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The Effects of Aging on Gut Microbiome Composition and Association With Age-Related Disease States: A Literature Review

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Abstract

Introduction: The gut microbiome is the collection of microbial species residing in the gastrointestinal tract that play an important role in metabolism and immune function. A reduction in microbial diversity and/or an altered composition of microbiota results in dysbiosis, which is speculated to place individuals at greater risk for neurological, metabolic, and physical disorders. The purpose of this study is to provide a review of the literature describing alterations in composition and species richness that occur during aging in the gut microbiome whilst identifying how these changes are linked to age-related diseases.

Methods: A review of the current literature was conducted by searching for applicable keywords using scientific, electronic databases. Keywords used to search for articles included ("gut microbiome" OR "gut microbiota" OR "bacteria flora") AND ("aging" OR "ageing" OR "old age") AND ("age-related disease" OR "disease"). Articles were screened and chosen for analysis based on the quality and relevance of the study.

Results: There are many changes that occur in the gut microbiome with aging, such as reduced short-chain fatty acid production, lack of overall diversity and increase in pathobionts from phyla Proteobacteria and Enterobacteriaceae. Many age-related diseases display distinct changes in microbiome composition which have been shown to be implicated in disease onset or progression. In cases of extreme longevity, the microbiome displays specific signatures associated with youthfulness and health such as stability, resilience, and taxonomic diversity.

Discussion: The alterations observed in the gut microbiome during aging are likely due to a concurrent deterioration of the immune system and reduction in intestinal function and motility. Microbial dysbiosis promotes a pro-inflammatory state in the gut which has implications for disease. Additionally, many microbial signatures of aging coincided with alterations attributed to diseased states, further supporting that dysbiosis in later years of life may accelerate or promote pathology. In contrast, the microbiome of centenarians and extremely long-lived individuals demonstrate a model for healthy aging and longevity.

Conclusion: The findings from this study highlight the importance of the microbiome in age-related diseases and proposes the microbiome as a potential target for the mitigation and treatment of disease in elderly populations.

Keywords: microbiome; aging; dysbiosis; age-related disease; inflammation; longevity; gut-brain axis

Introduction

Today's older population is rapidly increasing as the human life expectancy has extended dramatically in the past few decades [1]. Although lifespan is still on the rise, it does not translate to overall health or well-being in the older population [2]. Recent developments in the field of geroscience have allowed for the identification of the seven interconnected pillars of aging, including inflammation, epigenetics, stem cell regeneration, proteostasis and metabolism, along with their underlying mechanistic processes as they relate to diseased states [3]. Indeed, the link between aging and chronic disease is well established, with age being a significant risk factor for cardiometabolic disease, non-alcoholic liver disease, certain cancers, neurodegenerative diseases, and type two diabetes [3]. Thus, increasing the average health-span of the aging population is of particular interest to researchers in the clinical field.

The gut microbiome is a key organ in the human body that is gaining more and more recognition for its implications in the aging process and disease risk. The gut microbiome, as we understand it today, is a collection of micro-organisms that reside in the gastrointestinal tract (GIT) that engage in a symbiotic relationship with the host in a healthy state [4]. The human microbiome has a significant presence in the human body as it contributes approximately 360 times more protein-coding genes than the human genome and consists of trillions of organisms

outnumbering human cells by a factor of ten [5,6]. This organ plays a vital role in many physiological processes and helps to maintain immune homeostasis [6]. The microbiota has the unique ability to break down indigestible compounds such as dietary fiber and certain proteins to increase energy availability and produce metabolites such as short-chain fatty acids (SCFAs) [7]. In addition, the microbiome performs many other metabolic functions such as the synthesis of requisite vitamins, polyphenol activation, and secondary bile acid production [8,9]. Due to the presence of both beneficial and potentially harmful micro-organisms in the GIT, the immune system maintains close interactions with the microbiota and is critical in shaping the immune system of the host [10]. Further, the microbiota elicits many structural and protective functions to maintain immunity within the gut [11]. The gut microbiome and its metabolites are also capable of performing crosstalk with other organs including the brain, liver, and lungs [12].

