Correlation of Periodontitis and Incident Dementia: A Scoping Review

Hala Salman[1], Yara Sultan Khairi Sultan Sultan[2], Manar Eyad Adel Khanfar[3], Sudhir Rama Varma[4*], Asok Mathew[5], Jayaraj Narayanan[6], Ruba Odeh[7], Pradeep Kumar yadalam[8]

[1] *Department of Clinical sciences, Ajman University, Ajman, UAE. Email: halasalmann@hotmail.com*
[2] *Department of Clinical sciences, Ajman University, Ajman, UAE. Email: yarasultan29@gmail.com*
[3] *Department of Clinical sciences, Ajman University, Ajman, UAE. Email: manar.khanfar16@gmail.com*
[4] *Department of Clinical sciences, Ajman University, Ajman, UAE.*
Department of Clinical sciences, Center for medical & Bio-allied health sciences research, Ajman University, Ajman, UAE. Email: s.varma@ajman.ac.ae
[5] *Department of Clinical sciences, Center for medical & Bio-allied health sciences research, Ajman University, Ajman, UAE. Email: a.mathew@ajman.ac.ae*
[6] *Department of Basic sciences, Center for medical & Bio-allied health sciences research, Ajman University, Ajman, UAE. Email: j.narayanan@ajman.ac.ae*
[7] *Department of Clinical sciences, Center for medical & Bio-allied health sciences research, Ajman University, Ajman, UAE. Email: r.odeh@ajman.ac.ae*
[8] *Department of Periodontics, Saveetha Dental College and hospitals, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai- 600077*
Pradeepkumar.sdc@saveetha.com

**Corresponding author: Sudhir Rama Varma*

KEYWORDS
Periodontal disease; Periodontitis; Dementia; Incidental dementia; Alzheimer's disease.

ABSTRACT

Background: Bacteria involved in periodontitis is thought to have an effect on patients developing Dementia, particularly Alzheimer's disease, through the inflammation caused during periodontal disease which induces the production of inflammatory mediators that is likely to spread systemically causing dementia in all different age groups. This review was performed to further investigate around the scope of this idea proposed by several authors who have performed different clinical studies.

Materials and Methods: The analysis of five articles (clinical studies, cohort studies, cross-sectional studies) was done. These articles advocate about the possible correlation between periodontitis and dementia.

Results and discussion: From the available literature identified, the studies have indicated a positive correlation between periodontal disease and dementia. The cohort studies have inferred this from both prospective and retrospective studies.

Conclusion: Though the exact mechanism underlying this association remains unknown and not yet fully understood, it is believed that periodontitis and incident dementia are positively correlated according to the studies analyzed in this present study.

1. Introduction

Periodontitis is a multi-factorial inflammatory disease of the periodontium, resulting in the inflammation of the structures supporting the teeth.[1] Its primary clinical feature is the loss of periodontal attachment of teeth, known as 'Clinical Attachment Loss'; if neglected in more advanced stages, it can cause complete loss of the periodontal ligament surrounding the tooth structure, and this eventually results in tooth loss followed by alveolar bone loss.[2] When bacteria biofilm accumulates in the periodontium, it induces an inflammatory immune response by the host as a natural mechanism; the host body activates proteinases enzyme, which further leads to periodontal ligament breakdown; as the disease progresses, migration of the junction epithelium apically is noted. [3] Clinical presentation of this condition varies among individuals based on several factors, including the patient's age, severity, and location within the dental arch. [1] The degree of oral biofilm contamination of the dentition also influences the clinical presentation. Risk factors classified as non-modifiable and modifiable are associated with periodontitis. Age and Genetic factors are non-modifiable risk factors.[4] On the contrary, the modifiable factors are Poor oral hygiene, which motivates bacterial deposition, biofilm formation, and plaque accumulation, which

induces the inflammation cascade. One of the most modifying risk factors for periodontitis is smoking, and smokers have three times more risk of developing periodontal diseases as compared to non-smokers.

Evidence suggests that smoking alters the oral microbial flora, increases the level of certain periodontal microorganisms, and affects host response.[1] Nicotine has been shown to cause periodontal tissue breakdown, directly or indirectly, through interaction with other factors. Diabetes mellitus is a systemic risk factor that plays a detrimental role in periodontal disease development and progression. The association is due to modifications in the immune system of patients with uncontrolled diabetes, which result in abnormal neutrophil function or hyper-responsive macrophages producing pro-inflammatory cytokines. Furthermore, patients with uncontrolled diabetes exhibit alterations in connective tissue metabolism, modulating the periodontium's resorptive and formative processes.[3] Besides, the elevation of gingival crevicular fluid in patients is associated with increased levels of inflammatory mediators and cytokines. Moreover, stress can cause a significant reduction in salivary flow, which drastically increases the risk of developing periodontal disease. It has been proven that certain medications can also decrease salivary flow; these medications include tricyclic antidepressants, beta-blockers, antihistamines, and atropine. Medications like phenytoin, cyclosporine, and nifedipine are believed to stimulate gingival hyperplasia, making eliminating dental plaque more challenging.[2] Periodontitis exists in different forms, most commonly seen in Chronic Periodontitis, Aggressive Periodontitis, necrotizing, and Periodontitis as a manifestation of systemic diseases. The detection of a disease is known as a diagnosis. Identifying numerous periodontal tissue signs and symptoms that indicate a change in health allows for the clinical diagnosis of periodontal disease.[4]

