Inulin-Type Fructans in Healthy Aging¹,²

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Abstract

Worldwide, the population is aging, with estimates of 1 billion people aged 60 y or over within the next 20 y. With aging comes a reduction in overall health and increased morbidity and mortality due to infectious disease. Mortality due to gastrointestinal infections is up to 400 times higher in the elderly compared with younger adults. Recent studies have shown that the gut microbiota changes in old age, with an increased number of bacterial groups represented in the predominant elderly gut microbiota. This change in species "evenness" coincides with parallel changes in immune function, diet, and lifestyle and may contribute to disease susceptibility and severity in old age. The intestinal microbiota may thus be identified as an important target for improving health through reduced disease risk. Here, the application of prebiotics, especially the inulin-type fructans, and symbiotics (prebiotics combined with efficacious probiotic strains) will be discussed in terms of microbiota modulation and impact on disease risk in the aged population. Recent human intervention studies have confirmed the microbiota modulatory capability of the inulin-type fructans in the elderly and there is some evidence for reduced risk of disease. However, there is a need for more and larger human intervention studies to determine the efficacy of prebiotics in the elderly, particularly studies that take advantage of recent high resolution analytical methodologies like metabonomics, to shed light on possible prebiotic mechanisms of action. J. Nutr. 137: 2590S–2593S, 2007.

Introduction

Worldwide, the population is aging, with declining birth rates (especially in developed countries) and increasing life expectancy, contributing to the growing aged population. According to the WHO, there were 580 million people in the world ≥60 y in 1999 and this figure is expected to rise to 1 billion in the next 20 y (1). With aging comes a reduction in overall health and increased morbidity and mortality due to both chronic disease and acute infectious disease, many associated with the gastrointestinal tract. Up to 85% of the elderly population are likely to undergo medical intervention for single or multiple diseases at any given time and mortality due to gastrointestinal infections is up to 400 times higher in the elderly compared with younger adults (2,3). This increased disease burden has identified the elderly as a potential target population of particular interest for dietary modulation of the gut microbiota for prophylactic management of gut health. The premise is that by increasing numbers of bacteria considered beneficial within the intestinal tract of the elderly, disease incidence or associated morbidity may be reduced. To date, there are a limited number of intervention studies with functional foods targeting intestinal health in the elderly. The focus of this review is on the gut microbiota of the elderly and the efficacy of inulin-type fructans to modulate the intestinal microbiota of the elderly toward a more beneficial composition.

The gut microbiota in old age

The human intestinal tract is home to a diverse collection of bacteria, recently estimated to comprise some 1000 bacterial species (4). This diverse microbiota encodes an array of different enzymatic and metabolic capabilities, many complementary to human encoded functions, which even with genetic redundancy between different bacterial species represents a powerful extragenomic metabolic organ upon which the host relies for breakdown and transformation of complex dietary and xenobiotic compounds. Recent metabolic studies using ¹H-NMR have revealed that the metabolic output of this microbial organ changes with diet and with old age. Wang et al. (5) showed that the metabolite profiles of elderly dogs (9 y old) were strikingly different from those of younger dogs (13 wk and 1.5 y of age) and that these differences were mainly due to differences in aromatic metabolites and aliphatic amine compounds, both derived from microbial activities in the gut. Additionally, the effect of aging appeared to have a greater impact on urinary metabolic profile than diet (control diet compared with dietary restriction, 25% less energy than the control diet). Recent studies have also shown that the gut microbiota changes in old age. It appears that the number of bacterial groups represented in the dominant gut microbiota of the elderly is much increased compared with younger adults. This means that species or

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groups of bacteria that were present in relatively low numbers earlier in life come to the fore in old age and increase in population size. This occurs in parallel with changes in immune function, diet, and lifestyle and may contribute to disease susceptibility and severity in this age group. The intestinal microbiota may thus be identified as an important target for improving health through reduced disease risk.

Early studies on intestinal microbial ecology in the elderly suggested that age-related changes occur both in population levels of dominant groups of intestinal bacteria and in species richness of the dominant microbiota. Gorbach et al. (7,8) also reported that numbers of bifidobacteria decreased in old age and that numbers of Clostridium perfringens, lactobacilli, streptococci, and the enterobacteria were all present in higher population levels in the elderly. Similar observations were made by Benno et al. (9) examining the effect of aging on microbial ecology of the canine gut.

