Relationship between Periodontal Disease and Alzheimer - A Review

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Abstract

Background and aim: Alzheimer is a cognitive disorder which has irreversible conditions and causes difficulties in judgement and decision. The main mechanism of the disease would be through the inflammation in the brain which probably has a complex interaction with the environment, cardiology and genetics. The present information reinforces the idea that the periodontal pathogens are the potential factors for the inflammation of neurons and the occurrence of Alzheimer. Periodontitis is a common source of chronic systemic infection and junctional epithelium and periodontal pockets disease can be a conduit entry for bacteria into the bloodstream. Periodontopathic bacteria and systemic inflammation caused by them act as a bridge between these diseases and Alzheimer.

Materials and Methods: A literature review was performed by referring to the scientific papers on the internet from the PubMed and Google Scholar databases, between 1985 and 2016.

Results: Periodontal disease influences the Alzheimer through various mechanisms. Periodontal inflammatory molecules due to periodontal pathogens cause brain inflammation associated with Alzheimer. P. gingivalis in particular causes dementia by penetrating into the CNS. Vitamin B12 deficiency has been associated with cognitive disorders as well.

Keywords: Periodontal disease; Alzheimer; Periodontitis

Introduction

Alzheimer is a progressive cognitive disorder with some problems in decision-making and judgement, as well as behavioral/mental disorders [1]. It is a progressive irreversible condition which its main destructive mechanism would be through the inflammation in the brain. Sporadic and late-onset Alzheimer represents 98 percent of all cases of Alzheimer and potentially has a complex interaction with the environment, cardiology and genetics [2,3]. The current findings support the issue that periodontal pathogens are the possible factors of neuronal inflammation and sporadic and late-onset Alzheimer [4,5]. Alzheimer increases with age, significantly [1,3,6], it is not necessarily the result of aging, however its prevalence doubles with lasting every five years, from the age 65 onwards. Therefore, as the population gets older, higher percentage of people suffer from the Alzheimer [5,7-9, 11]. For this reason, identifying the underlying factors and mechanisms and employing prevention methods are very important [10]. Inflammation of effective environmental factors in Alzheimer [11] in patients with Down syndrome [1], and type 2 diabetes mellitus [9] acts as a bridge between these diseases and Alzheimer. Periodontal diseases as an infection of some chronic bacterial that affect the supporting tissues of the teeth such as the gums, periodontal ligament and alveolar bone [11], excrete a significant load of bacteria and inflammatory mediators in the body [4,8,9].

In patients with Alzheimer, oral hygiene due to the cognitive processes involved in learning, attention and memory which have progressively damaged, has been significantly reduced. When degeneration associated with Alzheimer's progresses, daily activities would be detected [5], which the progress even could cause disabilities and finally lead to the death [6,7].

Around 5-20 percents of the adults over 65 years old suffer from periodontitis as a common source of chronic systemic infection [7]. The non-keratinized periodontal pocket and junctional epithelium could be the inlet duct for entering bacteria and their endotoxin into the blood stream [4,5]. Moreover, periodontal pathogens could cause mechanisms that influence the systemic balance and inflammatory mediators in this local inflammation [4,8]. Periodontopathic bacteria and systemic inflammation caused by them is the basis for the relationship between periodontal and other systemic diseases such as diabetes, cardiovascular disease, kidney disease, and low birth weight [9,10].

Overall, a relationship between periodontal disease and the development of Alzheimer has been recently proposed [8]. The aim of this study was to review the present findings toward the relationship between periodontal diseases with Alzheimer.

Materials and Methods

In order to access to the scientific papers a comprehensive search on PubMed and Google Scholar databases was performed, and 63 articles from the years 1985 to 2016 were selected. The initial screening of the papers was based on the assessing of the titles and abstracts. Then, final evaluation using the full papers was performed and 3 original research papers together with 12 Review articles, both as a review or original article in English language were finally selected. The keywords which were used for searching purpose were included periodontal disease, Alzheimer and periodontitis. Since there were scarce number of original research articles in this field, every attempt was done to consider all of them and to select the most review articles to avoid missing any data.

