Acta Scientific Microbiology (ISSN: 2581-3226)

Volume 1 Issue 8 August 2018

Review Article

The Oral Microbiome in the Context of Aging and Cognitive Impairment

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Received: June 18, 2018; **Published:** July 03, 2018

Abstract

With the increase in life expectancy, the elderly population is growing rapidly. This represents a challenge for health institutions as health problems increase with age. Among these, cognitive impairment represents a consistently dramatic and increasingly common issue. The initial stages of the cognitive disorder are characterized only by behavioral changes. As the disease progresses the patient becomes less and less able to take care of himself, requiring extensive assistance. Within the oral cavity more than 700 microbial species live. As we age oral microbiome is believed to increase and undergo changes due to both extrinsic and intrinsic factors. Shifts in the oral microbiota contribute to the development of diseases and infections not only in the mouth, but also in other sites of the body, such as the brain. What happens in the oral cavity, both in periodontal and hard tissues, is strongly linked to whole body health, including brain functioning. In this review we focus on the relationship between aging oral microbiome and cognitive decline, in relation to Alzheimer's disease.

Keywords: Mild Cognitive Impairment; Alzheimer's Disease; Microbiome; Periodontal Disease; Immunology; Inflammaging; Immunosenescence

In the human body there are several bacterial communities that grow and live in various niches such as on the surface of the skin, the gastro-intestinal and urogenital tracts and the oral cavity.

These communities of bacteria constitute the human microbiome.

The word microbiome was coined to denote the relationship between bacteria and the host. There are different types of relationships, such as commensalism, mutualism and pathogenic. The role of the human microbiome in human biology is very important because it influences many physiological functions such as human development, nutrition, immunity and physiology. It represents approximately 1 - 3% of body mass and bacteria load is believed to increase with age.

Oral microbiome is the whole microbial community that lives in the oral cavity. Micro-organisms find several habitats to colonize such as gingival sulcus, attached gingiva, teeth, tongue, cheek, lip, soft and hard palate. With more than 700 species of bacteria, oral microbiota is composed by two major types of bacteria: Gram-negative and Gram-positive micro-organisms.

The aging process and the cognitive decline

The latest data from the World Health Organization (WHO) showed that in 2010, roughly 524 million people were aged 65 or older accounting almost 8% of the world's population. This is a meaningful large population of older individuals, which is expected to triplicate by 2050, reaching 1.5 billion people. This widespread increase in lifespan doesn't come without challenges, in fact there's a wide range of health problems that begin or worsen as we age. Most of them are chronic conditions, such as neurodegeneration and mental disorders, which are typically seen more frequently in older individuals.

The aging process is characterized by a low-grade systemic inflammatory status, even in the absence of signs of infections. This phenomenon is called Inflammaging and increases morbidity and mortality in the elderly and may interfere with the local microbial population of naturally infected sites of the human body, such as the oral cavity and the intestine. Besides, immune senescence, which indicates the wane of the immune system brought on by the natural advancing age, can contribute to increasing susceptibility

to bacterial infections in older people, further worsening the effects of inflammation.

Cognitive impairment in elderly people is a common condition, and 14% of subjects aged over 70 years of age has sufficient cognitive impairment to justify a diagnosis of dementia.

Dementia is a multi-etiologic brain disorder characterized by cognitive deficits. It mostly affects the elders, but neurodegenerative changes may begin at any age. Dementia could have many origins, among which the main cause is Alzheimer's disease (AD). A certain degree of cognitive slowing is typical with advancing age. The earliest manifestation of pathological cognitive impairment most seen in old people is the decline of memory efficiency, often manifested by re-asking of questions. The diagnosis of dementia is confirmed when cognitive impairment gets worse and compromises occupational and social aspects. Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, with conserved functional capabilities. Prevalence of dementia increases rapidly with increasing age, while prevalence of MCI is difficult to determine because it depends on the subtypes and definitions being studied.