Understanding what constitutes periodontal health is essential for the diagnosis of periodontal disease. Every patient should have a routine oral examination, including a periodontal assessment. All new patients should undergo a periodontal screening as part of continuous oral healthcare, using tools like the Basic Periodontal Examination/ Community Periodontal Index or Periodontal Screening Record. If periodontitis is discovered, a complete periodontal assessment is necessary.[1] This includes documenting complete mouth probing and bleeding data and evaluating additional pertinent factors such as plaque levels, furcation involvement, recession, and tooth movement. In order to assess bone loss in individuals with periodontitis, radiographic examination of alveolar bone levels is necessary. Periodontal therapy should focus heavily on risk assessment (such as determining a patient's diabetes status and smoking history) and risk management (such as encouraging smoking cessation).[3] Inflammatory changes are seen in the connective tissue supporting teeth in periodontitis. Various oral pathogens, including bacteria, fungi, and viruses, bring on inflammation. One of the body's early defenses against any external invader is inflammation. Unlike chronic inflammation, which can endure for months or even years, acute inflammation only lasts a few days.[5] Chronic inflammation caused by various inflammatory mediators occurs in periodontitis.

1. Lipopolysaccharide (LPS)

Which is composed of large molecules of lipids and polysaccharides and is considered an essential virulence component of Gram-negative bacteria. An endotoxin called the glycolipid LPS interacts with the host's immune system. High serum LPS levels cause macrophages, which control the body's immune system, to become activated. Inflammatory disorders in periodontitis may, therefore, benefit from macrophage-targeted therapy.[4]

2. Dementia

A clinical syndrome known as dementia is defined as a gradual loss in cognitive function that impairs one's capacity to function independently. Dementia symptoms develop gradually, continue, and progress. Cognitive, functional, and behavioral changes are expected in dementia patients. The four common types of dementia are Lewy body dementia, Alzheimer's, and vascular dementia.[6]

3. Alzheimer

Most frequently, short-term memory loss is the initial symptom. Progressive cognitive function losses over time influence many different cognitive domains. Cognitive and non-cognitive symptoms of AD are distinguished for purposes of assessment and treatment.[6] The latter are less predictable throughout the sickness while the former is typically present throughout the illness. Memory loss, aphasia, agnosia, apraxia, disorientation (poor perception of time, inability to identify familiar faces), impaired visuospatial function, and executive function impairment are more particularly considered cognitive symptoms.[6] Patients may also exhibit behavioral symptoms, including physical and verbal violence, as well as non-cognitive symptoms like depression. Early

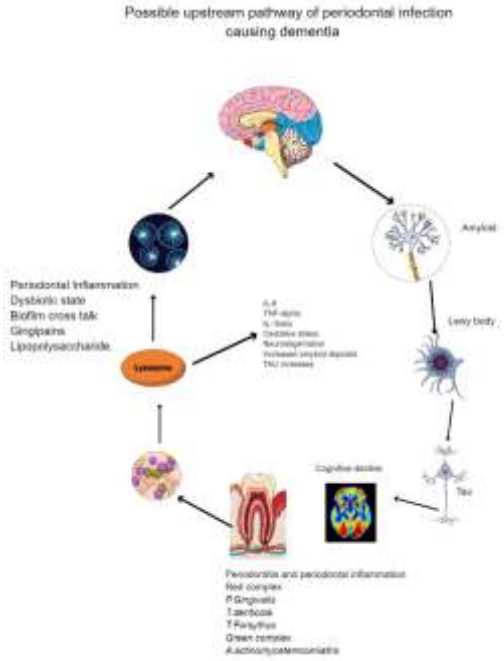
memory and visuospatial difficulties are typical characteristics of AD. When dementia is moderate to severe, hallucinations might happen.[7] Patients may present in the end stage with near mutism, unable to sit up, hold their head up, or follow objects with their gaze.

4. Vascular Dementia

Also called multi-infarct dementia is a disorder that blocks and restricts blood flow to the brain, depriving neurons of oxygen.[7] Frequent cause of vascular dementia is stroke. Symptoms might vary greatly depending on the part of the brain and the vessels affected.[8] The most noticeable signs of a severe stroke include confusion, disorientation, difficulty speaking, difficulty understanding speech, and visual loss.[7] Vascular dementia may not affect memory, but it can suddenly change executive function.