The human microbiome undergoes many significant changes throughout our lifetime. Upon birth, robust growth in microbial species leads to initial development of the infant's microbiome, which varies based off delivery method and the use of breast milk or formula [13]. After approximately three years of age, the gut microbiome begins to stabilize and becomes fully established [14]. These stabilizations will last until adulthood with slight changes occurring due to both diurnal variations and lifestyle factors including diet, smoking and exercise habits, antibiotic use, and geographical location [15].

Defining an ideal microbiome is extremely difficult due to the amount of individual variation in taxonomic composition, however, there are certain characteristics attributed with a healthy gut microbiome such as high taxonomic diversity, microbial gene richness and stability among microbial communities [16]. Among healthy adults, the relative abundances of each phylum remain consistent, Firmicutes and Bacteroidetes being most abundant with Actinobacteria and Proteobacteria presenting at a lesser extent [17]. It is also understood that despite individual taxonomic variations, most organisms in the microbiota exhibit similar metabolic and structural functions that are either harmless or beneficial for host health and development [18]. When the microbiota deviates from these normal characteristics, it can result in dysbiosis, a condition characterized by a reduction in beneficial microbiota, increase in potentially harmful organisms and/or an overall lack of species diversity [19]. The pathological alterations that occur in the microbiome contribute to inflammaging, a low-grade form of chronic inflammation that presents itself with progressive age [20]. Due to the important role that the microbiota plays in biological functioning and inflammatory processes, a decline in functionality of the microbiome may be a strong predictor of age-related disease states. The primary aim of this review is to identify patterns of age displayed by the gut microbiome and to examine how this relates to an increased incidence of disease states among older adults.

Methods

To conduct this study, a comprehensive review of available literature was performed. This was accomplished by using electronic scientific databases including PubMed, Google Scholar, and Ovid Medline. The main search terms used were: ("gut microbiome" OR "gut microbiota" OR "bacteria flora") AND ("aging" OR "ageing" OR "old age") AND ("age-related disease" OR "disease"). Recent publications from the year 2000 onwards were included to ensure that literature was up to date. Both primary and secondary research articles were included in the search strategy. Assessment for inclusion used a "3 pass approach" to critically analyze papers for both quality and relevance [21]. The first pass consisted of reading the title, abstract, introduction and conclusion to gain an initial sense of the publication and determine whether the paper met criteria for inclusion. Next, the related work sections and reference list were analyzed to find other potential studies for inclusion and to identify key researchers and publications within the field. Finally, a third pass was employed to gain an in-depth understanding of the publication, to the extent that its contents could be mentally re-created by the researcher.

Results

Age-Related Changes in the Gut Microbiome of Older Adults

The number of different taxa and evenness of taxa within a sample, referred to as alpha diversity of the microbiome, has been shown to decrease with old age [22]. In contrast, uniqueness of microbial profiles between samples known as beta diversity, was greater in older compared to younger individuals [23]. During aging, the gut microbiome demonstrates a reduction in genes involved in SCFA production as well as an expansion of pathobionts from the family Enterobacteriaceae [24]. Bacterial genera that offer benefits to the host such as *Bifidobacterium* and *Lactobacillus* are often lower in abundance with advanced age [25]. A similar trend was observed in fibrolytic organisms from *Eubacterium* and *Faecalibacterium* genera [26]. Conflicting results regarding levels of *Bacteroides* have been reported with some studies demonstrating decreased levels [26] and others suggesting an increase with age [27]. At the phylum level, bacterial composition in older adults typically displays fewer Actinobacteria compared with younger counterparts and demonstrates elevated levels of pathogenic species classified as Proteobacteria [28]. Another age-related change is a greater proportion of *Bacteroidetes* to *Firmicutes* in the microbiota [27]. Other bacterial species such as *Akkermansia muciniphila and Ruminococcus bromii*, involved in mucin and starch degradation respectively, have been shown to decrease with

age, while the species Ruminococcus gnavus, commonly associated with dysbiosis, increases [29]. Additionally, the microbiota displays greater impairment of metabolic function in older age groups, specifically through a decrease in vitamin, nitrogenous base, and essential amino acid synthesis [20]. Age-related dysbiosis and changes in microbial composition have also been shown to increase intestinal permeability in mouse models, due to chronic activation of inflammatory pathways, resulting in a leaky gut [30, 31]. Disrupted gut barrier integrity also showed strong correlations with old age in *Drosophila* and was found to be a strong indicator of all-cause mortality [32].