The altered state of the intestinal microbiota in old age has also been confirmed by more recent studies using 16S ribosomal RNA-based molecular techniques. Saunier and Doré (10), as part of the European Union-funded project Crownalife (which examined diet-microbe interaction in the elderly and dietary intervention with synbiotics in this age group; http://www.crownalife.be/), reported that Bacteroides, bifidobacteria, and Clostridium leptum 16S rRNA species decreased in terms of percentage microbiota composition in the elderly, whereas proportions of Lactobacillus 16S rRNA were elevated compared with younger adults. The authors confirmed that the microbiota of elderly people changed in species evenness compared with younger adults and infants using comparative sequencing of cloned 16S rRNA from fecal samples of different age groups. Statistically, the number of species recovered by this technique rose from 15 for infants to 168 for the elderly. Moreover, only 8% of 16S rRNA sequences recovered from elderly fecal samples were related to bacterial isolates deposited in culture collections compared with 20% for adults (11,12).

Using dot-blot hybridization, traditional culture-based microbiological techniques, and community cellular fatty acid profiles, Hopkins et al. (13) investigated the composition of the gut microbiota in 4 different groups of individuals: children (16 mo–7 y; n = 10), adults (21–34 y; n = 7), healthy elderly people (67–88 y; n = 5), and elderly patients diagnosed with Clostridium difficile diarrhea (68–73 y; n = 4). When the authors used both traditional microbiological techniques and 16S rRNA-based dot-blot probing to measure stool microbial make-up, they found that numbers of enterobacteria were significantly higher in the children than in adults. Numbers of bifidobacteria and Bacteroides spp. were much reduced and numbers of facultative anaerobes (enterobacteria, enterococci, and lactobacilli) and clostridia were higher in the C. difficile group. Relative population levels of Bifidobacterium spp. were lower in both the aged groups compared with the children and younger adults using the traditional culture-based technique, whereas dot-blot probing showed bifidobacteria to be lowest in the C. difficile patients. Hopkins and Macfarlane (14) examined microbial diversity within healthy adults and in elderly subjects and elderly patients with C. difficile-associated diarrhea (CDAD) using traditional culture techniques. Bacteroides thetaiotaomicron, B. ovatus, and Prevotella tannerae were commonly isolated from younger adults, whereas Bacteroides species richness was increased in the aged group. Species composition of the bifidobacteria tended to decrease with age, with B. adolescentis and B. angulatum being commonly isolated. In the CDAD patients, as observed in previous studies, numbers of Bacteroides spp., Prevotella spp. and Bifidobacterium spp. were reduced, whereas the species richness of facultative anaerobes (enterobacteria and enterococci), lactobacilli, and clostridia tended to be much higher. Although the impact of antibiotic therapy may have affected the microbial ecology of the CDAD stools, the authors suggested that Bacteroides spp. and Bifidobacterium spp. may play an important role in maintaining colonization resistance toward C. difficile in health, as these groups were much reduced in the CDAD patients. In any case, these studies clearly showed that the dominant groups of bacteria within the intestinal tract of the elderly differ from those in younger individuals. This altered evenness in the dominant gut microbiota may be due to groups of bacteria present at sub-dominant levels in younger individuals, becoming more dominant in the elderly, creating an increased richness in the species composition of the predominant elderly gut bacteria. This is a more likely scenario than de novo colonization of the intestinal tract with exogenous bacteria, considering the challenges encountered by invading bacteria in establishing within climax microbial communities.

Silvi et al. (15), as part of the Crownalife project, described the species composition of bifidobacterial and lactic acid microbiota of fecal samples taken from 12 healthy elderly Italian volunteers. Each individual had his or her own unique collection of species making up these 2 moieties. However, L. fermentum and B. longum were the most commonly isolated species of lactic acid bacteria. One hundred and nine of these bifidobacteria and lactobacilli were later screened for putative probiotic activities, including the ability to inhibit enteropathogenic and verocytotoxin producing strains of Escherichia coli, C. difficile and Campylobacter jejuni (16). Characterization of the gut microbiota at the species level is important in that many microbial activities relevant to human health occur at the species or even strain level and may be overlooked if relying on measurements at the genus level. Isolation of live bacteria is often critical for determining the particular ecological role of an organism, its metabolic or pathogenic capabilities, or in identification of potentially beneficial organisms that may then be screened for their use in probiotic functional foods (17).