5. Lewy body dementia

It is a type of dementia brought on by abnormal accumulations of the protein alpha-synuclein (Lewy bodies) inside neurons. It makes up between 5% and 15% of all dementias.[8] The most defining characteristics of LBD are repeated complex visual hallucinations, spontaneous parkinsonism, and fluctuating cognitive impairment with changes in attention and alertness. [6] (Figure 1)



6. Frontotemporal Dementia

It is a broad phrase used to describe conditions about the frontal and temporal lobes of the brain, such as Pick's disease. FTD often develops between the ages of 40 and 75, but AD does not. Characteristics of FTD include personality changes and behavioral abnormalities, which start developing early in the illness.[9] Visuospatial function is typically unaffected, unlike AD. Though dementia is known to occur due to old age, it can appear at younger ages, like the '20s, 30s, and '40s. This is because it is caused by loss or by periodic damage to the nerve cells and the connections between them, which, as a result, cause the signs and symptoms to arise. Though brain cells are lost with aging, people with dementia suffer at a faster-paced rate.[10] The signs and symptoms help raise awareness about the risk of dementia arising, and they include but are not restricted only to memory loss, signs of confusion, Repetitive questions, Mood changes, Mobility, Social reluctance, delusions, hallucinations, getting lost, and most importantly, loss of independence.[11] These symptoms do not occur simultaneously but rather depend on the current stage of dementia, whether its early or later stage manifestations. The later the stage of dementia, the more severe the symptoms, with an even more significant impact on the patient's daily life, causing the subject to be unable to carry out daily tasks independently and leaving the patient at risk of needing someone who can take care of him.[10,11]

Though formulating a definitive diagnosis of the exact type of dementia can only be made using an autopsy, probable diagnoses can be made using a variety of techniques and tests. History taking is usually one of the first

markers, and formulating a correct diagnosis is vital and dependent on a detailed history obtained from a close family member or a caretaker, if present.[12] Medical history and whether or not any substance or drug abuse occurred in the past are noted. Drug history is also recorded as some drugs have side effects that impair cognition, such as benzodiazepines, anticholinergics, and analgesics containing codeine.[13] Observed symptoms of cognitive decline and any safety concerns resulting from the cognitive symptoms are noted.

MRI or CT brain imaging can be utilized to evaluate signs of vascular or ischemic disease and determine if any atrophies are present.[13] Cognitive and neuropsychological tests, such as questionnaires and laboratory testing (Vitamin B12, calcium levels, and thyroid testing), are a few other methods to help diagnose dementia. The MMSE, Mini-Mental State Examination, is the world's most commonly used cognitive screening tool.[12] It is important to note that there are several types of dementia, each with its characteristics and neuropathological markers, each with more in-depth tests to help diagnose further which type of dementia is being tested for. Around 80% of Dementia cases are related to Alzheimer's, making it the most common neurodegenerative disease responsible for dementia.[6] It is believed to result from the accumulation of beta-amyloid plaques and neurofibrillary tangles, seen in the hippocampus, promoting injury to existing neurons and subsequently leading to their death. As a result, the decline in cholinergic neurotransmission brings about a loss of both cognition and memory. More precisely, neurotransmitter abnormalities include reduced acetylcholine synthesis and a reduced number of cholinergic neurons, which result in neurodegenerative dementias.[6] The histopathological hallmarks of Dementia or Alzheimer's, which can only be observed post-mortem, are: Amyloid plaques- extracellular amyloid deposits, & Cerebral amyloid angiopathy- amyloid deposits in the tunica media of several arteries in the brain.[6,13,14]

Currently more focus has been garnered around periodontal disease and dementia/cognitive impairment. Patients with periodontitis were found to have a higher risk of dementia (hazard ratio (HR) compared to those without periodontitis, even after adjustment for confounding factors.[15] Multivariate analyses showed a negative correlation between periodontitis sites and cognitive scores. Ironically, a cross-sectional study found that sites with defects/severe bleeding were not associated with cognitive outcomes. Additionally, study design, sample size, assessment of dementia/cognitive impairment, periodontal condition, and additional differences in confounding factors might relate to this discrepancy. Considering the challenges in the treatment of dementia and the possible available interventions for periodontal disease, it is essential to elucidate whether periodontal disease is a risk factor for dementia.[7] This current review aims to assess whether there is a correlation between periodontitis and Incident Dementia.

2. Materials and Methods

1. Search Strategy and Data Extraction:

The study was conducted by accessing articles from March 2016 until May 2023. Search engines such as Pubmed, Cochrane, MEDLINE, Embase, Web of science and Scopus facilitated the search. Keywords used were (Periodontal disease) OR (periodontitis)) AND (Dementia)) OR (Incident dementia)) OR (Alzheimer's disease)). The articles that detailed an association between periodontal disease and dementia more explicitly mentioning incidental dementia, were included. The type of studies included clinical trials, cross-sectional, and cohort studies.

2. Data Analysis and visualization:

To provide validity in assessment of periodontitis, studies that measured periodontal disease by any one of the following parameters: Pocket depth (PPD), Clinical attachment level (CAL), radiographic alveolar bone loss (RABL), gingival index (GI), plaque index (PI), Bleeding on probing (BOP), gingival bleeding index (GBI) and extensive population analysis such as community periodontal index (CPI). Exclusion criteria were abstract articles, articles not written in English, and case reports. (Figure 2) Articles were assessed based on SANRA- (scale for assessing narrative review articles) to provide clarity and validity in the search.

