyme is released after these organisms have passed through the stomach, as they are lysed by the pancreatic secretions. On the other hand, bacteria associated with bioyoghurts (*L acidophilus* and *B bifidum*) are stable to bile, and are thus less able to relieve lactose intolerance,³ and the well recognised probiotic strain *L rhamnosus* GG does not ferment lactose.⁴ Thus, ordinary live yoghurt is the preferred agent in elderly subjects with lactose intolerance.

Szilagy draws attention to the similarity of symptoms in lactose maldigestion and in irritable bowel syndrome, and suggests that mis-diagnosis of either condition could arise.²⁰ It is thus of interest that probiotics have been shown to be useful in irritable bowel syndrome.²¹

There is clear evidence from studies in animals and in man that prebiotics such as lactulose, inulin, FOS and GOS, given in large doses (10-40 g per day) can have beneficial effects of calcium bioavailability.²² An interesting result was obtained

by van den Heuvel *et al*, who showed in a double blind randomised trial that GOS taken at 20 g/day increased calcium absorption by 16% in a group of postmenopausal women.²³ As the excretion of calcium in the urine was not increased, it can be supposed that the extra calcium was retained. These studies clearly raise hopes that long term consumption of an appropriate prebiotic may reverse or prevent osteoporosis; the definitive investigations remain to be carried out.

PROBIOTICS, PREBIOTICS, AND CONSTIPATION

Constipation is common in elderly people.²⁴ The composition of the faecal flora changes with age, most markedly by a fall in numbers of bifidobacteria.^{25–27} While it is still not clear whether this a cause or the effect of constipation, it is known that changes in intestinal flora can alter intestinal motility, and the short chain fatty acids produced by probiotic bacteria (by bifidobacteria, in particular) have an important effect on transit time.^{28–29} A logical approach to relieving constipation is thus to increase the numbers of bifidobacteria, a strategy tried using prebiotics as well as probiotics.

As long ago as 1935, it was claimed that LAB could relieve constipation.⁷ Despite Ouwehand *et al* having recently stated “review of the literature does not substantiate this claim”,⁴ there are at least five positive reports, specifically in elderly subjects:

- Japanese workers reported improvements in stool frequency in the elderly after taking yoghurt containing bifidobacteria.³⁰
- Ouwehand *et al* themselves found that a commercially available mixture of *L rhamnosus* LC705 and *Propionibacter freundreichii* JS brought about a 24% increase in defecation frequency in group of elderly subjects.³¹
- Matsumoto *et al* reported that yoghurt with added *B lactis* LKM512 also significantly increased this measure.³²
- Salminen and Salminen refer to an unpublished trial in which they found that *L rhamnosus* GG increased the mean defecation frequency from 2.1 to 3.1 per week in elderly subjects in hospital.³³
- Umesaki cites two trials in which oral administration of *L casei* Shirota eased constipation and its related symptoms.³⁴

Prebiotics such as FOS, GOS, lactulose and inulin can act as dietary fibre,³⁵ as well as being substrates for LAB and thus encouraging their growth in the intestine. The widely used laxative lactulose³⁶ is also a prebiotic, as it is not attacked by human disaccharidases and is substrate for the bifidobacteria

in the colonic flora, that catabolise it to smaller molecules, creating an osmotic effect. Some other prebiotics have also proven effective:

- Rajala *et al*, as the result of a randomised double blind study, recommended a fibre-containing yoghurt sweetened with lactitol as “a natural and effective means of treating chronic constipation” in elderly hospitalised patients.³⁷
- Teuri and Korpela found that GOS (9 g/day) relieved constipation in some but not all elderly subjects, mainly by making defecation easier.³⁸
- Shitara reported that GOS was effective in Japanese subjects.³⁹
- Kleesen *et al* again found some subject-to-subject variation in their study comparing lactose and FOS (in the form of inulin), given to elderly subjects in dosages of 20 g increasing to 40 g/day; inulin had the more effective laxative action.⁴⁰

Larger studies are needed to confirm the usefulness of prebiotics other than lactulose, as the individual effects reported in the above studies usually did not reach statistical significance.

PROBIOTICS AND ANTIBIOTIC ASSOCIATED DIARRHOEA

Diarrhoea is perceived as a common adverse event after taking an antibiotic. However, much of the evidence for this is anecdotal; the most reliable figures—from controlled clinical trials carried out for registration purposes—suggest an incidence of <5% for most oral cephalosporins and co-amoxiclav.⁴¹ This type of diarrhoea may be due to overgrowth in the intestine of toxigenic *Clostridium difficile*, and elderly subjects in hospital appear to be more susceptible than other patient groups.⁴²

Probiotics, in particular the yeast *Saccharomyces boulardii*, have shown some promise in the prevention and treatment of antibiotic associated diarrhoea.⁴³ Only one trial has been done specifically in elderly subjects, and this showed no benefit from taking *S boulardii*.⁴⁴ However, this study is seriously flawed, as the dose used (226 mg daily) was too low: other workers have shown positive effects at a dosage of 1 g per day.⁴³ The authors of a recent meta-analysis of nine trials,⁴³ eight of which were carried out in general populations that included some elderly patients (the ninth being the one referred to above), concluded that probiotics may be useful, but further trials were needed *particularly in elderly patients* (present author’s emphasis).