Extreme Longevity, Healthy Aging and the Gut Microbiome

The gut microbiome displays a unique profile in cases of extreme longevity. Notably, the microbiota of centenarians displays many youth-associated signatures and lower levels of inflammatory bacteria [33]. A greater abundance of beneficial bacterial species from the Firmicutes and Bacteroidetes phyla was also observed in centenarians [33]. Another pattern observed in a study of the fecal microbiome of semi-supercentenarians, was a shift towards health-associated bacterial genera *Bifidobacterium*, *Akkermansia*, and *Christensenellaceae* [22]. Further, after a 1.5-year period, one study demonstrated a depletion in opportunistic bacteria from the Proteobacteria phylum in the microbiome of both healthy, young adults and long-lived individuals [33]. In contrast with older adults, those with extreme longevity display greater levels of alpha diversity with increased species evenness, which was linked to greater levels of microbial stability over time [34, 35]. Inter-individual differences become more prevalent with older age, a trend that was upheld in individuals who demonstrated signs of healthy aging, but not in those with declining health or increased mortality risk [26]. Additionally, microbial signatures in long-lived individuals demonstrate increases in functional pathways such as those involved in the production of SCFAs and cellular respiration, as well as metabolic pathways linked to the production of vitamins B2 and K2 [36, 37].

Implications of the Microbiome in Disease States

The gut microbiome also has implications in gastrointestinal diseases. Multiple studies have identified increases in opportunists including *Fusobacterium nucleatum, Bacteroides fragilis, Enterococcus faecalis*, and strains of *Escherichia coli* in individuals with colorectal cancer [37-39]. Microbial toxins produced from these bacteria become involved in signaling pathways related to cancer regulation, including cell propagation, cell growth cycle, differentiation, and apoptosis [40]. Additionally, perturbation of the physical and microbial barriers of the gastrointestinal tract, associated with buildup of bacteria from the Enterobacteriaceae family, is correlated with inflammatory bowel disease (IBD) [41]. Chronic gastrointestinal inflammation, characteristic of IBD, upregulates the process of inflammaging [42] and is recognized as a risk factor for many age-related diseases, including Parkinsons disease (PD) [43].

In instances of cardio-metabolic disease (CMD), the microbiome displays an enrichment of Enterobacteriaceae, specifically in bacterial strains *Escherichia coli, Klebsiella spp*. and *Enterobacter aerogenes* [44]. Functional pathways in the microbiome involved in the production of endotoxins and trimethylamine (TMA) have also been shown to increase in CMD [44, 45]. The production of TMA is especially relevant to CMD as it is oxidized by the liver into trimethylamine oxide (TMAO) which is recognized as a biomarker for arteriosclerosis [46, 47]. Furthermore, TMAO production derived from microbiota has been hypothesized to exacerbate ischemic heart disease or stroke risk [48]. Additionally, patients with hypertension tend show a reduction in species richness and evenness [49]. The results of one study demonstrated that the blood pressure of normotensive mice was elevated upon fecal microbiota transplant from the stool of mice with hypertension [50]. Furthermore, gut microbiota may enable hypertension and vascular dysfunction as shown by a reduction in blood pressure increase and cardiac inflammation in germ-free mice [51]. In non-alcoholic fatty liver disease (NAFLD) the gut microbiome demonstrates a greater abundance of species from *Prevotella*, *Streptococcus*, *Escherichia,* and *Lactobacillus*, compared with healthy controls, whereas *Coprococcus, Faecalibacterium and Ruminococcus* were less abundant [52]. One study also identified higher levels of pro-inflammatory cytokines, as well as mucosal barrier disruption among NAFLD patients [53]. Another source reported increased levels of pro-inflammatory bacterial strains belonging to *Proteobacteria* and *Enterobacteriaceae* in individuals with NAFLD [54]. Moreover, the microbiota of NAFLD patients has been shown to produce elevated levels of 2-butanone and 4-methyl-2-pentanone, which can induce liver toxicity [55]. Increased prevalence of alcohol-producing bacterial strains such as *Klebsiella pneumoniae* are attributed with NAFLD while expansion of *Escherichia spp.* may contribute to portal endotoxemia through the activation of nuclear factor-κB signaling pathways [56, 57].