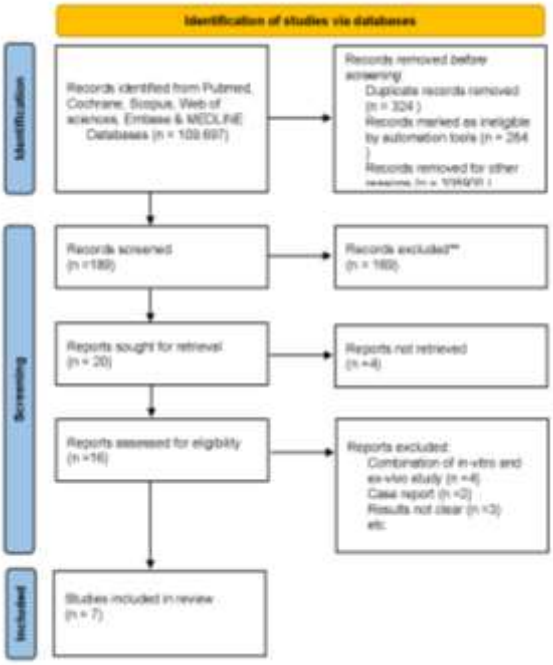


Figure 2: Flowchart highlighting the selection process of articles retrieved from digital databases

3. Results

A summary of the selected seven studies that explore the relationship between dementia or Alzheimer's disease and periodontitis were analyzed. (Table) According to a Chinese cohort research, dementia increases the risk of periodontitis. Another Brazilian study examined pre-clinical in vivo research and discovered a link between Porphyromonas gingivalis, bacterial polysaccharides, and the onset of Alzheimer's disease by activating the complement cascade. A Swedish cohort research revealed that both groups had a comparable rate of dementia regardless of whether they had deep periodontal/peri-implant probing pockets. A cohort study in the UK found that baseline P. gingivalis antibody levels were linked to baseline periodontitis, which was associated with a decrease in serum IL10 levels and a corresponding increase in serum TNF levels. Another retrospective matched cohort study from Taiwan found that exposure to chronic periodontitis for ten years increased the risk of developing Alzheimer's. Lastly, a prospective cohort study from Taiwan found that participants with periodontitis had a higher risk of developing dementia than those without. The available studies show a positive correlation between the two conditions.[15,16,17,18,19,20,21] (Table)

Table 1: List of Clinical studies enumerating the possible role of dementia due to periodontitis

Author	Date of Publication	Country of Origin	Type of study	Number of participants	Age range	Results
Jacob Holmer et al.	2022	Sweden	Cohort study	37,174	40-70	The study's findings demonstrate that both groups, whether or not they have deep periodontal/ peri-implant probing pockets depth, experienced a similar rate of dementia.
Ma KS et al	2022	Not specified	Retrospective cohort study	8640	Not specified	Dementia and Alzheimer were associated with a higher risk of periodontitis dependent of age and independent of systemic confounding factors

Mark Ide et al.	2016	United Kingdom	Cohort study	60	60-80- Mean Age range 77.7	The number of teeth and variations in blood inflammatory markers were not shown to be significantly correlated. However, baseline P. gingivalis antibody levels were linked to baseline periodontitis , which was associated with a decrease in serum IL10 levels and an increase in serum TNF levels.
Tzeng et al	2016	Taiwan	Retrospective cohort	2207	Not specified	Patients with chronic periodontitis and gingivitis have a higher risk of developing dementia.
Chang-Kai Chen et al.	2017	Taiwan	Retrospective matched cohort study	18,672	50 and above	According to this research, exposure to chronic periodontitis for ten years was linked to an increased risk of Alzheimer's disease by 1.707 times.
Yao-Tung Lee et al.	2017	Taiwan	Prospective cohort study	Not specified	60 and above	Participants with periodontitis had a higher risk of developing dementia
Oliver Laugisch et al.	2021	Germany	Cross sectional pilot study	40	50-70	No definitive results. Hypothetical

4. Discussion

Periodontitis is an inflammatory condition due to the dysbiotic progression of microorganisms within the supporting structures. It is multi-factorial and exists in different forms: Necrotizing Periodontitis, Chronic Periodontitis, Aggressive, necrotizing, and Periodontitis as a manifestation of systemic diseases.[1] Non-modifiable means they cannot be changed, regardless of measures taken to prevent them, while modifiable means they can be changed. Age and Genetic factors belong to non-modifiable risk factors.[4] On the contrary, the modifiable factors are Poor oral hygiene, which motivates bacterial deposition, biofilm formation, and plaque accumulation, which induces the inflammation cascade.[13] Smoking is a modifying risk factor for periodontitis; smokers have three times more risk of developing periodontal diseases as compared to non-smokers. Dementia is a clinical syndrome defined by a gradual loss of cognitive function that impairs one's capacity to function independently. Dementia symptoms develop gradually, continue, and progress. Cognitive, functional, and behavioral changes are expected in dementia patients.[6] The four common types of dementia are frontotemporal dementia, Lewy body dementia, vascular dementia, and Alzheimer. The most known important risk factor of dementia is aging, and this is due to being associated with old age. Non-modifiable risk factors include female sex, black race, Hispanic ethnicity, and genetic factors, such as autosomal dominant mutations in the genes PSEN1, APP, and PSEN2.[6] Modifiable risk factors include hypertension, diabetes, diet, and limited access to cognitive, social, and physical activities. Periodontitis may be linked with an increased risk of dementia and cognitive decline, including Alzheimer's disease.[16,17] The proposed mechanisms linking periodontitis and dementia include spreading oral bacteria to the brain by penetrating the blood-brain barrier, activating the immune system in response to oral bacteria, and releasing pro-inflammatory cytokines that can cause damage to brain cells.[16] Cytokines can lead to an invasion of the microorganisms in the brain that originate from the dental plaque biofilm. Inflammatory mediators from periodontitis have an affinity to enter the systemic circulation, leading to systemic illness. Researchers have proposed that periodontitis can accelerate the course of Alzheimer's disease by elevating pro-inflammatory cytokine levels and allowing microorganisms from tooth plaque biofilm to invade the brain.[18] These triggers neurodegenerative changes that could ultimately affect the progression of Alzheimer's disease.[21] (Figure 3)

