ABSTRACT

Alzheimer’s disease (AD) is a neurodegenerative disease that affects elder people. As the age increases, the prevalence of Alzheimer’s disease also raises. As AD, periodontitis is seen more often in elder people. Periodontal disease has been associated with some systemical diseases such as cardiovascular disease (CVS), diabetes mellitus, rheumatoid arthritis and preterm birth. Latterly, it has been investigated if there is a connection between Alzheimer’s disease. This review’s aim is, inspecting if the periodontal disease contributes to Alzheimer’s disease at literacy.

Keywords: Alzheimer’s disease, inflammation, periodontal disease, periodontitis

INTRODUCTION

Periodontal infections consist of due to the interaction between microbial film and host defenses. Gram negative anaerobes in mature biofilm stimulates host responses. Host response recruits neutrophils, other cells and their products of inflammatory mediators which are cytokines and prostaglandins. Recent studies show that host inflammatory response can be more crucial than bacterial biofilm formation than originally thought. Continued production of inflammatory mediators and the interactions at host response, results in the eradication of alveolar bone and connective tissue. Endotoxins, which are a lipopolysaccharide at cell wall of Gram negative bacteria start the inflammatory events of periodontal disease. Endotoxins stimulate some inflammatory cells like monocytes, macrophages, fibroblasts and T cells. By this way, cytokines and prostaglandins are secreted. The most crucial cytokines that are associated with periodontal disease are interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrotizing factor-alpha (TNF-α). IL-1 and TNF-α induce cells to produce CRP. In a number of studies, proinflammatory cytokines in gingival crevicular fluid and in inflamed gingival tissues were reported in a high amount at patients with active periodontal disease to the healthy group. In another research, acute phase proteins, including CRP, has been found at increased levels in gingival crevicular fluid. It is thought that the inflammatory mediators which are produced locally may get into the systemic circulation and leads to increased serum levels of cytokines and...
Acute phase reactants\(^9\). Moreover, daily bacteremias can occur by even after toothbrushing, flossing and after dental procedures\(^{10,11}\). It is suspected that patients with periodontal disease may experience transient bacteremia multiple times per day\(^{10,11,12}\).

The systemic inflammation that is induced by periodontitis has also been suggested as a riskfactor for some other diseases such as stroke\(^{13}\), cardiovascular disease\(^8\), diabetes complications\(^{14}\) and preterm birth\(^{15}\). Genco et al\(^9\) found that oral bacteria including \(P\).\(\text{gingivalis}\) and \(S\).\(\text{sanguis}\) has a direct effect on induction of platelet activation and aggregation that can lead to atheroma formation and thrombosis. Genco and colleagues\(^9\) also demonstrated that having heart attack increases with the severity of periodontitis.

Investigations about the correlation of diabetes and preterm birth with periodontal disease has also been reported. Offenbacher and colleagues\(^6\) found that mothers who have severe periodontal disease had 7.5 fold increase in the risk of having preterm, low birth weight baby. Moreover, it has reported people with poorly controlled diabetes improved metabolic control after periodontal therapy\(^7\). In addition, there are some studies about the linkage of periodontitis to rheumatoid arthritis. Rosenstein et al\(^8\) hypothesize that patients with severe periodontal disease display autoimmune responses like production of rheumatoid factor. Given the evidence for the relationship between periodontal disease and other systemic diseases, it is reasonable to suggest treatment of periodontitis does not only solve the intraoral problems, but also helps to maintain the systemic health of people.

The Characteristics of Alzheimer’s Disease and its Relationship between Periodontitis

Alzheimer’s disease which was first described by Alois Alzheimer in 1907\(^9\) is the main cause of dementia in elderly people. Other types of dementias are vascular dementia, dementia associated with Lewy bodies, frontotemporal dementia, Creutzfeld-Jakob disease and Parkinson’s disease. Between the age of 65 to 74 years, the prevalence is nearly 3%. However, this ratio increases by age and gets 19% between 75 and 84 years and 47% at older than 85 years\(^{20}\). AD is diagnosed more often in women, about two-thirds of AD cases\(^{21}\). 8-10 years after the first identifiable symptoms, the clinical course of AD can be seen but it can also be as long as 20 years\(^{22}\). Alzheimer’s disease can be diagnosed with Mini Mental State Examination\(^{23}\) and Clinical Dementia Rating Scale\(^{24,25}\).

The characteristics of this neurodegenerative disease are extracellular \(β\)-amyloid peptide which also often referred to as neuritic plaques or senile plaques, hyperphosphorylated tau protein(neurofibrillary tangles) and neuronal or synaptic loss\(^{26,27}\). The neuronal dysfunction affects cholinergic synaptic transmission that enhances attention and learning processes\(^{20}\). AD is severe when it progresses and contributes to impairment of cognitive skills\(^{27}\). As it becomes severe, memory loss, gradual disorientation in time and space, language problems, inability to learn new things and difficulties when performing daily activities occur\(^{27}\). In severe phase of AD, cognitive abilities are almost impaired, therefore complete loss of recent and remote memory happens\(^{22}\). AD patients have difficulties in motor skills, so they are at great risk for developing medical complications and stomatological disorders when they perform oral and personal care. For this reason, people with severe AD need caregivers\(^{28}\).