Table 2 Summary of possible uses of probiotics and prebiotics in the elderly

Indication	Usefulness of probiotics	Usefulness of prebiotics
Nutrition		
Malnourishment	Possibly, by extrapolation from results in children	
Lactose intolerance	Yoghurt organisms helpful	
Calcium availability		GOS shown to be effective
Bowel problems		
Constipation	Helpful: at least five successful trials	Lactulose well established; other substances show promise
Antibiotic associated diarrhoea	Possibly, from results of trials in general populations	
Immune system	Some immunological markers improved; effects on clinical status yet to be shown	Some immunological markers improved; effects on clinical status yet to be shown

PROBIOTICS, PREBIOTICS, AND THE IMMUNE SYSTEM

The ability of the body to mount an effective defensive response to disease declines with age, a phenomenon known as immunosenescence. Elderly people may indeed be regarded as immunocompromised.⁴⁵ Cellular immunity seems to be the most seriously affected, with decreased numbers of circulating CD3+ lymphocytes and diminished activity of natural killer (NK) cells. Clearly, any strategy that can boost immunity in the elderly is to be welcomed.

Various probiotic bacteria, including yoghurt organisms, *L. johnsonii* La1, *L. acidophilus*, *L. casei* and *B. lactis* Bb12, have been shown on the basis of in vitro and ex vivo models to have immunostimulatory properties, including modulation of cytokine production, increased phagocytic activity of polymorphs, adjuvant effects on specific humoral responses, T lymphocytic function, and NK activity.⁴⁶⁻⁴⁷

Several investigations show that probiotics stimulate the immune system in elderly subjects. Gill and colleagues report in a series of papers the beneficial effects of three week courses of *L. rhamnosus* HN001 or *B. lactis* HN019 in elderly healthy volunteers; they found significant increases in levels of α -interferon, total lymphocyte counts, circulating counts of CD4+ and CD25+ cells, and NK tumoricidal activities.⁴⁸⁻⁵¹ Of particular interest were the findings that improvements in immunological functions were more marked in subjects aged over 70 and in those with poor pretreatment parameters. Van de Water *et al* found that yoghurt consumption for one year decreased the incidence of allergies and serum IgE levels in a group of healthy elderly subjects.⁵²

Guigoz *et al* investigated the effects of giving the prebiotic FOS, 8 g daily for three weeks, to frail elderly subjects in a nursing home.⁵³ An increase in numbers of faecal bifidobacteria was accompanied by significant rises in counts of total lymphocytes, CD4+ and CD8+ cells. An unexpected finding was a fall in phagocytic activity of polymorphs and monocytes, as well as reduced expression of interleukin-6 mRNA in peripheral blood monocytes; the authors attributed these changes to a general decrease in inflammation. However, Bunout *et al* found that a prebiotic mixture of inulin and oligofructose did not augment the results of vaccination with influenza and pneumococcal antigens.⁵⁴

It remains to be demonstrated whether the apparently beneficial effects of probiotics and prebiotics on various immune parameters, as outlined above, is of practical significance. An interesting finding in this respect was made by Turchet *et al* who supplemented the diet of a group of healthy elderly subjects with *L. casei* for three weeks, and reported that the duration of "winter infections" (gastrointestinal or respiratory) was decreased by 20% compared with a control group.⁵⁵

OTHER POSSIBLE USES OF PROBIOTICS IN THE ELDERLY

Probiotics have been shown in clinical trials to be effective in a wide variety of conditions other than those discussed above.^{3-4 56} Although these studies have not specifically involved elderly subjects, it is not unreasonable to suppose that the results could also apply to this group.

An intriguing possibility is that LAB may have a role in prevention of malignancy. In vitro and animal studies suggest various possible anticarcinogenic effects, possibly by altering faecal enzymes so that production of potential carcinogens, such as nitrite and azo compounds, is minimised.⁵⁷ The action of probiotics, described in the previous section, in increasing the activity of NK cells, whose targets include tumour cells, may also have a part to play in the prevention of development of cancers. There are grounds for optimism from epidemiological studies, some of which show

lower incidences of some types of cancer associated with regular consumption of fermented milk products.⁵⁸

Two randomised clinical trials from Japan indicated that *L. casei* Shirota significantly decreased the chance of recurrence of bladder tumours in man.⁵⁹⁻⁶⁰

CONCLUSIONS

Review of the literature suggests that three problems common in the elderly, namely, undernutrition, constipation, and the decline in efficiency of the immune system leading to a reduced capacity to resist infection, may all be beneficially affected by appropriate probiotic organisms (table 2). These are most conveniently taken either as yoghurts or as specific supplements. Much further work is necessary to determine long term outcomes and the most suitable probiotic strains. Prebiotics may also have a similar role.

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