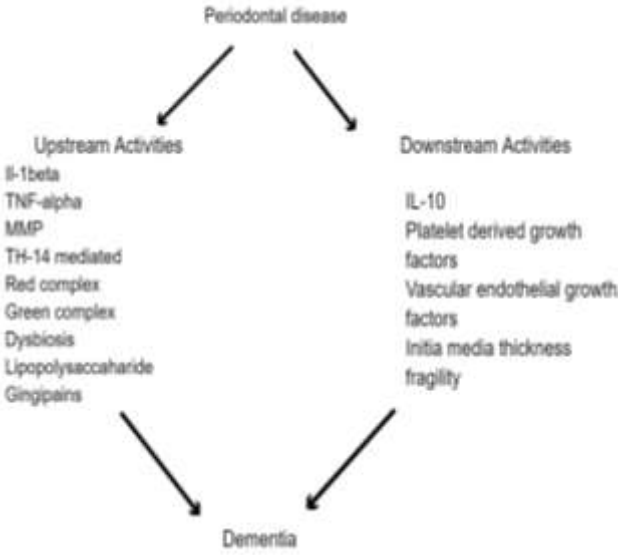


Figure 3: Possible bidirectional periodontal inflammatory pathways leading to dementia

It is also noted in this study that impairments in chewing, as a result of the progressing neurodegeneration, increase the risk of periodontal problems.[16,19] Possible pathological mechanisms by which periodontitis may contribute to Alzheimer's were proposed. Microbial endotoxins and pro-inflammatory mediators make a port of entry and damage the vascular system.[21,22] In moderate to severe periodontitis cases, spirochetes and Treponema denticola are often identified as isolated bacteria. These microorganisms have also been found in those with Alzheimer's, indicating that periodontopathic bacteria can enter the brain via peripheral nerve routes and systemic circulation.[21,22,23,24]

Current evidence from the literature supports a positive correlation between periodontitis and dementia or cognitive deterioration, few studies on this subject have been limited by small sample size and their cross-sectional design between periodontitis and dementia.[17,20] The others though having large sample size, the possibility of confounding variables have been reported to a possibility of bias in correlating dementia with periodontal disease, nevertheless, the studies have reported possible association given the strength of the sample size.[16,18,19,21] One study has reported a possible correlation dependent of age and independent of systemic confounding factors.[18]

A recent longitudinal cohort study analyzed IgG levels in those with periodontitis and followed them for the development of mild cognitive impairment.[19] The levels of the antibodies produced in response to periodontitis increased years before the onset of cognitive impairment, which in turn suggests that periodontal disease may aid in increasing the onset risk of dementia.[25] Possible explanations for the association between dementia and chronic periodontitis have been put forth, despite the lack of a clear mechanistic link.[15,25] A local increase in cytokines is brought initially on by Periodontitis.[15] Many pro-inflammatory mediators are in the blood as the inflammation intensifies and spreads. The cytokines may then affect the brain's previously primed glial cells, which may also cause vascular alterations. The vascular alterations may encourage thrombogenesis and eventually result in cerebral microvascular disease, while the glial cells may intensify the inflammatory response and hasten the course of dementia.[15] In addition, it can be said that the correlation can be bidirectional with patients having periodontal disease developing dementia, as well as patients with dementia developing periodontal disease. Those with dementia may have trouble remembering simple everyday tasks, like teeth brushing, flossing, or oral health maintenance. Over time, this may lead to them developing oral diseases and the progression of oral disease, which leads to periodontitis. They may forget to set and attend appointments at the dental office. Decreased visits lead to accumulated plaque levels, increased caries and gum disease risk, and teeth lacking periodontal support. As a result, this leads to a lack of oral health care and neglect which aggravates any existing periodontal disease.

Few studies have reported varying degrees of association between periodontitis and cognitive decline/dementia, with some studies showing a stronger association than others. The study by Sparks Stein et al. (2012) found that individuals with severe periodontitis were more likely to develop dementia and Alzheimer's disease over a 10-

year follow-up period than those without periodontitis.[26] However, the article did not report the exact strength of the association. Tzeng et al. conducted a study that revealed that patients who had periodontal disease for at least eight years exhibited a significantly higher risk of developing dementia and neurodegenerative disease in comparison with healthy groups.[21]

Overall, our study suggests that there may be an association between periodontitis and cognitive decline, including Alzheimer's. However, more research is needed to fully understand the relationship between the two conditions and determine the association's nature.