In relation to diabetes, disruption of microbial diversity in the intestine has also been shown to impair blood glucose homeostasis [58]. This is supported by findings indicating that individuals in the pre-diabetic state were shown to have dysbiotic signatures, including a reduction in overall diversity and a decrease in butyrate-producing bacteria from the Bifidobacterium genera [59]. The gut profile of individuals with type two diabetes was found to be associated with increased pathogenic bacteria including *Escherichia coli*, *Fusobacterium* as well as the *Clostridium*, genus which has been shown to be negatively correlated with fasting glucose and glycosylated hemoglobin [60]. The functional profile of the microbiome in diabetes reflects an increase in sugar and branched chain amino acid transport,

a subsequent decrease in vitamin production and disruption of gut barrier integrity [61, 62].

The microbiome is also implicated in neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Particularly, individuals with PD display enrichment of mucin-degrading genera *Akkermansia*, *Lactobacillus*, and *Bifidobacterium* [63]. PD is also linked to depletion of important SCFA producers such as the *Lachnospiraceae* family as well as the *Faecalibacterium* and *Protevotella* genus, which possess anti-inflammatory effects by increasing activity of regulatory T cells [63-65]. Additionally, levels of α-synuclein, a protein found in neurotoxic Lewy bodies which accumulate in the PD brain, were lower in germ free mice compared to regular mice within an α-synuclein-overexpressing (ASO) model of PD [66, 67]. Notably, specific pathogen free (SPF) mice who had undergone a fecal transplant from PD patients displayed an over-expression of α-synuclein, which was not observed in SPF mice with transplants from healthy patients [67]. *Escherichia coli* has also been linked to α-synuclein formation in the gut through the production of an amyloid protein, curli [68]. An increase in intestinal α-synuclein aggregation was also correlated with greater intestinal permeability [69], as the persistence of pro-inflammatory cytokines has been shown to induce oxidative stress to neurons [70]. SCFAs are postulated to possess neuroprotective effects through improved modulation of neuroinflammation, mitochondrial function or increased activity of antioxidative enzymes [71-73], reinforced by a reduction in SCFAs observed in fecal samples of PD patients [74, 75].

Microbiota composition is also related to AD onset. With regards to specific alterations in the gut microbiome, *Proteobacteria*, *Bifidobacterium* and *Phascolarcto-bacterium* were more abundant in AD, whereas *Firmicutes*, *Clostridiaceae*, *Lachnospiraceae* and *Rikenellaceae* were less abundant in AD when compared with healthy controls [76]. Functional alterations in the gut microbiome of AD mice also show higher levels of amino acids phenylalanine and isoleucine in feces and in the circulation, which promotes helper T-cell proliferation and differentiation, that correlates to microglia-predominated neuroinflammation [77]. Interestingly, individuals in the preliminary stages of disease progression have a lowered microbial diversity in the gut and similar signs of dysbiosis to counterparts with later-stage AD [78]. One study demonstrated that mouse models of AD brought up in germ-free conditions had a reduced accumulation of β-amyloid protein as well as Iba-1-positive microglia, leading to an overall reduction in neuroinflammation [79]. Another experiment involving fecal transplants from healthy mice into an AD mouse model showed reduced formation of β-amyloid protein plaques, neurofibrillary tangles, glial reactivity, and cognitive impairment [80]. This study also identified that the intestinal epithelial barrier was compromised within the AD mouse model.