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Note:MMSE (Minimal-Mental State Examination): Mini-Mental State Examination to measure the quality of diagnosis and screening of dementia consciousness with the maximum score of 30. PIB (Pittsburgh compound B): A radioactive analog of thioflavin T, which in Positron emission tomography is used for scanning beta-amyloid plaques in nerve tissue. CAL (Clinical Attachment Loss): The loss of attached gingiva (PPD to CEJ) is called: CAL

<table>
<thead>
<tr>
<th>Research Studies</th>
<th>Target</th>
<th>Sample Size</th>
<th>Method</th>
<th>Result</th>
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<tbody>
<tr>
<td>Okamoto N et al. [10]</td>
<td>Exploring the effect of the low number of teeth on the growth and progression of mild memory impairment.</td>
<td>2335 Person.</td>
<td>5 years follow up MMSE test Pocket depth review by two skilled dentist and the use of universal code of periodontal index.</td>
<td>Direct link between the low number of teeth with lesser degree MMSE test.</td>
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<tr>
<td>Kamer et al. [11]</td>
<td>The relationship between periodontal disease and cerebral amyloid load.</td>
<td>38 cognitively normal subjects.</td>
<td>Examining periodontal disease by counting the teeth, the presence of plaque on the 6 levels of tooth surfaces and measuring CAL or Michigan probe PIB-PET scan.</td>
<td>CAL more than 3mm was associated with increased uptake of PIB and periodontal disease associated with beta amyloid load in brain.</td>
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<td>Kiani YF et al. [13]</td>
<td>To investigate the effect of non-surgical periodontal therapy on serum levels of anti-cardioliopin antibodies (aCLA) that potentially plays a role in the pathogenesis of cardiovascular diseases in the patients with periodontitis.</td>
<td>20 volunteers (11 females and 9 males) with the mean age of 40.55 years.</td>
<td>This examination included measurement of probing Pocket Depth (PD) and clinical Attachment Loss (AL). The Plaque Index (PI) and Gingival Index (GI) were recorded, as well. After baseline examination, all the subjects received full mouth non–surgical periodontal treatment. The subjects returned for the final visit 6 weeks after the last session of the scaling for reevaluation of the periodontal parameters. At baseline and final visits, two milliliters of venous blood was collected from each patient and a commercially available enzyme-linked immunosorbent assay (ELISA) was used for analyzing aCLA (IgM and IgG).</td>
<td>A significant difference was found regarding the mean levels of both forms of aCLA before and after the treatment for IgM and IgG. In addition, the study results showed significant reductions in the periodontal parameters after non-surgical periodontal therapy.</td>
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Table 1: Summary of the two research papers dealing with probable mechanisms of Periodontitis and Alzheimer

<table>
<thead>
<tr>
<th>Research</th>
<th>Sample Size</th>
<th>Target</th>
<th>Mechanisms and Result</th>
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<tr>
<td>Cerajewska TL et al. [5]</td>
<td>It has not been mentioned</td>
<td>The latest evidence about the association between periodontitis and sporadic Alzheimer and late</td>
<td>The relationship between periodontitis and Alzheimer's disease are supposed by several mechanisms; 1. The direct effect of pathogens. 2. Systemic inflammation caused by periodontal pathogens. 3. Vascular changes and a reduction in cerebral blood flow due to atherosclerosis plaque that periodontal pathogens have been created. 4. Genetic factors include IL1, TNF-α gene polymorphism and environmental factors such as smoking.</td>
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<tr>
<td>Gurav AN et al. [6]</td>
<td>73 studies</td>
<td>The relationship between Alzheimer's disease and periodontitis (pathophysiology examining and possible consequences of this relationship).</td>
<td>Periodontitis affects the appearance and progression of Alzheimer. Periodontitis through inflammation and oxidative damage associated with Alzheimer's disease. Periodontitis is a changeable risk factor in Alzheimer's disease which with the treatment its progress can be slowed. Atherosclerosis-induced platelet aggregation and accumulation of tau proteins and inflammation is of the pathophysiology of Alzheimer's disease.</td>
</tr>
<tr>
<td>Gaur S et al. [7]</td>
<td>133 studies</td>
<td>The possible relationship between chronic periodontitis and Alzheimer's disease.</td>
<td>Periodontitis through the role of bacteria and the production of inflammatory molecules from the nerve ganglia brought to the brain and affects its response.</td>
</tr>
<tr>
<td>Shaik MM et al. [9]</td>
<td>82 studies</td>
<td>Periodontal disease as a potential risk factor for Alzheimer.</td>
<td>Periodontal disease through the pathogenic bacteria involved in periodontitis which with the production of inflammatory molecules cause inflammation of the brain, associated with Alzheimer.</td>
</tr>
<tr>
<td>Singhrao SK et al. [4]</td>
<td>126 studies</td>
<td>The relationship between Porphyromonas gingivalis bacteria and its role on the progression of Alzheimer.</td>
<td>Periodontal disease through the bacterium Porphyromonas gingivalis bacteria which with the release of cytokines and cross the blood-brain barrier affect the brain activity, associated with Alzheimer's disease.</td>
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<tr>
<td>Noble JM et al. [2]</td>
<td>It has not been mentioned</td>
<td>The connection between poor oral hygiene and the incidence and prevalence of cognitive impairment and its mechanisms.</td>
<td>Tooth loss due to periodontal disease and tooth decay can cause malnutrition (lack of vitamin B12 and thiamine) and cognitive disorders. Periodontal disease also-induced platelet aggregation and accumulation of cytokines and angiogenic causes cognitive disorders. (Production of IL1, IL6, TNFα, CRP, IgG).</td>
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The link between periodontitis in people with Down syndrome and high risk of Alzheimer and its possible mechanisms. People with Down syndrome experience the higher prevalence and severity of periodontal disease. Their periodontal disease is more severe (aggressive) and it may be linked to the neurodegenerative diseases like Alzheimer.