Periodontal disease is connected with a higher risk of Alzheimer's disease and mild cognitive impairment within the parameters of the publications that were taken into consideration. Another study reported a link between a higher risk of mild cognitive impairment, the number of remaining teeth, and a low MMSE score.[27] Possible scientific causes for this connection were also discovered, including periodontal disease, genetic risk factors, and the degeneration of periodontal mechanoreceptors. The length of the edentulous phase was similarly related to cognitive function, and participants with edentulous conditions were likelier to have low MMSE scores. Tooth loss or periodontal disease may have an additive effect on cognitive performance because the CPI code, a measure of periodontal tissue's current health, did not demonstrate a significant link with it.[27] This cross-sectional study lacked information regarding the timing and causes of tooth loss and the lack of an APOE genotyping study. More research is required to understand further the origins of the connection between tooth loss and cognitive impairment. It reported an association between a higher risk of mild cognitive impairment, a reduction in remaining teeth, and a low MMSE score.[27]

However, the study has several limitations, such as the absence of APOE genotyping and information on the timing and reasons for tooth loss. Another study indicates that moderate and severe periodontitis elevates the risk of dementia and that there is an association between periodontitis and cognitive impairment.[28] However, more high-quality cohort studies are needed to validate this association and determine the forms and severity of dementia. Additionally, the study is constrained by the clinical heterogeneity of the included studies, which could influence the accuracy of the results. Periodontal disease, genetic risk factors, and the deterioration of periodontal mechanoreceptors are potential contributors to this association.[28] The previous studies indicate a link between cognitive decline and periodontal disease. To completely comprehend this relationship, more investigation is required into the types and severity of dementia that are linked to periodontitis, as well as the precise processes through which periodontal disease and tooth loss impair cognitive function.

Additionally, it discusses the typical dental treatment reasons for these individuals as well as the negative consequences of dementia medication. The study underlines the difficulties in treating dementia patients with dental care, particularly given their incapacity to maintain good oral hygiene and communicate clearly.

According to recent studies, APP mutations may enhance the likelihood of cells dying in response to injury and cause beta-amyloid formation.[29,30] Neurons can be harmed by infection, trauma, and pollution, which raises the risk of Alzheimer's disease. Pathogenic microorganisms that produce chronic periodontitis can be a factor in any illness.[30] The goal of the Alzheimer's disease prevention strategy is to optimize the oral microbial flora by reducing systemic inflammation. This can be done by consuming practicing good dental hygiene, avoiding sugar, exercising regularly, consuming moderate amounts of alcohol, limiting exposure to pollution, avoiding trauma, and getting enough sleep.[30]

According to another study, nursing home residents with better oral health also tend to have higher oral health-related quality of life. When compared to older people living in the community, nursing home residents were shown to have lower OHRQoL. It has been determined that significant factors impacting OHRQoL include the presence of natural teeth and prosthetic restorations.[31] Reduced chewing effectiveness and social and psychological issues impacting OHRQoL have been linked to poorly fitting and less retentive dentures. Treatment requirements connected to dentures considerably impacted OHRCoL.[31] This study indicated a higher prevalence of treatment needs compared to earlier research. According to the study, better OHRQoL is positively correlated with increasing age. OHRQoL was similar for those with dementia and those without it. However, the study had a dropout rate of about 40%, which suggests that conclusion should be taken with caution.[31]

Reviewing the articles, we have found that most authors have agreed on a correlation between dementia and periodontal disease. A different cross-sectional study, on the contrary, stated that periodontal disease, regardless of the severity, is not linked with the decline in cognitive functions and vice versa.[17] Nonetheless, it has been

thought that due to cognitive impairment, dementia patients have lost the capability to maintain their oral hygiene and thus, as a result, have developed periodontal disease, as the correlation was said to be unclear.[17]

The belief is that the behavioral changes linked with the onset of dementia, specifically worse levels of oral hygiene, are the primary cause of an individual with Alzheimer being more susceptible to periodontal disease.[20] Correspondingly, oral hygiene should be carefully taken care of, and all measures should be applied to prevent the development of periodontitis.

Furthermore, few studies have proposed periodontal disease and dementia are linked. While periodontal disease affects the tooth-supporting tissues and the host's immunological responses, eventually leading to tooth loss, Alzheimer's disease (AD) is distinguished by two histologic diagnostic markers at autopsy: extra-neuronal amyloid plaques and intraneuronal neurofibrillary tangles.[22,32,33]

Neuronal and synaptic loss, neuroinflammation, and cerebral amyloid angiopathy are further lesions that do not play a role in the neuropathologic diagnosis of AD but are essential in understanding the disease's etiology and development. The long-held belief that persons with dementia or AD-associated dementia have a higher frequency of longitudinally developing periodontitis than those who do not is a barrier to understanding the link between AD and Periodontitis. This viewpoint assumes that Alzheimer's disease-related dementia is a risk factor for periodontal disease.[34.] Though the articles used in our current study are from 2016 till the present, only a few articles that recorded moderate results of significance could be found. These focused-on cohort studies, and clinical findings were more hypothetical [35-37].