Gavini et al. (18) determined the differences within the bifidobacteria and enterobacteria moieties of the fecal microbiota of children (3–15 y), young adults (30–46 y), and the elderly (69–89 y). E. coli was present in 93% of fecal samples and its occurrence was independent of age, whereas Enterobacter and Klebsiella species were isolated more frequently in children and the elderly than in adults. Species of Proteus and Providencia, also within the Enterobacteriaceae, were common in the elderly. The authors concluded that the enterobacterial microbiota of the elderly and of children was more diverse than that of the adults. Many of the enterobacterial, including Enterobacter, Klebsiella, Proteus, and Providencia, have been shown to cause diarrhea or are frequently isolated from diarrheal stools, which may be of particular clinical relevance in the elderly for whom diarrhea may be associated with increased morbidity. Conversely, differences in species composition of genera considered beneficial for intestinal health also differed between the elderly and younger individuals. B. longum was more common in children and in the younger adults, whereas B. adolescentis was more common in the elderly.

More recently, Mueller et al. (19) in a cross-sectional study of 130 healthy individuals found marked age and location (1 of 4 European locations in France, Germany, Italy, or Sweden) differences in species composition of fecal microbiota. These authors used an extensive panel of 14 different group- and
species-specific 16S rRNA gene probes and fluorescent in situ hybridization coupled with flow cytometry to characterize bacterial prevalence in stool samples collected in the different countries. The dominant bacteria in all groups examined belonged to the phylogenetic groupings *Eubacterium rectale*, *Clostridium cocoides*, *Bacteroides-Prevotella*, or *Faecalibacterium prausnitzii*. Age-related changes were observed in these groups of bacteria, although such differences were not always observed in the different geographical locations. For example, the proportion of the *E. rectale* group was higher in elderly Germans compared with the younger German age group, whereas the inverse was true for the Italian aged and younger adults. In the German cohorts, the elderly had 2- to 3.5-fold lower proportions of *Bacteroides-Prevotella* than their younger compatriots, whereas the elderly Italians had the lowest proportion of this phylogenetic group of all group studies. In the Swedish groups, *Faecalibacterium prausnitzii* predominated, although there was a distinct age effect for this phylogenetic cluster in Italy, with the elderly showing higher levels than the younger group. In the German and Swedish groups, Atopobium spp. population levels were higher in the elderly. Geographical location had a significant effect on population levels of the bifidobacteria, with the Italian groups having a 2- to 3-fold higher population levels compared with the other countries. Of the less dominant bacterial groups enumerated, the Enterobacteriaceae were significantly higher in the elderly, irrespective of country, whereas age-related differences in proportions of the *Lactobacillus/Enterococcus* group were country specific. This study clearly showed that age does affect the proportions of the main bacterial groups making up the gut microbiota but that other cultural factors, such as diet or lifestyle, can also affect species composition.

**Dietary modulation of the gut microbiota using inulin-type fructans**

A prebiotic is a nondigestible food ingredient that beneficially effects the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon and thus improves host health (20). The majority of prebiotics are oligosaccharides or short polysaccharides. Prebiotic functional foods with the strongest scientific support include the inulin-type fructans (inulin and inulin-derived products such as the oligofructose and Synergy), galactooligosaccharides, and lactulose (21). A defining feature of prebiotics and one that distinguishes them from other dietary fibers is their selective fermentation by bifidobacteria and/or lactobacilli within the colonic microbiota. In the case of inulin and oligofructose, this specific modulation of the gut microbiota has been repeatedly proven in human feeding studies and appears to be brought about at doses of prebiotic ranging from 4–15 g/d (22). There is now growing scientific support that consuming inulin-based prebiotics directly affects risk of chronic disease, not just within the gastrointestinal tract but also systemically, reducing the risk of coronary vascular disease or improving bone health. Evidence mainly from animal feeding studies, but also from some human dietary interventions, indicate that supplementation with inulin-derived prebiotics may improve gastrointestinal motility (23), reduce symptoms and inflammation in ulcerative colitis (24–26), protect against colon cancer (27–30), lower blood triglycerides and protect against coronary heart disease (31–33), and improve bone health through increased mineral absorption (34,35).