The relationship between periodontitis and Alzheimer's disease through oral systemic condition. Three mechanisms of bacterial products, inflammatory mediators and vascular changes are ultimately caused Alzheimer's. Pathogens with activating microglia and destroying the neurons, mediator with the accumulation of beta-amylloid in the brain and phosphorylation of tau protein and formation of neurofilibrillary tangle (d), vascular changes through the atherosclerosis cause dementia and Alzheimer.

The relationship between Alzheimer and periodontal disease. Dementia associated with interactions between systemic inflammation status and genetics. Its two mechanisms; 1) response to the microorganism and increase in cytokines which pass the blood-brain barrier, 2) entering available microorganisms in dental plaque biofilms to the blood and then peripheral nerve and causing inflammation CNS. TNF-α plays an important role in the process of destroying nerves.

The emphasis is on current knowledge about the relationship between Alzheimer's disease and periodontitis. In chronic periodontitis, LPS B, flagellin and cytokines IL-1β and TNF-α secreted by macrophages, activate receptors IL-1R / TNFR and TLRs on the surface leptomeninges, and also activate microglia. This cell releases inflammatory cytokines and causes the expression, activity of BACE1 gene, and ultimately protein amyloid-beta production in the brain.

The relationship between inflammation and Alzheimer's disease. Systemic inflammation has a significant relationship with the Alzheimer's disease. Anti-inflammatory drugs cannot prevent the Alzheimer's, but they could slow down its progress.

Note: A. Central nervous system; B. Bacterial lipopolysaccharide; C. They are proteins that stabilize microtubule. In the central nervous system neurons are frequently found, in astrocytes, and oligodendrocytes are found to a lesser extent. These proteins which have lost their function in stabilizing microtubule are the main cause of related dementia diseases such as Alzheimer and Parkinson's; D. The result of tau proteins accumulation, which are known as a primary marker in Alzheimer’s disease

### Results

Summary of the results obtained from the two research papers, and also the mechanisms which cause the relationship between the periodontal disease and Alzheimer, have been shown in table 1 and 2, respectively. According to the literature, the periodontal disease influences the Alzheimer in various mechanisms. This effect in some papers has been expressed directly. Phosphorylated tau protein aggregation causes suppression of blood-brain barrier due to inflammatory response can be a good example.

### Discussion and Conclusion

The results of recent studies show that the periodontal disease affects Alzheimer through different mechanisms. The serum IgG levels have been associated with the risk of Alzheimer. Increased expression of the receptor IgG (FcyRIIb) in beta-amylloid cells justifies the relationship between Alzheimer and periodontitis in chronic inflammation [12]. Although there is not much studies about measuring changes in serum levels of IgG and IgM after scaling and root planning in patients with chronic periodontitis, one study has indicated the reduction of IgG level following phase 1 periodontal therapy [13]; this means that in patients with Alzheimer, perhaps by scaling and phase 1 periodontal treatment, serum IgG levels decrease and thereby make the progression of the periodontal diseases slower down. Poor diet and lack of vitamin B12 is one of the possible causes of dementia. This relationship caused by the loss of teeth due to periodontal diseases in patients along with using full or partial dentures in elders. In other words, periodontal disease causes tooth loss and malnutrition; vitamin B12 deficiency in particular, and a cause and effect relationship between periodontitis and dementia can be justified. In a prospective study, vitamin B12 was inversely associated with PPD and CAL. In other words, it can be assumed that reducing vitamin B12 may be associated with increased pocket depth, and thereby increases the risk of Alzheimer. By the way, the link between reduced folate, vitamin B12 and the progression of Alzheimer has been referred, directly.

