Journal of the California Dental Association

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ucda20

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To cite this article: Lauren Berard & Miou Zhou (2024) The Impact of Edentulism and Periodontitis on Cognition, Journal of the California Dental Association, 52:1, 2289696, DOI: 10.1080/19424396.2023.2289696

To link to this article: https://doi.org/10.1080/19424396.2023.2289696

Published online: 31 Dec 2023.

JOURNAL OF THE CALIFORNIA DENTAL ASSOCIATION
2024, VOL. 52, NO. 1, 2289696
https://doi.org/10.1080/19424396.2023.2289696

The Impact of Edentulism and Periodontitis on Cognition

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ABSTRACT

Background: Masticatory dysfunction and periodontitis are independently linked to cognitive decline. This article aims to highlight the individual and common roles that periodontitis and tooth loss play in cognition. Specifically, we aim to summarize the behavioral effects on learning and memory that result from each pathology, explore mechanisms that may explain these effects, and review the commonalities between the two.

Methods: The PubMed database was used to implement searches of relevant clinical studies on the correlations between edentulism and cognitive decline as well as periodontitis and cognitive decline. Additional searches were done to investigate animal studies that provided behavioral and mechanistic findings to explain these relationships. The clinical and animal studies were summarized and analyzed in this review to reveal the commonalities and differences between these comorbidities.

Results: The clinical studies summarized in this review report significant correlations between both periodontitis and partial/full edentulism with cognitive decline. The behavioral and mechanistic findings in animal model studies are summarized to support the cognitive effects. Both in vivo and in vitro studies have identified key pathogens, molecules, or cellular pathways that contribute to a more comprehensive understanding of the pathophysiologic processes that link different types of oral disease to cognitive brain function.

Practical Implications: The correlation between oral disease and cognitive impairment has been well established but further exploration of the molecular and cellular mechanisms underlying these relationships can provide therapeutic implications and stress the importance of oral health and preventative care.

Abbreviations

AD: Alzheimer's Disease; **AFT**: animal fluency test; **BOP**: bleeding on probing; **BGI**: biofilm-gingival interface; **CAL**: clinical attachment loss; **CDT**: clock drawing test; **CERAD**: Consortium to Establish a Registry for Alzheimer's Disease word learning test; **CNS**: central nervous system; **CP**: chronic periodontitis; **DSST**: digital substitution test; **IL-1β**: interleukin 1β; **IL-6**: interleukin 6; **LC**: locus coeruleus; **MMP**: matrix metalloproteinase; **MMSE**: Mini-Mental Status Examination; **MoCA**: Montreal Cognitive Assessment; **MRI**: Magnetic Resonance Imaging; **MWM**: Morris water maze; **NO**: nitric oxide; **PDL**: periodontal ligament; **PISA**: periodontal inflamed surface area; **PP2A**: protein phosphatase 2A; **RABL**: radiographic alveolar bone loss; **RANKL**: Receptor activator of nuclear factor-κB ligand; **SCT**: spatial copying task; **TLR4**: toll-like receptor 4; **TNF-α**: tumor necrosis factor α; **Vmes**: Mesencephalic trigeminal nucleus.

ARTICLE HISTORY
Received 1 June 2023
Revised 29 October 2023
Accepted 27 November 2023

KEYWORDS
Edentulism; periodontitis; cognition; mastication; learning and memory; Alzheimer's disease; cognitive decline

Introduction

The oral cavity is a critical component of the body that allows for many functions fundamental to survival and quality of life. Oral health is multifaceted and contributes to physical, social, and psychological well-being.[1] Therefore, many oral diseases have become among the most prevalent diseases in the world and are connected to major systemic comorbidities. This contributes to the necessity for a more thorough understanding of oral disease processes and their connections to other major systems of the body such as the brain's cognitive function. Periodontitis, an inflammatory disease that results in the degradation of the periodontium surrounding teeth, is associated with diabetes, obesity, rheumatoid arthritis, cancers, respiratory diseases, and cognitive disorders, especially Alzheimer's disease (AD).[2] Similarly, edentulism, considered "the ultimate marker of disease burden for oral health", has been linked to many of the same comorbidities with the addition of malnutrition.[3,4] Out of these, the effects of periodontitis and edentulism on cognition have become a popular topic of interest.