Alzheimer's disease is a chronic neurodegenerative disorder that usually starts slowly and worsens over time. Difficulty in remembering recent events is the most common early symptom. As the disease advances, symptoms can include problems with language, disorientation, problem solving ability, loss of motivation, mood swings and behavioral abnormalities. Gradually, bodily functions are lost, ultimately leading to death. The cause of AD is poorly understood. Approximately 70% of the risk is believed to be genetic with many genes usually involved. AD is the most common form of dementia representing 60% - 80% of all cases.

The disorder usually occurs after 60 years of age, the so-called "late-onset". AD people express a decline in their ability to perform routine tasks, stay oriented in time and space and learn new information. With the progression of the disease patients lose their ability to care for themselves and eventually they lose motor function, leading to immobility and then to death.

The prevalence of AD increases quickly with age. For people aged 65 to 74 years it's 3%, 19% for those aged 75 to 84 years and 47% for those aged 85 years and older. Studies show that women are more at risk of developing the disorder than men. Life expectancy is approximately 10 years after the onset of dementia but varies depending on the degree of severity of cognitive impairment, the presence of other diseases, the age of onset and other factors.

The most used scale to define the degree of severity of the disorder is the Global Deterioration Scale (GDS), which consists of 7 stages that measure its progression. Loss of episodic memory is the main symptom of AD, but the disease is also characterized by other types of cognitive impairment such as movement and speech language and disorders referred to as the triad aphasia- apraxia-agnosia.

AD affects many areas in the brain including the frontal and temporal cortices, the hippocampus and the cholinergic basal forebrain. The two diagnostic neuropathological features are numerous neurofibrillary tangles (NFTs) which are intracellular fibrillar deposits of hyperphosphorylated tau proteins and extracellular deposits of fibrillar amyloid-beta peptides (Aβ-plaques). These deposits break up synaptic function, then leading to neuronal death.

Within the brain of AD people an inflammatory response is believed to be present. To the sites of inflammation astrocytes (a sub-type of microglia) are recruited and once activated, become hypertrophic contributing to the inflammatory processes through the release of proinflammatory cytokines such as interleukin-1β(IL1β) and tumor necrosis factor α (TNFα). Moreover, activated astrocytes produce apolipoprotein E (Apo E) which could be involved in Aβ fibrillization. For a period of months or years, the continuous release of pro-inflammatory cytokines and amyloidosis aggravates neuronal damage.

Effects of age on the oral microbiome

Various studies have shown changes in the oral cavity happening with age. These changes may be expressions of physiological aging or the result of pathological processes or the consequence of medical treatments to cure the disease. Therefore, it's extremely difficult to validate the effects of specific factors on variations in the microbiota composition.

Although some authors agree in stating that the dominant species that constitute the adult microbiota do not alter in elders, a study by Garcia-Pena in 2017 [1] reported that with age there are important alterations in the composition and proportion of microbial communities, leading to a reduction in the diversity of microbiota, as well as an increase of pathogens that could bring to chronic inflammation. Bacterial changes have been demonstrated in many geriatric diseases, like Alzheimer's and Parkinson's.

The oral microbiota is very complex in organization, has a huge diversity and ability to change rapidly in response to a wide range of environmental stimuli. It's a dynamic structure, as it must constantly adapt to an evolving environment, from birth to oldness.

Factors such as geographic location, oral hygiene and smoking are examples of environmental and local stresses that may modulate shifts in the oral microbiota, which could also exasperate host inflammatory response.

Environmental conditions changing with advancing age in the oral ecosystem might influence the growth, metabolism and attachment of micro-organisms. In the first half of life the variety of surfaces available for microbial adhesion increases. Initially dental enamel offers the only surface for bacterial colonization. Then with age, exposure of dentine extends the non-shedding area and the damage of oral hard tissue accumulates and is essentially irreversible. Many studies have reported differences in plaque development on rough and smooth surfaces, then confirming the influence of features that facilitate plaque retention, such as incongruous margins of fillings or fixed restorations, on subgingival microbiota composition.

Some authors investigated the effects of dental-wearing and age on the prevalence of specific micro-organisms, in fact they reported that proportions and count of lactobacilli and yeasts in saliva increased with age and were higher in partial-denture wearers.

In elderly patients, Feres., *et al.* [2] recorded higher Plaque Index (PI) scores and the development of gingivitis was more severe and more rapid than in younger subjects. Nevertheless, no difference in counts of various microbial morphotypes has been observed. The authors stated that gingival recession was seen more frequently in the older individuals. Hence, the increased tendency to inflammation was probably due to the alteration of hard tissue morphology, which provides a large dentine surface for plaque growth.

Numerous studies analyzed the prevalence of some selected bacteria and noted that the prevalence of A*ggregatibacter actinomycetemcomitans* appeared to be age related and decreased with age. On the contrary, the prevalence of *Porphyromonas gingivalis* increased with age. Apparently, the role of *Prevotella* intermedia didn't show changes with increasing age.

Feres., *et al.* [2] investigated the effects of the aging process on the composition of the oral microbiota in a group of 79 subjects divided into four groups according to age: 20-39, 40-59, 60-79 and more than 79 years. The authors reported no difference among age groups for the prevalence of Spirochetes species and Streptococcus mutans, instead statistically significantly higher proportions have been detected for Actinomyces species in the supragingival biofilm of individuals over 60 years of age.

Some authors suggested that older individuals reveal higher prevalence of *Pseudomonas* species and enteric rods than younger subjects.

Although several studies demonstrated that the oral microbiome has a long-term stability, some authors reported that certain host actions and health changes may lead to broad disturbance on the bacterial community. These variations in the microbiome may derive from extrinsic factors, such as exposure to different types of food, medications and physical environments or from intrinsic factors, including the immune system.

Some studies reported that older individuals responded more strongly and earlier to microbial accumulation than younger subjects, developing more severe gingivitis and appeared to have higher volume of GCF, more severe inflammatory infiltrate and higher GCF levels of IgG3.

The aging oral microbiome and its relationship to cognitive impairment and Alzheimer's disease

The progressive aging process is accompanied by numerous health problems, including the cognitive impairment and many neurodegenerative disorders like Alzheimer's disease.

The role of pro-inflammatory conditions in the pathogenesis of dementia and cognitive decline is of increasing interest. Elevated levels of inflammatory markers like interleukin-6 have been linked to cognitive decline and cognitive impairment, and cytokines have been linked to dementia.

Recent studies have reported a possible association between decline in cognitive function and oral health conditions.

Authors found that loss of periodontal attachment, tooth loss and gingival bleeding were associated with worse cognitive function, with a strong association between worse psychomotor speed and attention and gingival bleeding together with loss of periodontal attachment.

After age increases, bacterial load is believed to grow as our humoral and cell-mediated immune system decreases in favor of the less efficient innate immunity. There is increasing evidence that the microbiome composition, the distribution and density of micro-organisms may influence quality of life of elderly people. Gradually, as the innate immune system predominates over time, some specific bacteria may proliferate and trigger more harmful reactions. In a context of an increased bacterial load it's important to preserve the integrity of the blood-brain-barrier (BBB). The

BBB is a semipermeable membrane barrier that separates the circulating blood from the brain and extracellular fluid in the central nervous system (CNS).

It plays an important role in protecting the brain from circulating pathogens and may become leaky in selected neurological and systemic diseases, such as liver failure. The blood-brain-barrier becomes more permeable during inflammation, allowing phagocytes to move across it. Weakening of the BBB could serve to raise the tendency of bacteria or endotoxins to have access to the brain, start neuropathology and modify brain function.

It's worth noting that the oral dysbiotic biofilm may contribute to the beginning of pathologies and imbalances not only locally but also at systemic level in areas far from the mouth.

A recent study by Shoemark., *et al.* in [3] demonstrated the high presence of spirochetes, such as Treponema, in the brain of Alzheimer's individuals with a density 7 times greater and higher variety compared to cognitively normal subjects.

The link between increased tumor necrosis factor-alpha (TNFα) and AD is firmly established, in fact, research has shown that AD individuals presented augmented serum antibodies to *Tannerella forsythia*, *P. gingivalis* and *A. actinomycetemcomitans* and elevated serum TNFα.

If oral bacteria themselves or endotoxins released by them get access to the brain, the result will probably be microglial activation, a well-known marker of AD, which results in raised production of proinflammatory cytokines such as IL1β and TNFα. Studies reported that cytokines and leukocytes, oxidative stress and blood vessel damage may be capable to induce neurodegeneration, brain injury and neuronal loss.

Elevated concentrations of TNFα for a prolonged period weakens the BBB making it more permeable to the entrance of endotoxins or bacteria. These mechanisms would be exacerbated by the immune senescence that comes with age, probably leading to a raise in levels of specific bacteria of the oral microbiota and their systemic diffusion.

Many reports indicate high levels of pro-inflammatory cytokines such as TNF-α, IL-6 or IL-8, IL- 1α/β, in the blood, brains and cerebrospinal fluid of AD individuals.

It has been proven that neuronal cells exposed to spirochetes produce Aβ and that neuronal cells challenged with LPS from bacteria produce hyperphosphorylated tau proteins.

LPS from *P. gingivalis* has proteolytic enzymes like gingipains which can lead to the degradation of endothelial cell tight junction proteins, provoking the loss of the protective BBB.

A study compared the levels of *P. gingivalis* IgG among cognitive impaired subjects and normal ones. The levels were higher in those patients with impaired performance, presenting poor delayed verbal memory and calculation in relation to the microbial amount.

Several studies have researched the relationship between periodontal disease and cognitive impairment and especially AD. Periodontal disease is very common in elders and might become more common in AD because of a diminished ability to carry out daily hygiene as the disorder progresses. The authors assume that the elevated systemic pro-inflammatory state associated with periodontal bacteria may be related to an increase of cognitive decline. Other authors stated that the presence of a source of pro-inflammatory mediators, as periodontal disease, may not start AD but exasperate the systemic inflammation and make the neurodegenerative lesions worse. Some authors reported that levels of pro-inflammatory cytokines TNF-α, IL-1, IL-6 and anti-inflammatory mediators like IL-10, raise with a worse periodontal condition and cognitive decline.

A study focused on the association between serum IgG antibodies levels to periodontal bacteria and incident AD. Elevated serum of *Actinomyces naeslundii* IgG antibody has been related to an increased risk of incident AD. *A. naeslundii* is associated with early dental plaque accumulation, dental caries and gingivitis and has a pathogenic role in osteoclasts activation.

Many authors have stated that *Fusobacterium species* were among the most commonly identified bacteria in elderly subjects. These micro-organisms may provide some degree of protection against dementia by occupying the subgingival environment, warding off the accumulation of microbial species that cause more inflammation.

As we get older the production of saliva progressively decreases and this is subsequently reduced by inactivity. Adequate hydration is requested for appropriate saliva production and in many old people there's a notable decrease in hydration for many reasons. Saliva is essential in maintaining oral health. It can influence the oral biofilm configuration, through the action of various antimicrobial agents such as histatins, lactoferrin, immunoglobulins, lysozyme and peroxidases. Thus, the combined effects of poor hydration, aging, inactivity and any treatment that determine oral dryness, can affect the oral flora and promote microbial over-

growth in the oral cavity. Pathogens than may escape into blood circulation and affect host cell behavior.

A study by Aragon., *et al.* in [4] evaluated the saliva of AD patients in comparison to healthy subjects. It was found that AD patients secrete a significantly lower quantity of saliva per minute; then their saliva present lower buffering capacity and is more acidic. AD individuals than presented higher levels of *Lactobacillus* species and *Streptococcus mutans.*

Furthermore, Carro., *et al.* [5] investigated the role of lactoffer in as a potential biomarker in saliva for the early diagnosis of mild cognitive impairment and AD. Lactoferrin is one of the major antibacterial peptides in saliva and plays a key defensive role by provoking a large spectrum of antimicrobial effects against fungi, bacteria, viruses and yeasts, thanks to its ability to reduce biofilm development, microbial growth, reactive oxygen formation, iron overload, and controlling the inflammatory response. Authors studied the levels of lactoferrin in the saliva of healthy subjects comparing them with those of MCI and AD patients. They reported that salivary lactoferrin levels were significantly lower in the disease group, but a negative association was found between stages of cognitive impairment and the lactoferrin levels. Moreover, it seems that the decline of salivary lactoferrin occurs in a later stage of the preclinical AD process, especially when slight cognitive deficit begins to occur. Thus, there's evidence that salivary lactoferrin can be useful to detect apparently healthy individuals suffering from advanced stage preclinical MCI and AD, a large number of which is underdiagnosed.