AD has multifactorial etiology like family history, apolipoprotein E, advanced age, low educational level, cardiovascular disease, head trauma, Down’s syndrome and female gender\(^{26}\). However, the greatest risk factor accounts for older age and family history of disease. Neuropathological cascade of this disease is still unknown. Latterly, the major cause of AD is considered as involvement of oxidative stress in which free radical levels excel antioxidant defenses\(^{29,30}\). Aging and accumulation of amyloid-\(β\) proteins occur due to the progressive oxidative modification of proteins\(^{31-33}\). It is hypothesized that AD is triggered by the formation of A\(β\) plaques\(^{34}\). Amyloid peptides activate microglial cells\(^{35,36}\) which are distributed throughout the grey and white matter of nervous system. Microglial cells are specialized immune cells, related to macrophages and they can attack and phagocyte when activated. Activated microglial cells secrete upregulated inflammatory mediators, migrate to inflammatory site and exhibit scavenger responses to abnormal protein accumulations and damaged tissue. This process can be seen abundantly in pathologically vulnerable regions of AD brain.

After the treatment of patients who have AD, they improve cognitive and functional performance\(^{28}\).
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...decrease behavioral disturbances, stabilize mood, delay loss of daily living activities and improve the life quality. In older people, life quality and general health is enhanced by maintaining natural teeth and having well-fitted prosthesis. Thinking of AD patients who have decreased cognitive and motor abilities, it is very difficult to enhance the adequate biofilm control and oral hygiene. Subject with AD can forget to remove their prosthesis which can leads to accumulation of food debris and dental biofilm on their own teeth. At this point, important duty comes to caregivers. However, most of caregivers are not educated about maintaining the oral hygiene. So, they should be informed about it. In a study, the comparison between healty and AD group, the number of natural teeth, number of decayed, missing and filled teeth (DMTF), oral health index (OHI), removable prosthesis conditions, oral pathologies and General Oral Health Assessment Index (GOHAI) were investigated. GOHAI values found similar in both groups. Subjects with AD had higher age, DMTF, OHI, number of pathologies. Patients with AD should be recalled frequently for preventing the progression of periodontal disease.

The increased inflammatory mediators at periodontitis like interleukin-1β (IL-1β), interleukin-6 (IL-6) and Tumor Necrotizing Factor-α (TNF-α) participate at molecular pathways that leads to neurodegeneration. It is demonstrated that one of the periodontal pathogens, Treponema species (including Treponema denticola) has been present at higher frequency in the brain of AD patients compared to healthy subjects. Stein et al. reported that antibody levels of F. nucleatum and P. intermedia were significantly increased at patients with AD compared to control group. In another research, it is reported that high levels of serum TNF-α had fourfold increase in cognitive decline when compared to control group. Noble et al. found that patients who have high levels of serum antibodies to periodontal bacteria have lower scored on delayed word recall and calculation tasks. Bretz et al. investigated the IL-6 serum level at periodontal disease patients. The results were significantly higher than the control group. This result is very prerequisite because IL-6 is associated with local production of amyloid proteins.

The number of pathogenic bacteria that reaches the systemic circulation is low at people with good oral hygiene. On the other hand, people with periodontal disease, this ratio increases twofold to tenfold. In a study, it has been reported that %55 of patients with severe periodontal diseases have positive cultures of oral bacteria in arterial blood.

At the end of 19th century, it was suggested that brain infections and abscesses were resulted from oral bacteria’s lodgement at weak points in brain. In fact, there are some researches about the relationship between brain infections and oral bacteria specifically linked to periodontal pathogens. It has been demonstrated that Actinobacillus actinomycetemcomitans is associated with coagulative necrosis of cortical cells and white matter.

Recent researches have shown brain receptors are specific for gram-negative bacteria, which are the main flora of periodontal disease. Latterly, gram-negative bacteria have been connected to Alzheimer’s etiology, especially late-onset sporadic AD. In another study, 17 of 19 post mortem Alzheimer’s brains were affected by gram-negative Chlamydia pneumonia, while control groups were not affected. Another post mortem research has reported that 14 of 16 Alzheimer’s brains contain oral Treponema, but only 4 of 18 control brains include them. Those studies show that, pathogenic oral bacteria reach bloodstream and after reaching brain, they start or progress existing lesions.

Summarizing all of those researches, it is reasonable to suggest neuropathological changes can occur due to the continued exposure of inflammatory mediators that are caused by periodontal pathogens.

**CONCLUSION**

There are several studies about the relationship of Alzheimer’s disease and periodontal disease recently. The etiology of AD is still not known but the most important risk factor is the inflammation at brain. Periodontal disease is also investigated if it is one of the reasons of inflammation at brain by its antienflammatory cytokines. This review’s aim is to inform the connection between AD and periodontal disease with the studies at literacy.
REFERENCES