Discussion

There are many similarities in the bacterial flora in aging and age-related disease states that are reflective of dysbiosis and predispose individuals to a pro-inflammatory state. One such example includes a reduction in commensals that assist with maintaining the chemical barrier of the intestine and mitigating the expansion of pathobionts like *Enterobacteriaceae* and *Clostridium spp*. [81, 82]. An elevation of pathobionts such as those belonging to Proteobacteria, a phylum associated with dysbiosis [83], is also observed in disease states and aging [28]. Another signature in both aging and many diseases is disruption of intestinal barrier integrity, which permits the unregulated passage of bacterially produced endotoxins and metabolites into the bloodstream [84]. Lipopolysaccharides (LPS) are endotoxins released by bacterial strains from *Enterobacteriaceae*, a family associated with old age, NAFLD and CMD [24, 44, 54] as well as PD [68]. LPS production elevates secretion of local inflammatory cytokines, inducing a heightened immune response [85]. A leaky gut has been attributed to a reduction in anti-inflammatory metabolites such as SCFAs [86] which help to maintain intestinal barrier function, promote epithelial cellular proliferation, and serve as a primary energy source for colonocytes [87].

The gut microbiome is largely connected to other organ systems which are in turn affected by alterations in composition and intestinal permeability. For example, the intestine is responsible for delivering over 70% of blood to the liver, which can expose it to the harmful metabolites or toxins that enter the circulation due to a leaky gut [88]. Besides the liver, another important interaction is the gut-brain axis, the two-way connection between central and enteric nervous systems (ENS) [89, 90]. This connection has implications for neurological disease, as the results demonstrate that inflammation induced by gut bacterial species promotes neurodegeneration in both AD and PD [69, 70, 77, 79]. The ENS also has functional connections with other organs and tissues of the body such as the heart, muscle, pancreas, and bone that are influenced by microbiota activity [91]. Thus, disruption of microbial communities in the gut can negatively affect these pathways and induce pathology throughout the body via inflammaging [92].

These findings also highlight the unique gut profile of long-lived individuals, which offers important insights into successful aging as these individuals have been able to mitigate disease states and reduce pro-inflammatory status over time [22]. This implies that 'youthful' or beneficial microbial signatures displayed in later stages of life may not only be a key indicator of longevity but a pathway to preserving health as well [33].

A decline in functional and compositional richness with old age may be rationalized by factors such as a reduction in diet quality and residential status, with adults in long-term care displaying lower microbial diversity compared to community-dwelling adults [93]. Moreover, increased antibiotic use is common among the elderly which can cause disturbances in the microbial environment, resulting in a reduction in taxonomic richness, diversity, and evenness [94]. Other significant factors that lead to a decline in microbial stability include increased sedentary behaviour and decreased intestinal function and motility [95, 96].

Conclusions

Despite clear links between age-related disease and microbiome composition, it remains unclear whether the age-related changes in the microbiome are reflective of or caused by aging. There are many factors that contribute to disease states with ties to the microbiome such as gut-barrier integrity, interactions with other organ systems or microbial compositional alterations, rendering it more difficult to determine a causal relationship with age-associated changes. Although this study has focused on the negative implications of the microbiome in aging and disease, these findings outline the potential of improving microbial composition in the gut to prolong the health span of older individuals. This may be accomplished through interventions such as fecal microbiota transplant and supplementation of probiotics, prebiotics, or a combination of the two [25]. Future studies are encouraged to investigate the validity of these therapies in delaying some of the pathophysiological consequences of aging.

List of Abbreviations Used

AD: Alzheimer's disease
ASO: alpha-synuclein-overexpressing
CMD: cardio-metabolic disease
ENS: enteric nervous system
GIT: gastrointestinal tract
IBD: inflammatory bowel disease
LPS: lipopolysaccharide
NAFLD: non-alcoholic fatty liver disease
PD: Parkinson's disease
SCFA: short chain fatty acids
SPF: specific pathogen free
TMA: trimethylamine
TMAO: trimethylamine oxide

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

No ethical approval or participant consent was required for this study as this review was conducted solely from pre-existing literature.

Authors' Contributions

ALK: made contributions to the design, collected, and analysed data from pre-existing literature, drafted the manuscript and gave final approval of the version to be published.

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