The elderly may form a subset of the population for which microbiota modulation through dietary prebiotics may be especially relevant. Changes within the gut microbiota, as detailed above, suggest an age-related reduction in bifidobacterial numbers and a concomitant change in species evenness within the dominant gut microbiota and elevated population levels of enterobacteria. In younger individuals, prebiotics have proven effective in increasing numbers of indigenous probiotic bacteria within the gut and have on occasion been shown to reduce numbers of potentially disease-causing Enterobacteriaceae and offer some protection against the onset or clinical course of diarrheal infections (22,36,37).

**Dietary modulation of the gut microbiota in the elderly using inulin-type fructans**

Although the ability of oligofructose and inulin to beneficially modulate the gut microbiota toward a more beneficial composition has been well established in the younger adult population, only a few studies have examined the impact of these inulin-type fructans on the gut microbiota of elderly subjects. Kleesen et al. (38) in 1997 investigated the relative impact of lactose or inulin on the gut microbiota composition of 25 elderly constipated subjects in a parallel double-blinded feeding study. The subjects were fed 20 g/d for the first 8 d, followed by a gradual increase to 40 g/d between d 9 and 19. Using traditional microbiological culture techniques, the authors reported that numbers of fecal bifidobacteria increased significantly in the inulin-fed subjects compared with pretreatment samples. There was also a concomitant reduction in numbers of enterococci and the enterobacteria. Conversely, upon lactose feeding, clostridia and the lactobacilli decreased whereas numbers of enterococci increased. Nine of the 10 elderly subjects fed inulin also showed decreased constipation. Bartosch et al. (39) examined the impact of a symbiotic containing *Bifidobacterium bifidum* and *B. lactis* and the inulin-type fructan-based prebiotic, Synergy (a mixture of oligofructose and long chain inulin) on the gut microbiota composition of 18 elderly subjects in a placebo-controlled, double-blind, parallel feeding study. The volunteers consumed $3.5 \times 10^{10}$ colony forming units (CFU) of each probiotic plus 6 g/d Synergy for 28 d or a placebo. Using traditional microbiological culture techniques, the authors observed significantly higher numbers of bifidobacteria and lactobacilli in the stool samples of the symbiotic-fed subjects compared with the placebo group. Using group- and species-specific 16S rRNA gene primers, the authors were also able to demonstrate higher numbers of bifidobacteria in the symbiotic-fed group and also higher numbers of *B. bifidum* and *B. lactis* in this group, as might be expected, compared with the placebo group. It appears that the increased bifidobacteria upon symbiotic ingestion was greater than the sum of the 2 probiotic bifidobacterial strains ingested with the symbiotic, demonstrating that the prebiotic too contributed toward the bifidogenic effect of the symbiotic treatment.

Recent microbiological analysis of the gut microbiota in old age has highlighted that the dominant gut microbiota in the elderly appear to be made up of a greater number of bacterial groups than found in younger adults and that population size of the enterobacteria is elevated. Studies have shown that the elderly also display lower population levels of bacteria considered beneficial toward human health, the bifidobacteria. The ability of inulin-type fructans to mediate a beneficial modulation of the gut microbiota, with increased proportions of bifidobacteria in particular, has been repeatedly shown in healthy adult subjects. However, on only a few occasions has the impact of prebiotics on the elderly gut microbiota been investigated. Two double-blind, placebo-controlled studies have shown that the inulin-type fructans, whether ingested alone or in combination with probiotic strains, have a similar impact on fecal bifidobacterial...
population levels in the elderly. The EU-funded project Crownlife too has investigated the impact of inulin-type fructans (in a symbiotic preparation) on the composition of the elderly gut microbiota. Again, an increase in fecal bifidobacteria was observed (S. Müller, C. Hanisch, K. Saunier, J. Doré, L. Norin, A. Cresci, C. Koebnick, H. Zunft, and M. Blaut, unpublished data). However, there is need for more and larger human intervention studies to determine the efficacy of prebiotic intervention in the diseases of old age, in particular studies taking advantage of recent high resolution analytical technologies such as metabolomics, to shed light on possible prebiotic mechanisms of action (40).

Literature Cited