Periodontal diseases are more common in developing countries [14]. On the other side, it has been shown that most people with dementia are living in developing and developed countries. China and its neighboring countries in the Western Pacific ocean have the highest number of people with dementia (6 million) [15], and also over 35 million people around the world are suffering from dementia, and it has been predicted that will be doubled in future years [11]. This increase may be due to an increase in the average age of the world’s population and changes in lifestyle, hence identifying influencing factors would be helpful. To justify this outbreak, a possible cause could be outlined, which in developed and developing countries, life expectancy in recent years has been increased, and due to improvement in oral health, individuals use much of their natural teeth until the elderly ages and are visited by the dentists for the periodontal treatment, frequently. Since Alzheimer is a normally aging disease, both diseases show higher prevalence after the age of 65 years. Alzheimer may be prevalent in underdeveloped areas and the Third World countries, but usually in these countries people do not have life expectancy after 65 years and often die before the onset of Alzheimer. According to the European Alzheimer organization (http://www.Alzheimer-europe.org), prevalence of Alzheimer in Sweden has been reported 1.82% of the general population, which is higher than the average in Europe. In an article on the epidemiology of periodontal health in 19-year-old Swedish adults, it has been shown that the amount of plaque and gingivitis in these patients is high. It can be assumed that due to the high prevalence of periodontal disease in young Swedish, high prevalence in the elderly population can also be seen (epidemiologic study of Swedish aging population has not been found) and the prevalence of Alzheimer in this population may strengthen the connection between the two diseases. Unfortunately, epidemiologic article associated with Iranian population has not been found [16,17].
There is a high incidence of periodontal disease in Down syndrome. In 14 years age, 58 to 92 percent of patients with Down syndrome are suffering from periodontitis [1]. Moreover, the pattern of periodontal disease is much more severe, which may be due to immune deficiency in these patients [1]. Concurrent with this phenomenon, we are witnessed a high incidence of Alzheimer in Down syndrome patients, so that the Down syndrome so that the Down syndrome could be considered as a pre-clinical condition of Alzheimer. [1]

Although the mechanisms involved in Alzheimer are known, likely etiologic factors which launch these mechanisms are not yet certainty [3, 4]. Recent evidences suggest that neuronal destruction is being made by the immune system inflammatory conditions such as chronic periodontitis [7]. In a study reported that in elderly, periodontal pathogens such as P. gingivalis, Tannerella forsythia, and Treponema denticula create low-grade chronic inflammation [4,7]. In contrast, viral infections such as CMV, HVS 1 and HVS 2 have a more active role in progressive loss of cognition. Both HSV and CMV viruses are neurotropic viruses and their activity causes nerve damage in the brain. In addition, significant homology between glycoprotein B in HSV 1 and index Aβ in Alzheimer has been reported. Although both viruses do not directly affect the gingival tissues, their increased levels of chronic periodontitis can increase the risk of Alzheimer in the future. Oral bacteria can cause similar reactions, although their role is still unclear. For example, Treponema which has been generally found in periodontitis; has been isolated from the brain, blood and cerebrospinal fluid of Alzheimer. The antigens of some bacteria were found in the trigeminal ganglion and pons which shows they had found their way to the brain through ganglia, however, some studies have refuted this hypothesis [7]. P. gingivalis can directly access the central nervous system [4], this situation may lead to neurodegenerative activities in patients with inflammatory conditions [4].

In another mechanism, pre-inflammatory molecules passing through the blood-brain barrier (BBB) leaky capillaries induce signaling molecules for producing cytokines into the brain along with increasing permeability of the BBB and activating brain endothelial cells. These molecules can increase the pre-inflammatory cytokine concentrations, locally in the brains, or indirectly to stimulate the glial cells to produce more pre-inflammatory cells. If glial cells get activated at optimum level in Alzheimer, the stimulation will lead to exaggerated responses and overproduction of the pre-inflammatory molecules. Neural pathway is another mechanism in which the cytokines can stimulate afferent nerve fibers which leads to an increase in cytokines in the brain, or can enter into the brain through the channels that associated with the peripheral nerves. The interesting point is that, even if these cytokines are focused locally, not systemically, they still make the brain cytokines to rise. Pre-inflammatory molecules in the oral cavity with the same mechanism may affect the brain. On the other hand, bacterial products such as LPS in Gram-negative bacteria increase pre-inflammatory cytokines and the immune response by activating CD14 receptors [3]. Since chronic periodontitis is an inflammatory disease that creates localized inflammatory cytokines, it seems cytokines surrounding the nerve endings of the trigeminal ganglia, may strengthen ponds cytokines in the brain. On the other hand, bacteria involved in periodontitis have mostly been gram-negative, and may activate the brain cytokines to develop Alzheimer [3,4].

At the end, due to the importance of lifestyle and the fact that Alzheimer's and periodontal diseases have a serious impact on it, we suggest conducting further studies in order to identify the contributing and biologic pathways of the diseases. Every effort should be done through phase 1 periodontal treatment and maintenance phase to slowing down the progression of Alzheimer and plaque accumulation.

References