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Review article

The aging gut and the role of prebiotics, probiotics, and synbiotics: A review

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ABSTRACT

The United States (US) Census Bureau estimates the current US population at 301 million with elderly people (>65 years old) accounting for 36 million. Within this group, the fastest growing segment of the population is >85 years of age, which currently numbers ~5 million and is expected to rise to ~20 million by 2050. Over the decades there has been speculation that gastrointestinal structure and function decline with age. Therefore, the physiological changes in the gut with aging and their clinical implications have become important topics for discussion. This review also attempts to document the role of probiotics in enhancing gut activity in older persons.

1. Introduction: the aging intestines

The small intestine does not reveal structural and functional deteriorations with aging under normal conditions. This is explained on the basis of increased small bowel enterocyte proliferation and apoptosis in elderly people, which helps maintain the mucosal architecture.[1] Thus, small bowel intestinal histology and permeability do not appear to change with aging.[2] However, the hyperproliferative state and exaggerated apoptosis can result in cellular immaturity, which contributes to some impaired absorptive function under conditions of stress in elderly people.

2. Microbiota changes

Commensal intestinal flora plays an important role in the maintenance of the host health by providing nutrients and a protective barrier against invading organisms. There are, however, reports of shifts in the composition of intestinal microbiota with age, with increased numbers of facultative anaerobes and Gram-negative bacteria (mainly *Enterobacter*) and a decrease in the number of beneficial organisms such as lactobacilli and bifidobacteria.[3] These changes, along with a general reduction in species diversity in most bacterial groups, and changes to diet and digestive physiology such as intestinal transit time, may result in increased putrefaction in the colon and a greater susceptibility to disease and infection.[4] Besides, these microbiota changes are believed to induce a subclinical intestinal inflammation in elderly people, leading to a low systemic inflammatory status and chronic disease in this population.[5]

2.1. Small bowel bacterial overgrowth

Small bowel bacterial overgrowth (SBBO), defined by an abnormal increase in the number of bacteria in the small intestine, is found in elderly people. SBBO has been associated with nutrient malabsorption and diarrhea, which lead to malnutrition and weight loss in elderly people. Various trials using antibiotics to decrease SBBO in older persons have led to improved anthropometric and nutritional measurements, further cementing the role of SBBO in malabsorption and its consequences with aging.[6–10] Clinically nonapparent SBBO and few mucosal changes may be important causes of lactose malabsorption in elderly people.[11]

2.2. Carcinogenic transformation

Age-associated enterocyte hyperproliferation and decreased apoptosis in the colon have been implicated as potential causes of carcinogenic transformation in elderly people.[12] This can partly be explained by increased activity of epithelial growth factor receptor (EGFR) and its family members, which in turn may be due to

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decreased expression of its negative regulator, EGFR-related protein.[13] In addition, depleted levels of cell-cycle and apoptosis regulator protein-1, a novel protein associated with apoptosis signaled by EGFR, are seen with aging in the colonic mucosa.[14]

2.3. Nutrient absorption

Malabsorption of carbohydrates, lipids, amino acids, minerals, and vitamins has been described in elderly people. Elderly people are also at risk for malnutrition due to poor dentition or decaying teeth and dysphagia that may interfere with eating, loss of smell or taste sensations, chronic illnesses that interfere with digestion or absorption of food, and increased nutritional requirements. Other factors such as medication side effects; depression; social isolation; functional, visual, and cognitive impairment; and economic barriers to obtaining high-quality foods all can lead to malnutrition.[15] The ability of the intestine to adapt may be impaired in elderly people and this may lead to further malnutrition.[16] Of particular concern is reduced calcium absorption in elderly people. This decrease could be due to a decline in either the active calcium transport or diffusion component of the calcium absorption system.[17] Furthermore, there have been reports of decreased numbers of enterocyte vitamin D receptors and reduced intestinal responsiveness to the action of 1,25-dihydroxyvitamin D3. This defect could lead to compensatory increases in parathyroid hormone secretion and 1,25-dihydroxyvitamin D3 production, which maintains calcium absorption and serum ionic calcium, but at the expense of increased bone loss.[18,19]

2.4. Neurodegeneration of the gastrointestinal tract with aging

Aging is associated with degeneration of the enteric nervous system with the loss of neurons in both the submucosal and myentric plexuses. This process seems to affect selectively the cholinergic neurons and interstitial cells of Cajal with inhibitory n1 (including nitrergic) neurons being spared. The enteric glia is also depleted with the distal gut most severely affected, and this may be responsible for age-related functional problems of constipation, incontinence, and evacuation.[20–24]