However, the present study also possesses some limitations that should be noted. There are no concrete findings that associate a relationship between dementia and periodontitis. Most studies are based on hypothetical inference, and though few studies have reported significant findings, more clinical trials and longitudinal studies must be done to corroborate these results.

5. Conclusion

From the available literature, it can be inferred that periodontitis and incident dementia could be positively correlated. Several studies mentioned in our present study have reported that individuals who have periodontitis carry a higher risk of developing dementia compared to non-periodontitis patients. Though the exact mechanism underlying this association remains unknown and not yet fully understood, it is believed that the chronic inflammation and bacterial infection that is associated with periodontitis may contribute to the development and progression of dementia. This can happen by transgressing the blood-brain barrier. Other mechanisms have also been proposed as possible ways to explain the correlation. Dementia can also be a factor that aids in the development of gum disease due to the neglect of oral health that comes with the forgetful nature of those with dementia. Regardless of what information is known today, further studies are needed to confirm this association and determine the exact mechanisms involved. It is also important to note that periodontitis is a complex disease with various confounding factors, and it is doubtful to be the sole cause of dementia. Nonetheless, maintaining good oral hygiene and seeking prompt treatment for periodontitis may have potential benefits in reducing the risk of incident dementia.

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions: All authors contributed to the study conception and designs Sudhir Rama Varma: Conceptualization, methodology, validation, investigation, resources, writing original draft and supervision. Hala Salman; Yara Sultan Khairi Sultan Sultan; Manar Eyad Adel Khanfar; Asok Mathew; Jayaraj Narayanan; Ruba Odeh & Pradeep Kumar Yadalam: Methodology, investigation, resources, writing-review and editing.

References

1. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Periodontol 2018 ;89 Suppl 1:S159-S172. doi: 10.1002/JPER.18-0006.
2. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim) 2017; 11(2):72-80.
3. Kwon T, Lamster IB, Levin L. Current Concepts in the Management of Periodontitis. Int Dent J. (2021) 71(6):462-476. doi: 10.1111/idj.12630
4. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey B.L.; Papapanou PN, Sanz M,

Tonetti MS. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol. (2018) 6 (89) Suppl 1:S1-S8. doi: 10.1002/JPER.18-0157

5. Preshaw PM. Detection and diagnosis of periodontal conditions amenable to prevention. BMC Oral Health. (2015) 15 (Suppl 1):S5. doi: 10.1186/1472-6831-15-S1-S5.
6. Duong, S, Patel T, Chang F. Dementia: What pharmacists need to know. Can Pharm J (Ott). (2017) 150(2):118-129. doi: 10.1177/1715163517690745.
7. Bhuyan R, Bhuyan SK, Mohanty JN, Das S, Juliana N, Juliana IF. Periodontitis and Its Inflammatory Changes Linked to Various Systemic Diseases: A Review of Its Underlying Mechanisms. Biomedicines. 2022;10(10):2659. doi: 10.3390/biomedicines10102659
8. Cunningham EL, McGuinness B, Herron B, Passmore AP. Dementia. Ulster Med J. 2015;84(2):79-87.
9. Puppala GK, Gorthi SP, Chandran V, Gundabolu G. Frontotemporal Dementia - Current Concepts. Neurol India 2021; 69(5):1144-1152. doi: 10.4103/0028-3886.329593
10. Younes K, Miller BL. Neuropsychiatric Aspects of Frontotemporal Dementia. Psychiatr Clin North Am 2020; 43 (2):345-360. doi: 10.1016/j.psc.2020.02.005
11. Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin 2017; 35 (2):339-374. doi: 10.1016/j.ncl.2017. 01.008.
12. Emmady PD, Schoo C, & Tadi P. (2022). Major Neurocognitive Disorder (Dementia). In StatPearls [Internet]. StatPearls Publishing
13. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA 2019; 22:322(16):1589-1599. doi: 10.1001/jama.2019.4782
14. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011; 1(1):a006189. doi: 10.1101/cshperspect.a006189
15. Lee YT, Lee HC, Hu CJ, Huang LK, Chao SP, Lin CP, Su EC, Lee YC, Chen CC. Periodontitis as a Modifiable Risk Factor for Dementia: A Nationwide Population-Based Cohort Study. J Am Geriatr Soc 2017;65(2):301-305. doi: 10.1111/jgs.14449
16. Chen CK, Wu YT, Chang YC. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther 2017; 9(1):56. doi: 10.1186/s13195-017-0282-6.
17. Laugisch O, Johnen A, Buergin W, Eick S, Ehmke B, Duning T, Sculean A. Oral and Periodontal Health in Patients with Alzheimer's Disease and Other Forms of Dementia - A Cross-sectional Pilot Study. Oral Health Prev Dent 2021;19(1):255-261. doi: 10.3290/j.ohpd.b1248937
18. Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY, Kantarci A, Wei JC. Dementia and the Risk of Periodontitis: A Population-Based Cohort Study. J Dent Res 2022; 101(3):270-277. doi: 10.1177/00220345211037220.
19. Holmer J, Eriksdotter M, Häbel H, Hed M I, Jonsson A, Pussinen PJ, Garcia-Ptacek S, Jansson L, Sandborgh-Englund G, Buhlin K. Periodontal conditions and incident dementia: A nationwide Swedish cohort study. J Periodontol 2022; 93(9):1378-1386. doi: 10.1002/JPER.21-0518
20. Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, Fuller J, Ibbett P, Raybould R, Thomas R, Puenter U, Teeling J, Perry VH, Holmes C. Periodontitis and Cognitive Decline in Alzheimer's Disease. PLoS One 2016; 11(3):e0151081.doi: 10.1371/journal.pone.0151081.
21. Tzeng NS, Chung CH, Yeh CB, Huang RY, Yuh DY, Huang SY, Lu RB, Chang HA, Kao YC, Chiang WS, Chou YC, Chien WC. Are Chronic Periodontitis and Gingivitis Associated with Dementia? A Nationwide, Retrospective, Matched-Cohort Study in Taiwan. Neuroepidemiology 2016;47(2):82-93. doi: 10.1159/000449166.
22. Dioguardi M, Crincoli V, Laino L, Alovisi M, Sovereto D, Mastrangelo F, Russo LL, Muzio LL. The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review. J Clin Med 2020; 9(2):495. doi: 10.3390/jcm9020495.
23. Shi T, Wang J, Dong J, Hu P, Guo Q. Periodontopathogens Porphyromonas gingivalis and Fusobacterium nucleatum and Their Roles in the Progression of Respiratory Diseases. Pathogens 2023;12(9):1110. doi: 10.3390/pathogens1209111
24. Costa MJF, de Araújo IDT, da Rocha Alves L, da Silva RL, Dos Santos Calderon P, Borges BCD, de Aquino Martins

ARL, de Vasconcelos Gurgel BC, Lins RDAU. Relationship of Porphyromonas gingivalis and Alzheimer's disease: a systematic review of pre-clinical studies. Clin Oral Investig 2021; 25(3):797-806. doi: 10.1007/s00784-020-03764-w.

25. Noble JM, Scarmeas N, Celenti RS, Elkind MS, Wright CB, Schupf N, Papapanou PN. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS One 2014; 9(12):e114959. doi: 10.1371/journal.pone.0114959
26. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, Dawson. D 3rd. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement 2012; 8(3):196-203. doi: 10.1016/j.jalz.2011.04.006.
27. Dhingra AK, Chopra B, Jain A, Chaudhary J. Imidazole: multi-targeted therapeutic leads for the management of Alzheimer's disease. Mini Reviews in Medicinal Chemistry 2022; 22(10): 1352-73.doi:10.2174/1389557522666220104152141.
28. Okamoto N, Morikawa M, Okamoto K. et al. Relationship of tooth loss to mild memory impairment and cognitive impairment: findings from the fujiwara-kyo study. Behav Brain Funct 2010; 6 (77). doi: 10.1186/1744-9081-6-77.
29. Chiappelli F, Bauer J, Spackman S, Prolo P, Edgerton M, Armenian C, Dickmeyer J, Harper S. Dental needs of the elderly in the 21st century. Gen Dent 2002; 50(4):358-63.
30. Collyer TA, Murray AM, Woods RL, Storey E, Chong TT, Ryan J, Orchard SG, Brodtmann A, Srikanth VK, Shah RC, Callisaya ML. Association of Dual Decline in Cognition and Gait Speed with Risk of Dementia in Older Adults. JAMA Netw Open 2022; 5(5): e2214647. doi:10.1001/jamanetworkopen.2022.14647.
31. Klotz AL, Hassel AJ, Schröder J, Rammelsberg P, Zenthöfer A. Oral health-related quality of life and prosthetic status of nursing home residents with or without dementia. Clin Interv Aging 2017; 12:659-665. doi: 10.2147/CIA.S125128.
32. Liccardo D, Marzano F, Carraturo F, Guida M, Femminella GD, Bencivenga L, Agrimi J, Addonizio A, Melino I, Valletta A, Rengo C, Ferrara N, Rengo G, Cannavo A. Potential Bidirectional Relationship Between Periodontitis and Alzheimer's Disease. Front Physiol 2020; 11(683). doi: 10.3389/fphys.2020.00683.
33. Jungbauer G, Stähli A, Zhu X, Auber A L, Sculean A, Eick S. Periodontal microorganisms and Alzheimer disease - A causative relationship? Periodontol 2000 2022; 89 (1):59-82. doi: 10.1111/prd.12429.
34. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol 2021; 21(7):426-440. doi: 10.1038/s41577-020-00488-6.
35. Nedumaran N, Ramamurthy J. Evaluation of C-reactive Protein and Interleukin-6 Levels in Periodontitis Patients: An Experimental Study. World. 2024 Sep;15(9):773.
36. Kumar KM, Varghese S, Jayaraman S, Ganapathy D, Karobari MI. Comparative Evaluation of Gingival Crevicular Fluid Sulfiredoxin Levels in Patients with Periodontitis Prior and after Periodontal Therapy: A Prospective Clinical Trial. World. 2024 May;15(5):395.
37. Arumuganainar D, Krishna Naik V, Ramadoss R, Balasundaram A, Victor DJ. Evaluation of CD44 antigen in type 2 diabetic patients with periodontitis: An immunohistochemical study. Dental and Medical Problems. 2024;61(2):225-31.