A correlation between oral disease and cognitive decline has been well established. One of the key pathogens present in periodontitis, *Porphyromonas gingivalis*, not only has direct effects on the brain but produces virulence factors that are found to be neurotoxic and have damaging effects on blood-brain barrier epithelial cells. Inhibition of these virulence factors has been found to slow down the progression of cognitive impairment in mice models.[5] Additionally, specific inflammatory mediators have been identified in the mechanism linking periodontal disease to neurodegeneration. Since periodontitis

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is one of the most common causes of tooth loss, it is difficult to treat periodontitis and edentulism as mutually exclusive events within the topic of oral diseases. With that being said, many early studies highlight the overall correlation between oral health and cognition without distinguishing between the two separate relationships that periodontal inflammation and lack of masticatory function possess with cognition. Although periodontitis and edentulism may share similar behavioral effects on cognition, it is important to distinguish the individual roles that each of these different etiologies plays in cognitive decline and the specific mechanisms by which they do so. Namely, the loss of somatosensory feedback and diminished cerebral blood flow inherent to edentulism regardless of a former periodontitis diagnosis is linked to the progression of cognitive deficits. Most of the recent literature investigates the individual roles that these two oral diseases play in cognitive decline over time. In summary, this review provides a brief overview of both the individual and common effects that periodontal inflammation and loss of masticatory function have on the progression of cognitive impairment. A thorough understanding of both the distinct and common underlying pathophysiologic mechanisms that connect periodontitis and edentulism to cognitive decline could contribute to therapeutic advances that slow the progression of oral disease-associated dementia.

Edentulism and Cognition

Mastication and Edentulism

Mastication is a coordinated multiplex process that includes both afferent and efferent components. Periodontal mechanoreceptors present in the periodontium, masticatory muscles, ligaments, and joint capsules play a key role in providing feedback to the central nervous system (CNS). These special afferent signals are required to control the proper motor output involved in chewing.[5] Specifically, mechanoreceptors are critical in important reflexes involved in chewing that protect one from traumatizing occlusal forces.[5] For example, if one bites into something hard, proprioceptive signals communicate with the trigeminal motor nucleus to inhibit jaw-closing muscles and activate jaw-opening muscles.[6] Many of these proprioceptor nerve endings are located in the periodontal ligaments (PDL) that surround each tooth. Therefore, when patients undergo tooth loss or become edentulous, they lose a portion of this proprioceptive ability.[7]

Edentulism refers to the complete loss of all teeth and is recognized as "the ultimate marker of disease burden for oral health".[3] There are many etiologies that contribute to tooth loss including dental caries, impactions, and trauma.[8] However, one of the most common causes of tooth loss in adults is periodontitis.[9] Periodontitis is an inflammatory disease that leads to the destruction of the periodontium which consists of the ligaments, cementum, and alveolar bone surrounding teeth.[10] Without these supporting structures, teeth can become mobile, and the prognosis of the dentition is dramatically decreased. Both the tooth loss secondary to periodontitis as well as the chronic inflammation of the disease serve as two separate roles by which the brain can be pathologically affected.

When one becomes fully edentulous, this completely alters their masticatory function. The lack of nutrition in soft diets that edentulous patients are confined to contributes to not only overall health decline but also cognitive deficits as well.[11–13] Those with decreased masticatory function have a lower intake of high-fiber foods, vegetables, fruits, and carotene in addition to a higher intake of saturated fats and cholesterol. This change in diet contributes to the cardiovascular disease and gastrointestinal disorders that edentulous patients are at increased risk for.[11] Another train of thought looks at the loss of somatosensory feedback to the CNS that occurs when one becomes edentulous and how cognition is affected. Although many systemic issues are associated with loss of masticatory function, what is of particular interest here is the correlation with cognitive decline.

Masticatory Function and Cognition

Clinical Studies of Edentulism and Cognition

Many studies have shown that tooth loss is associated with cognitive decline.[14–16] A 13-year-long study done within a population of older Chinese adults found that cognitive decline increased with each less tooth present in the mouth.[17] Cognition was assessed via a Mini-Mental Status Examination (MMSE). The MMSE includes observations that test many cognitive functions such as memory, learning, and attention.[18] Statistical analysis showed that for each patient that had one more tooth, an increase in MMSE score was observed. This implied that a higher number of teeth was significantly correlated with higher cognitive ability. Time was also considered and having more teeth was also associated with a slower rate of cognitive decline over a given amount of time.[17] In a cross-sectional study done in Japan, community residents 65 or older were examined and showed that tooth loss was associated with mild memory impairment.[19] In a group aged 60 years or older in rural Ecuador, those with less than 10 teeth scored significantly lower on the Montreal Cognitive Assessment (MoCA), which tests one's ability in language, short-term memory, attention, calculation, and visuospatial-executive functions.[20] These studies support that tooth loss is associated with cognitive decline.

Although most longitudinal studies report that edentulism is significantly correlated with poor cognitive function, some studies have reported contradictory findings. For example, no significant association between edentulism and cognitive decline was reported in a middle-aged population.[21] In this 4-year-long study, while there was a linear relationship found between edentulism and poor cognitive function in the elderly participants, there was no significant association between baseline edentulism and cognitive decline in the 45–59 middle-aged population.[21] The age difference and the data collection method could serve as a potential explanation for this contradictory finding. In this study, edentulism was not measured clinically but by verbally asking the participants whether he/she had lost all of their teeth or not. In addition, the length of time since the participant became fully edentulous was not considered. Since younger participants had most likely been edentulous for a shorter amount of time than those older than 59, the duration of edentulism may serve as the confounding variable rather than age.

Animal Studies of Edentulism and Cognition

Besides clinical studies, the specific effects that tooth loss has on behavior, learning, and memory have been widely explored using animal models. Different types of maze tests can be implemented to observe the cognitive behavioral effects in mice with tooth loss. In a group of aged mice that had undergone maxillary molar extraction, working memory was negatively affected in the Y-maze test, and in contrast, there was no significant difference between the young extraction and control groups.[22] This implies that edentulism may have a larger effect on cognition in older ages. Motor function was also examined using the rotor-rod test, in which no difference was observed between the aged tooth extraction group and the aged control group, suggesting that tooth extraction in aging individuals may more impact cognition than motor function. In addition to behavioral changes, the molecular changes in the brains of the mice were measured as well. Decreased levels of *Bdnf*, *RBfox3*, and *Fos* and increased levels of *Cdkn2a* and *Aif1* were observed in the hippocampus and hypothalamus of aged mice with extracted maxillary molars. *Bdnf*, *RBfox3*, and *Fos* are genes that have important roles in neuronal growth, differentiation, maturation, and plasticity. *Cdkn2a* is an indicator of senescence while *Aif1* is an indicator of microglial activation.[22] These molecular findings suggest that the mechanism underlying the effects of edentulism on cognition may include the induction of neuroinflammation and neuronal dysfunction in the hypothalamus and hippocampus with aging.

Many studies have attributed hippocampal degeneration seen in mice with impaired masticatory function to stress and the rise of plasma corticosterone levels. Plasma corticosterone levels were found to be increased in mice that underwent early tooth loss and were suspected to cause suppression of synaptophysin in the hippocampus.[23] Synaptophysin is a protein found in neuron presynaptic vesicles.[24] This suppression of synaptic protein in the hippocampus caused by increased stress hormone levels supported the behavioral observation that compared to control mice, mice with early tooth loss took a significantly longer time to complete a Morris water maze (MWM) test, a task widely used to measure spatial learning and memory in rodents.[23]

The correlation between edentulism and poor cognition may also be explained via effects on neurogenesis.[25] A decrease in neuronal progenitor cells was found in a group of mice fed a soft diet in comparison to a control group. These decreased levels correlated with decreased levels of neurons in the dentate gyrus, a portion of the hippocampus responsible for receiving sensory input. BDNF, a regulator of neuronal stem cells, was also found to decrease in mice fed a soft diet.[25] Both BDNF and neurogenesis are critically involved in synaptic plasticity learning and memory.[26] Therefore, the correlation between lack of masticatory function and memory dysfunction may be explained via a mechanism that results in impairment of neurogenesis and its regulation.

Another pathophysiological mechanism proposed to explain the association between partial/full edentulism and cognitive impairment is by vascular changes in the brain that occur when masticatory function is lost. Mastication increases cerebral blood flow and lack of blood flow to tissues in the brain due to the loss of mastication could contribute to cognitive decline over time.[27] Rats that have undergone tooth loss were found to experience similar cognitive impairment to those with chronic cerebral ischemia. Additionally, concentrations of nitric oxide (NO) in the hippocampus were found to be similarly elevated in both edentulous rats and those with chronic cerebral ischemia.[28] Since high levels of NO are produced as a direct effect of ischemia and are associated with neurotoxicity in the brain,[29] the presence of it in excess in edentulous rats suggests that NO and its synthase play a role in causing cognitive impairment.[28]

In addition to increased plasma corticosterone levels and impaired neurogenesis and blood flow, proprioceptor degeneration in the edentulous may play a role in amyloid-β (Aβ) accumulation in the brain, a pathophysiologic process that characterizes AD.[30] One of the areas in the brain that is suspected to be first affected by Aβ accumulation is the locus coeruleus (LC).[31] The LC is a nucleus in the pons that plays a role in the production of dopamine and is located near the mesencephalic trigeminal nucleus (Vmes), a brain region where the cell bodies of first-order proprioceptors in the head and neck region reside.[32] In 4-month-old triple transgenic (3×Tg)-AD mice, aggregated Aβ was found in Vmes neurons. Tooth extraction in these mice resulted in neuronal death in the Vmes, release of cytotoxic Aβ, and increase in CD86 immunoreactive microglia, which together lead to the damage of the LC. Using fluorogold labeling, it was found that destruction in the LC caused a reduction in neurons in the CA1 and CA3 regions of the hippocampus. Impaired spatial learning and memory were observed in 5-month-old 3×Tg-AD mice 1 month after tooth extraction, similar to the memory deficits in control 8-month-old 3×Tg-AD mice, suggesting that tooth extraction could lead to an earlier shift to dementia-like behavior in individuals expressing AD risk genes.[30] These results support that the Vmes may be the key initiator in downstream hippocampal damage and cognitive decline after tooth extraction in the pre-dementia stage, and the neurodegeneration spread from the Vmes, LC, to the hippocampus, accelerates the onset of dementia.

In addition to experiments analyzing the effects of edentulism, one study compared changes in edentulous mice and mice that underwent molar extraction followed by prosthesis placement.[33] Using a radial arm maze test which measures spatial working and reference memory, the denture mice made more errors than the control group, and the edentulous mice consistently made even more errors than both the control group and denture mice. Histological analysis revealed that hippocampal CA3 pyramidal cell counts were much lower in the denture-wearing and edentulous mice compared to the control group, and the edentulous group showed a lower number of pyramidal cells in the CA1 region of the hippocampus compared to the denture-wearing group.[33] These results imply that though complete edentulism appears to have a more detrimental effect on cognition than tooth loss followed by restoration of occlusal support, denture wearing still impairs cognition compared to those with natural dentition.

Periodontal Inflammation and Cognition

Periodontitis

The pathogenesis of chronic periodontitis (CP) includes a disruption in the microbiome that provokes dysregulated inflammatory processes resulting in the destruction of the periodontium. It is not one bacterial species that causes periodontitis but rather the dysbiosis of the oral microbiome.[34] Receptor activator of nuclear factor-κB ligand (RANKL) is produced by activated T and B lymphocytes, and osteoblasts in the periodontium. RANKL binds to RANK on immature osteoclasts, activating maturation and eventually resorption of bone.[35] Matrix metalloproteinases (MMP) are present in gingival fibroblasts and activated by many molecules such as interleukins, reactive oxygen species, and lipopolysaccharides of bacterial cells.[35] MMPs are involved in the breakdown of periodontal soft tissue and the overall resulting clinical attachment loss. Clinical attachment loss (CAL) refers to the loss of ligamentous attachment between a tooth and its surrounding connective tissue. CAL serves as a measurement taken for periodontal disease diagnoses and prognoses.[36]

While dental biofilm is the initiator of periodontitis in most cases, many local and systemic factors contribute to increased risk and overall development of the disease as well. Tobacco use, diabetes mellitus, obesity, and osteoporosis are among a few of the most prominent risk factors associated with periodontitis.[37] While we focus on reviewing the role of periodontitis within the development of dementia, it is important to note the well-established correlations between periodontitis and many systemic conditions such as cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease, and nonalcoholic fatty liver disease.[38] With that being said, a more thorough understanding of the relationship between periodontitis and cognitive decline may contribute to the already abundant list of systemic comorbidities that periodontal health is connected to.

Periodontitis and Cognition

Though periodontitis can lead to tooth loss which has detrimental effects on cognition, the inflammatory nature of the disease regardless of eventual tooth loss perhaps plays a more defined role in the development of neurodegeneration. Both molecular and behavioral studies support inflammatory-driven mechanisms underlying the association between periodontitis and cognitive decline. Many studies have reported a positive correlation between periodontal disease and increased cytokine levels in the brain tissues of mice.[39,40] This can be well understood due to the inducing effect that systemic inflammation has on cytokine levels and further neuroinflammation present in AD.[41–43] Significant evidence points to the role of *Porphyromonas gingivalis* in proposed mechanisms. While the net disruption within the overall oral microbiome is the etiology of periodontal disease, *P. gingivalis* is one of the keystone pathogens prevalent in chronic periodontitis that may have direct neurotoxic effects.[5]

Clinical Studies of Periodontitis and Cognition

Epidemiological Studies. Though many epidemiological studies have illuminated the strong correlation between periodontitis and cognitive impairment, a crude overview of seven key studies is summarized here. The following cohort studies reveal that the incidence of severe periodontitis is associated with some form of cognitive impairment.[44,45] In a study done among elderly Koreans, those with a history of periodontitis measured according to radiographic alveolar bone loss (RABL) were assessed using the MMSE. After controlling for systemic confounding variables, those with a history of periodontitis were found to be about two times as likely to show some degree of cognitive impairment. However, there was no significant dose-dependent relationship between the severity of periodontitis and cognitive impairment, and periodontal status was only measured according to RABL.[45]

In a similar 5-year-long cohort study that also assessed cognitive function using the MMSE, dentate individuals were classified as having "severe" or "not-severe" periodontitis after measuring probing pocket depths, gingival recession, and bleeding on probing (BOP) according to both the Centers for Disease Control/American Academy of Periodontology (CDC/AAP) and European Workshop in Periodontology Group C (EWP) definitions.[44] They were also further divided according to the level of periodontal inflammation by using calculation of periodontal inflamed surface area (PISA).[45] Participants' cognitive function was assessed at 1, 2, 3, and 5 years after original periodontal assessment using the MMSE and neurological exams conducted by neurologists with cognitive diagnoses made according to the DSM-0 V criteria. Severe periodontitis according to either definition was found to be significantly associated with incident mild cognitive impairment, and periodontal inflammation assessed using PISA was also significantly associated with an increased odds ratio for mild cognitive impairment.[44] The more robust periodontal evaluation and definition of periodontitis used in this study strengthen similar findings. A Swedish cohort study published in 2018 suggested a more causal relationship between a history of periodontitis and cognitive decline since only individuals who scored higher than 25 on the MMSE at baseline were included.[46] This is because those with lower cognitive function at baseline may exhibit changes that affect contributing factors like oral hygiene as impairment progresses. The population sample consisted of 715 participants evaluated at baseline and at a 6-year follow-up. Those with a history of periodontitis, defined as RABL on more than 30% of sites, showed a significant association with incident cognitive decline. In this case, cognitive decline was defined as a deduction of 3 points or more at the 6-year follow-up.[46]

The decline in cognitive function associated with periodontitis is not only measured using the MMSE and is also supported when using various means to assess cognitive function. In 2022, a cross-sectional study used the National Health and Nutrition Survey for 3 years to assess the relationship between periodontitis and cognitive performance. It was found that out of 1,883 subjects aged 60 years old or above, those with higher staged periodontitis (Stage III and IV) performed lower on cognitive assessments such as a Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word learning test, animal fluency test (AFT), and digital substitution test (DSST).[47] The CERAD test is used to evaluate immediate and delayed recall by asking the participant to remember words in three

immediate trials and one delayed trial. The AFT examines verbal fluency by scoring patients according to their ability to name animals within one minute. The DSST assesses higher levels of cognitive ability and speed as participants are instructed to match symbols paired with numbers within two minutes.[47] Interestingly, Li et al. found that those with Stage III periodontitis scored lower on all cognitive assessments while those diagnosed with Stage IV did not show a statistically significant association with decreased animal fluency test scores.

An additional question to explore is how periodontitis correlates with more severe types of dementia rather than cognitive impairment. In 2019, a 10-year-long retrospective cohort study investigated the risk for general dementia and AD within a population from the Korean National Health Insurance Service-Health Screening Cohort.[48] Using a final population sample of 262, 349 participants, CP was diagnosed using the *International Classification of Diseases, Tenth Revision* in patients who had a history of CP treatment. Participants were considered to have dementia if prescribed drugs according to a diagnosis of AD. It was demonstrated that patients with chronic periodontitis had a statistically significant increased risk of general dementia and AD.[48] In a much shorter observational study with a small sample size of 52 participants, baseline periodontitis was significantly associated with decreased Alzheimer's Disease Assessment Scale (ASAS-cog) scores in AD patients.[49] These results indicate that periodontitis is correlated with a marked progression of dementia-associated decline in cognitive function. What is also interesting about this study is that there was no significant correlation between decreasing MMSE scores and periodontitis over time, which has been demonstrated in many other longitudinal studies.[49] The limitations here may be the sample size and length of observation being 6 months.

Lastly, there are similar findings reported using varying study designs. A 2015 case-control study implemented in Spain reported a statistically significant association between clinical attachment loss and cognitive impairment after controlling for confounding variables such as sex, age, education level, and hyperlipidemia.[50] The adults included in this study were reportedly dentate and assessed on CAL, tooth loss, probing depths, bleeding index, and oral hygiene regimen. Periodontitis was defined by attachment loss and cognitive impairment was diagnosed using both neurologic exams and the Phototest. The Phototest is a cognitive evaluation implemented in clinical settings that does not require participants to be fully literate.[50] The risk of cognitive impairment was three times greater in participants with severe periodontitis than those with none or mild periodontitis. Though this study design cannot highlight a cause-and-effect relationship, it contributes to the strength of correlation supported by varying study designs. With that being said, the statistical evidence supporting a strong correlation between periodontitis and varying levels of cognitive impairment is supported by an extensive body of evidence that has been widely developed over the past decade. The consistent statistical significance given a multitude of varying methods used to assess periodontal disease and cognitive function indicates the strength of this evidence. Additional development of clinical in vitro studies and animal studies would not only strengthen the proposed causal relationship between these two comorbidities but also illuminate the mechanisms underlying this association.

Mechanistic Studies. Furthermore, clinical studies have also supported a distinct association between periodontitis-specific pathogens and cognitive impairment. For example, in a 2020 cohort study, 20 patients diagnosed with primary degenerative dementia via Magnetic Resonance Imaging (MRI) and routine laboratory tests were examined. In five of the patients with clinical signs of higher-staged periodontitis, strains of *T. denticola*, *T. forsythia*, and *P. gingivalis* were found and these participants had the lowest MMSE and clock drawing test (CDT) scores.[51] More specifically, a main finding in this study was the significant correlation between *P. gingivalis* levels found in saliva and lower MMSE scores. This suggests that in humans with high-stage periodontitis, periodontal pathogens, especially *P. gingivalis*, may directly contribute to the molecular and cellular changes underlying the progression of cognitive defects.

Multiple mechanistic clinical studies support this as well. Gingipains are unique cysteine proteases secreted by *P. gingivalis* and have been identified as periodontopathic virulence factors in AD.[52] Dominy et al. provided evidence that gingipains along with *P. gingivalis* were found in postmortem AD brains and correlated with AD diagnoses and tau load in humans, a key hallmark of AD that has been identified as a downstream effect of *P. gingivalis* infection.[5] Gingipains consist of lysine-gingipain (Kgp), arginine-gingipain A (RgpA), and arginine-gingipain B (RgpB). Specifically in this study, there was a significantly higher amount of RgpB and Kgp in the brains of AD patients compared to the control. There was also an additional significant correlation between RgpB and tau load and ubiquitin load, respectively.[5] Ubiquitin is a small protein tag that marks damaged proteins for degradation by proteasomes and it accumulates in both tau tangles and Aβ plaques.[53] Another study done in 2022 explored the role of gingipains within the progression of neurodegeneration in vitro. When *P. gingivalis* supernatants were added to mediums with human cerebral endothelial cell lines, the proteases were found to increase the permeability of human cerebral endothelial monolayers and have a degradative effect on the tight junction proteins connecting the endothelial cells.[52] These findings suggest that gingipains may have an additional direct role in the blood-brain barrier compromise.

P. gingivalis itself may also have a more direct contribution to neurodegeneration aside from downstream effects resulting from gingipain release. Transmission electron microscopy has revealed that *P. gingivalis* is incorporated into the neurons derived from human stem cells and perturbs the cytoskeleton.[54] In this in vitro study, infected neurons showed characteristics of destruction such as the presence of autophagosomes and multivesicular bodies, supporting a potential direct neurotoxic effects of *P. gingivalis* infection in the brain.

Altogether, these clinical findings support the necessity to explore mechanisms underlying neurologic changes secondary to periodontitis to strengthen the evidence of a causal

relationship over observed correlation. Therefore, animal models have been used to study both the cognitive and neurologic effects of periodontal infection.

Animal Studies of Periodontitis and Cognition

Finally, in vivo animal studies have contributed to the growing body of evidence to support the clinical findings summarized here. In an animal study in which female mice were infected with *P. gingivalis*, learning and memory impairment were observed in the middle-aged *P. gingivalis*-infected mice compared to both the control and the younger infected mice.[39] Both control and *P. gingivalis* infected mice were trained and tested in the MWM, in which spatial learning and memory were measured by the latency it took for mice to find the submerged platform within a swimming arena or the number of platform crossings during a probe test.[55] The escape latency of middle-aged infected mice remained high throughout the training trials which suggests a lack of learning for this group of mice, while the escape latency of the control middle-aged group and *P. gingivalis* infected young mice did reduce drastically. Additionally, the infected middle-aged mice crossed the platform less often compared to the control group, indicating an impairment of precise memory of the platform location. These results implied that *P. gingivalis*-induced periodontal infection had a significant effect on spatial learning and memory in middle-aged mice and suggested a synergistic effect between aging and *P. gingivalis* periodontal infection.[39] Additionally, qPCR, ELISA, and immunohistochemistry results revealed a marked increase of tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β) in the brains of the middle-aged infected mice. This implied that *P. gingivalis* may contribute to the observed learning and memory deficits via the release of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β.[39]

Hu et al. observed similar spatial learning and memory defects in *P. gingivalis*-infected Sprague-Dawley rats. In the MWM test, infected rats had a statistically longer escape latency and were unable to locate the target quadrant (where the platform used to be located) in the probe test.[56] In the infected rats, an increase in activated microglia increased cytokine levels in both plasma and brain cortices, and increased cortical levels of $A\beta_{1-42}$ and Tau proteins were observed. Each of these molecular effects and microglial activation were reduced upon the administration of TAK-242, an inhibitor of toll-like receptor 4 (TLR4). qPCR results showed a significant increase in mRNA levels of TLR4 and its coreceptor CD14, indicating that the observed spatial learning and memory defects could be via the TLR and Nuclear factor kappa B (NF-κB) pathway.[56]

Gingipains produced by *P. gingivalis* are not only studied in humans but also animal models. In the previously mentioned clinical study by Dominy et al., it was also found that oral *P. gingivalis* infection in mice resulted in increased production of $A\beta_{1-42}$. When orally infected mice were treated with synthesized small-molecule inhibitors targeting gingipains, gingipain inhibition blocked $A\beta_{1-42}$ production, reduced neuroinflammation, and protected neurons against *P. gingivalis* and gingipain-induced toxicity in the hippocampus. This finding suggested the involvement of gingipains in $A\beta_{1-42}$ production and neurodegeneration in AD.[5] The clinical correlation observed between gingipains and tau load observed by Dominy et al. has also been observed in rats. In the hippocampus of rats with *P. gingivalis* injection, there was increased phosphorylated tau at the sites Thr181 and Thr231 and activated astrocytes.[57] Additionally, protein phosphatase 2A (PP2A) was also inhibited in the hippocampus. The levels of the IL-1β, IL-6, and TNF-α in serum and hippocampus were also increased, suggesting increased neuroinflammation after *P. gingivalis* injection. Further, IL-1β also induced tau hyperphosphorylation in vitro.[57] These findings suggest that *P. gingivalis* leads to tau hyperphosphorylation possibly via inhibition of PP2A by causing neuroinflammation.

It is possible that Cofilin 2, a known protein identified in the pathophysiology of AD, may also play a role in linking CP to AD development in mice.[58] A behavioral experiment was implemented using the MWM test, and the CP mice showed a much longer escape latency time and significantly decreased platform crossing time in the probe test. The study also reported that the levels of Cofilin 2 in the hippocampi of CP mice strongly correlated with CP progression. In vivo results showed that inactivation of PP2A and increased levels of tau proteins correlated with increased Cofilin 2 levels.[58] These results suggest Cofilin 2 may be a key player in the molecular mechanism that connects the two pathologies (i.e., CP and AD). Additional studies exploring the downstream neuropathologic effects of increased Cofilin 2 levels would strengthen this proposed mechanism.

Combined Effects of Periodontitis and Tooth Loss on Cognition

While the epidemiological studies summarized in this paper confirm the independent longitudinal effects that both tooth loss and periodontitis have on cognition, the question remains regarding how the extent and rate of cognitive decline in patients undergoing both diseases concurrently compare to those with only one. Additionally, it is also of interest to investigate the behavioral and molecular changes observed in animal models that are confirmed to have both periodontitis and impaired masticatory function to identify a potential synergistic effect on neurodegeneration. Though our findings did not reveal any current publications using animal models to investigate altered pathways when both periodontitis is induced and mastication is impaired, it is important to highlight the commonalities between the proposed individual pathways and what these may indicate for future research development.

Though there is a lack of epidemiological evidence that particularly investigates whether periodontitis and partial edentulism have a synergistic effect on cognitive decline, there are some longitudinal studies that have considered both the number of teeth remaining and periodontal status when investigating cognitive function. A 32-year-long prospective study followed 597 men from the Veterans Affairs Dental Longitudinal Study began in 1968. Dental examinations were administered every 3 years where a periodontist measured the number of remaining teeth, caries, restorations, pocket depths, and RABL.[59] Cognitive function was assessed using the MMSE

and a spatial copying task (SCT), which requires participants to draw geometric shapes of different difficulty after viewing them and they were scored according to the number of correct drawings. Kaye et al. observed that the progression of tooth loss and periodontitis independently increased the risk of impaired cognitive function. Specifically, they concluded that with each tooth lost every decade, the risk increased from 9% to 12% for a low MMSE score. Similarly, with each tooth that showed surrounding alveolar bone loss or increased probing depths, the risk increased from 2% to 5%.[59]

Interestingly, in an 8-year long prospective study published in 2014, lower cognitive function scores were associated with partial/complete edentulism while periodontitis and number of teeth did not show a significant association.[60] In this study probing depth, bleeding on probing (BOP), gingival crevicular fluid collection, and number of remaining teeth were all measured. Periodontitis classification was measured according to the biofilm-gingival interface (BGI) index. Cognitive function was assessed using exams such as delayed word recall, DSST, and word fluency. An additional finding from this study that was not consistent with prior studies was that complete edentulism was associated with a slower rate of cognitive decline. The participants in this study were middle-aged adults compared to the older populations usually involved in similar studies, which could have contributed to these findings.[60]

Another study involving 775 older adults in Sweden assessed both periodontal disease and tooth loss when considering the effect on cognitive function.[61] In this study, dental examinations were carried out by a dental hygienist where the number of remaining teeth was recorded, and periodontal disease was measured based on PD and RABL. The MMSE and clock test were used to examine cognitive ability. Those with periodontitis showed a higher risk for lower MMSE scores that remained consistent whether the periodontal disease was defined as ≥4 mm or ≥5 mm at ≥ 30% readable sites. Additionally, a lower number of remaining teeth was associated with impaired cognitive function.[61] Overall, these studies support the epidemiological evidence investigating the independent correlations between periodontal disease or tooth loss and cognitive decline but take a more comprehensive approach in measuring different types of oral diseases.

As mentioned, it is also of interest to identify the similarities highlighted in the proposed mechanisms connecting these two individual disease processes to neurodegeneration. Tooth loss has been shown to induce similar neuroinflammatory effects in the hippocampus as periodontitis. Chronic neuroinflammation driven by microglial activation and release of pro-inflammatory cytokines, IL-1β, and TNF-α, are key players in the exacerbation of AD pathology.[62,63] Periodontal microbes and their virulence factors can activate microglial cells, leading to the downstream neurodegenerative processes in dementia.[40,64,65] In the previously mentioned study by Tang et al. Sprague-Dawley rats injected with *P. gingivalis* showed progressive levels of IL-1β, TNF-α, and IL-6 in the hippocampus at 4- and 12-weeks post-injection.[57] Comparable results were observed when Aβ expressing mice underwent maxillary molar extractions in a study done by F. Taslima et al. in 2021. Not only was there an observed decrease in neuronal activity and synapse dysfunction which was consistent with many other prior studies, but microglial activation, increased levels of TNF-α, IL-6, and IL-1β, and astrogliosis were observed in the hippocampus of the mice underwent molar extractions compared to the control.[66] This neuroinflammation and astrogliosis led to neuronal cell death in the CA1 and CA3 segments of the hippocampus. Goto et al. reported similar findings when they observed the same destruction in the CA1 and CA3 portions of the hippocampus following microglial activation in the locus coeruleus and Vmes in response to the release of cytotoxic Aβ.[30] These findings support that glial activation occurs in response to tooth loss, but it remains unclear exactly how this occurs. On the contrary, recent experiments have begun to explore the potential pathways to explain how periodontal pathogens cause microglial activation. Some proposed mechanisms include the receptor TLR2/TLR9-mediated pathway and C1q complement protein activation.[67,68] The overlap in microglial activation and release of pro-inflammatory cytokines induced by periodontal pathogens and tooth loss deserves attention (Figure 1). How these mediators are affected when both periodontitis and mastication are impaired, and if this results in amplified glial activation and cytokine levels compared to individuals with only one disease deserve further investigation. This is of clinical importance since periodontitis is one of the most common causes of tooth loss and therefore many patients who have CP also have impaired masticatory ability due to extensive tooth loss.

Conclusion

The exploration of the bidirectional relationship between oral health and cognitive function has evolved tremendously over the past two decades. Ongoing research has identified the inflammatory nature of periodontitis, aside from tooth loss, as a key initiator in the development of dementia, especially AD. Current research supports many different pathophysiologic processes that are involved in the behavioral and cognitive effects caused by periodontitis. Exploring these proposed mechanisms may supply therapeutic implications that can slow down the progression of dementia in patients with periodontitis. For example, pretreatment with a combination of gingipain inhibitors was shown to block the neurodegeneration and Aβ accumulation that occurred in mice infected with *P. gingivalis*.[5] With clinical trials and animal model studies continually exploring the pathophysiologic mechanisms, this can potentially lead to therapeutic advancements to slow down dementia progression in patients with periodontitis and impaired mastication. The definition of clinical tooth loss is ambiguous and can be attached to a broad range of underlying pathologic etiologies. Periodontal disease, caries, trauma, occlusal disease, etc. are only some of the causes of tooth loss. In addition, many individual disease processes contribute to oral health problems, which proposes a challenge when attempting to identify the distinct roles that these varying disease processes have in affecting cognitive function. Therefore, it is important to highlight the current literature regarding how periodontal

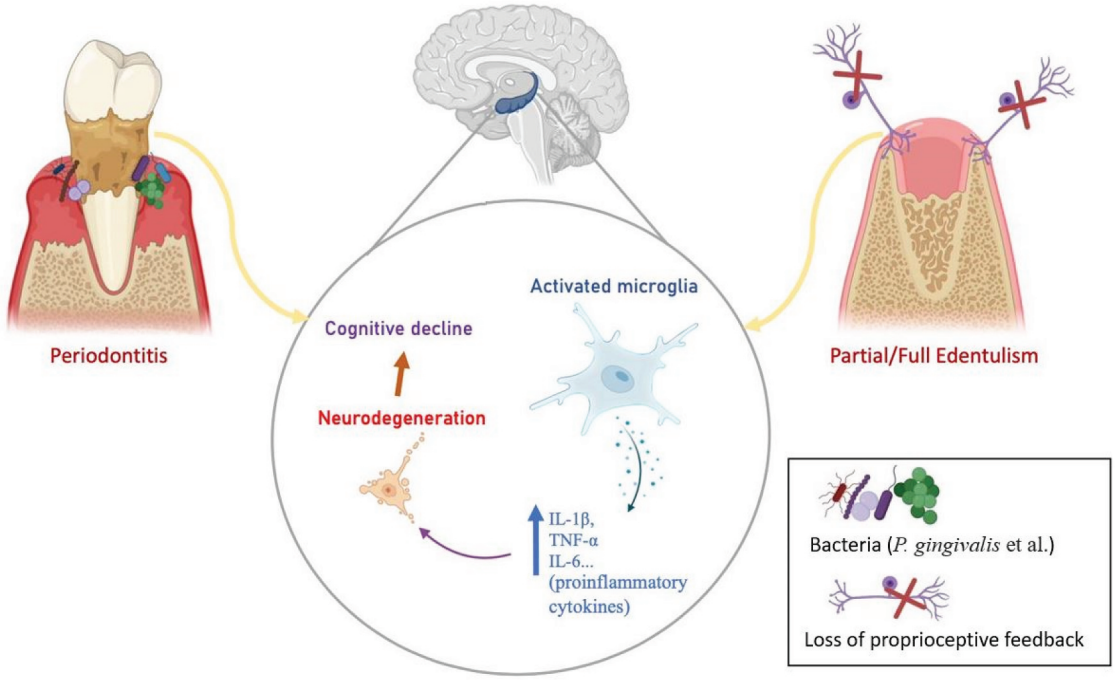

Figure 1. Effect of edentulism and periodontitis on neurodegeneration and cognitive decline. