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Review

Probiotics and prebiotics and health in ageing populations

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ABSTRACT

In healthy adults microbial communities that colonise different regions of the human colon contribute nutrients and energy to the host via the fermentation of non-digestible dietary components in the large intestine. A delicate balance of microbial species is required to maintain healthy metabolism and immune function. Disturbance in this microbial balance can have negative consequences for health resulting in elevated inflammation and infection, that are contributory factors in diabetes and cancer. There is a growing awareness that the microbial balance in the colon may become increasingly perturbed with aging and therefore hasten the onset of certain diseases. Societal and dietary factors influence microbial community composition both in the short and long term in the elderly (>65 years old) whilst immunosenescence may also be linked to a perturbed distal gut microbiota and frailty in the elderly. Significant progress has been made in defining some of the dominant members of the microbial community in the healthy large intestine and in identifying their roles in metabolism. There is therefore an urgent need for better awareness of the impact of diet, prebiotic and probiotic strategies in driving human colonic microbial composition in order to understand the possibilities for maintaining healthy gut function and well-being in an increasingly elderly population. Here we review gut microbial changes associated with aging and how diet, prebiotics and probiotics may modulate the gut microbiota to maintain health in the elderly.

Contents

1. Introduction

The aging population is fast becoming an urgent global health priority as it is predicted that soon, and for the first time ever in our history, the number of people over 65 years old will outnumber the very young (under five years olds). To a certain extent this is due to advances in medicine and socioeconomic development. Nonetheless it is becoming imperative that the well-being of the elderly should be optimised to promote a good quality of life and to dampen the potentially overwhelming demand and cost to the healthcare system.

The gut microbiota and their metabolites play a central role in modulating gut health and disease [1,2] in all age groups and

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perhaps particularly the elderly [3]. For example, changes in the composition of the gut microbiota have been linked with inflammatory and metabolic disorders including inflammatory bowel disease [4], irritable bowel disease [5], diabetes, cardiovascular disease, colorectal cancer [6,7] and with frailty [8].

The majority of bacteria in the colon are anaerobes that possess wide ranging metabolic activities. For example, many colonic anaerobes can ferment a wide variety of dietary carbohydrates that escape digestion by the host enzymes, to form short chain fatty acids (SCFAs) and the major anions detected include acetate, propionate and butyrate that have a distinct role in promoting gut health [9]. Furthermore, certain bacterial species have a role in peptide and amino acid metabolism and there are a number of different bacterial species that can metabolise the aromatic amino acids including tryptophan [10], microbial metabolism of which influences the precursor pool for serotonin [11]. It has also been proposed that the gut microbiota can influence brain chemistry, brain function and even anxiety [12] all of which are relevant to the elderly.

The association between the mammalian host and microorganisms that colonise the intestinal tract has co-evolved over a considerable time frame and our understanding of changes in the composition of the gut microbiota linking diet, microbiota and health at different life stages has progressed considerably [13–16]. Understanding the role of the gut microbiota in nutrition and maintenance of health is highly complex and certain microorganisms, which traditionally include bifidobacteria, are considered beneficial for health, although the supporting evidence and mechanistic basis for these benefits remains rather incomplete, ambiguous and sometimes controversial [17].

More recently, studies based mainly on the analysis of the 16S rRNA gene, revealed that there are a number of dominant bacterial species (or phylotypes) that predominate in the healthy large intestine [16,18,19]. One of the most abundant species in the healthy colon, *Faecalibacterium prausnitzii*, [16] has been reported to possess potent anti-inflammatory activities [20]. The gut community can also include organisms that have the capacity for adverse effects via their metabolic outputs and gene products. The balance of benefit and harm for the host therefore depends on the overall state of the microbial community in terms of its distribution, diversity, species composition and metabolic outputs.

Here we examine how the composition of the gut microbiota changes through life stages, consider the stability and resilience of the microbiota and reflect on how dietary carbohydrates, prebiotics and probiotics may modulate microbial composition along with their potential to maintain a beneficial microbial balance to promote health in the elderly.

2. Changes in the composition of the gut microbiota through life stages

The microbial composition of the gastrointestinal tract in humans undergoes remarkable changes in our life time [21–23]. At birth the gastrointestinal tract of babies is perceived to be sterile but is rapidly colonised by bacteria from the mother and the environment during and following birth. The development of the microbiota in babies will depend on their mode of delivery [14,24] and feeding regime. Breast fed babies tend to mainly favour bifidobacteria in their gastrointestinal tract whilst those of bottle fed babies harbour a more diverse population [25]. After the introduction of solid food the microbial composition of the colon of infants increasingly develops towards that of adults with increased diversity (Fig. 1) and in particular an increase in the abundance of anaerobic Firmicutes [16].

In adults, the colon sustains a total of around 10^{14} bacterial cells that outnumber host cells by around 10-fold and the gut microbiome possesses approximately 150-times as many genes as the human genome. The dominant bacterial phyla in the healthy state in post weaned children and adults (<65 years old) are the Firmicutes, Bacteroidetes and Actinobacteria, with Proteobacteria and Verrucomicrobia also present in lower numbers [26]. Despite the diversity at the level of phylotypes or species, certain species are commonly detected in high numbers in most adult faecal samples. Most healthy adults usually have a relatively stable climax microbial community in the colon although the intestinal community might exist in a small number of discrete states or 'enterotypes' [27,28]. Fresh evidence indicates significant geographic variation in dominant phylotypes [29] with *Prevotella* species dominating in stool samples from African children consuming an unrefined carbohydrate-rich diet compared to Italian children consuming a diet rich in starch and protein which resulted in an enrichment of *Bacteroides* species. This suggests that there are long-term impacts of regular diet on the composition of the gut microbiota although this may be further modulated by short term dietary change [30].

At the finer level, Tap et al. [19] reported 66 particularly abundant species (or phylotypes) among 17 healthy individuals and Walker et al. [18] found 50 dominant phylotypes that each represented more than 0.5% of total 16S rRNA sequences from faecal samples from adult males. Many of the most abundant species are recognised butyrate producers and include *F. prausnitzii*, *Eubacterium rectale* [16] and the recently defined species *Anaerostipes hadrus* [31] (Table 1). Of course, it is important to note that these less abundant species in the colon may also play critical roles within these complex microbial communities. Moreover, whilst an element of this phylogenetic variation may be functionally redundant it may also include species that possess rather rare or unique functional properties and can be considered as keystone species, as exemplified by the remarkable ability of *Ruminococcus bromii* to degrade resistant starch [32].

Importantly, in the elderly there seems to be a decline in microbiota diversity [21] with lower numbers of bifidobacteria and an increase in *Enterobacteriaceae* [23] and certain Proteobacteria are suspected to play a role in the causation of bowel disease [33]. Bacteroidetes become more abundant and Firmicutes less abundant in elderly compared to younger adult controls. In a large prospective study [15] a cohort of 178 non-antibiotic treated elderly (mean age 78; range 64–102 years) were recruited according to their community residence status and were compared with 13 young adults (mean age 36 years; range 28–46 years) that were used as a control group. Data was acquired from more than 5 million sequence reads generated from 16S rRNA gene amplicons and revealed that the composition of the gut microbiota of an individual separates depending on where individuals live. Community-dwelling individuals had a greater number of Firmicutes and lower proportion of Bacteroidetes than those in long stay residential care. Based on the enterotype divisions [15] six co-abundance groups (CAGs) were detected. The dominant genera in these CAGs were *Bacteroides*, *Prevotella*, *Ruminococcus*, *Oscillibacter*, *Alistipes* and *Odoribacter* CAGs. The transition from healthy community-dwelling subjects, to frail long-term care residents, is accompanied by distinctive CAG dominance, most significantly in abundances of *Prevotella* and *Ruminococcus* CAGs in their community cohort and *Alistipes* and *Oscillibacter* CAGs long-stay resident cohort. It is not yet evident how these changes correspond to changes in health status nor is it apparent to what extent they are driven by altered dietary intake, physical activity or altered immune function.

3. Microbial metabolism in the colon

Changes in the composition of the gut microbiota in the elderly, as discussed above, along with their metabolic activity