Low salivary flow combined with an acid pH increase the risk of developing caries and diminish remineralization capacity. Increased hyposalivation can promote the development of oral lesions such as chelilitis and ulcers. Aragon., *et al.* [4] assessed the oral health status of subjects with AD, noting that patients with cognitive impairment had a worse periodontal and dental health. This is also confirmed by another research in which a poor dental status had been related to cognitive impairment and increased incident of dementia. The DMFT values were significantly higher than healthy patients. AD individuals presented a higher incidence of cheilitis and candidiasis. These results may be due to decreased salivary flow or to improper oral hygiene. According to authors, brushing efficacy could be another factor for dental problems, in fact it is related to the progression of the disease. Even in the first stages of AD depression and apathy lead to lack of interest to carry out adequate oral hygiene methods and at moderate stages the cognitive decline generates difficulty or inability to perform proper daily hygiene.

Studies by Feres., *et al*. [2] and Shoemark., *et al*. [3] found that diet could affect oral microbiome and have results also on the CNS, in effect, being rich in phospholipids, vitamins and other micronutrients it is crucial for forming new synapses. It's well established that vitamins deficits have important results on both cognitive performance and periodontal tissues.

Studies demonstrate that low serum levels of 25-hydroxyvitamin D could increase the risk of dental caries and periodontal disease, which, in turn, are risk factors for cognitive impairment.

Another important vitamin which is crucial to create a protection against the onset and progression of AD is vitamin B. Foods like eggs, fish and meat provide proper amounts of vitamin B12 to the body. Insufficient levels of vitamins of group B like folate, B12 and B6 relate to cognitive impairment and incidence of dementia in the elderly, probably because lower levels of these micronutrients elevate plasma homocysteine (HCys). The latter is a vasotoxic and neuro metabolite that might lead to depressed S-adenosylmethionine-dependent methylation reactions, which is essential for CNS working. Even in the absence of a vitamin B12 deficiency at a clinical level, if its levels are below a certain range considered normal there is evidence of poor mnemonic performance and a decreased microstructural integrity of the hippocampus, which is the brain area first affected by the cognitive disorder.

Therefore, many elements included in the diet are antibacterial and they are believed to reduce the risk of developing AD. Taken regularly these dietary components are likely to settle on the oral mucosa, being able to influence the composition of the oral microbiome. The Mediterranean diet has long been considered as an aid to avoid AD being rich in foods with proven antibacterial activity such as olive oil, garlic, curcumin, cinnamon and honey. Furthermore, resveratrol, which is a polyphenol present in red wine, has been found to reduce Aβ-induced toxicity by activating specific proteins involved in proteostasis and thus reducing the amount of aggregated Aβ[6-20].

Conclusion

In conclusion, elderly population worldwide is quickly increasing thanks to an increase of life expectancy. With advancing age many health problems can begin, or some diseases may get worse. In this review we've seen how aging could influence the oral microbiome. With age it seems that bacterial load gradually grows and undergoes variations in its composition. Oral bacteria and their products could reach circulation and trigger inflammation in other organs, like the brain. In older people cognitive impairment

is very common. It includes both mild forms such as MCI and more severe forms like Alzheimer's disease. Researchers found that oral micro-organisms are able to get access to the brain and may be implicated in the cognitive disorder onset or more likely in progression of the disease. With these assumptions, it seems important to be able to control oral bacteria both in their quantity and composition. It's necessary to follow old people as much as possible in their oral hygiene techniques, in order to rebalance the oral ecosystem, disfavouring and reducing the growth of gram-negative micro-organisms.

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