2.5. Immune function in elderly people

Aging affects both the innate and adaptive immune responses. There is a decrease in phagocytosis, alteration of cellular migration, changes in cell populations and numbers, and decreased antibody production. It has been reported that gut microbial flora have a significant effect on the host immune system and can lead to autoimmune-related disease such as rheumatoid arthritis, inflammatory bowel diseases, and type I diabetes if microbial flora are altered as in overuse of antibiotics.[25]

3. Probiotics, prebiotics, and synbiotics: Fountain of life?

Probiotics are defined as viable microorganisms; sufficient amounts of which reach the intestine in an active state and thus exert positive health effects. Numerous probiotic microorganisms (e.g., *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, bifidobacteria, and certain strains of *Lactobacillus casei* or the *Lactobacillus acidophilus* group) are used in probiotic food. A prebiotic is "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon the host's well being and health". Inulin-type fructans, selective fermentable chicory fructans, are the major prebiotics used and synergistic combinations of probiotics and prebiotics are called synbiotics.

3.1. Immunomodulatory effects of probiotics

Aging is associated with immunosenescence characterized by depleted cellular immunity, which may predispose to increased risk of infections in elderly people. Probiotic supplementation has been demonstrated to increase natural killer cell and phagocytic activity, with the maximum benefit being in the elderly population.[26–28] Moreover, probiotics may ameliorate the detrimental effects of malnutrition on immunity in elderly people by improving the nutritional and immune status, as demonstrated by increasing levels of serum albumin and intestinal immunoglobulinA (IgA) production (seen in trials on aged mice).[29–31]

3.2. Changes in intestinal microbiota with prebiotics and probiotics and the clinical implications

Probiotic and synbiotic administration have been documented to increase intestinal levels of beneficial lactobacilli, bifidobacteria, and enterococci, with reduced levels of enterobacter. This may well counter the age-related changes in the intestinal microbiota and therefore reduce the risk of infections.[32,33] An interesting effect of probiotics may be a reduction in *Clostridium-difficile*-associated diarrhea; one of the most common nosocomial infection in aged individuals.[3,34] A study has shown that administration of prebiotics also results in increased numbers of beneficial intestinal flora (especially bifidobacteria), increased anti-inflammatory cytokines, and decreased proinflammatory cytokines, which result in a decrease in overall gut inflammation in elderly people.[35,36]

3.3. Inhibition of carcinogenesis

Prebiotic and synbiotic administration is believed to stimulate the growth of beneficial bifidobacteria and lactobacilli in the intestine.[37] They have been demonstrated to inhibit the development of aberrant crypt foci in the colonic mucosa, suggesting the tumor-inhibiting properties of chicory fructans. Animal trials have also shown reduced colonic mucosal proliferation and decreased activities of colonic mucosa and tumor ornithine decarboxylase and ras-p21.[38,39] Prebiotics via their interaction with gut flora give fermentation products, and these short chain fatty acids (butyrate and propionate) inhibit growth of colon tumor cells and histone deacetylases. Butyrate also causes apoptosis, reduces metastasis in colon cell lines, and protects the body from genotoxic carcinogens by enhancing expression of enzymes involved in detoxification.[40–42]

3.4. Prebiotics, probiotics, synbiotics, and nutrient absorption

Prebiotics/synbiotics have been demonstrated to increase mineral absorption, particularly that of calcium and magnesium.[43,44] The underlying mechanisms are manifold: increased solubility of minerals because of increased bacterial production of short-chain fatty acids, which is promoted by the greater supply of substrate; an enlargement of the absorption surface by promoting proliferation of enterocytes mediated by bacterial fermentation products, predominantly lactate and butyrate; increased expression of calcium-binding proteins; improvement of gut health; degradation of mineral complexing phytic acid; release of bone-modulating factors such as phytoestrogens from foods; and stabilization of the intestinal flora and ecology.[45] Increased calcium absorption would therefore make inulin-type fructans, promising substances that could help to improve the supply with available calcium in human nutrition, thus contributing to bone health.[46–49] Supplementation of probiotics and yogurt influence the colonic bacteria, and increase the number of main groups of colonic microflora,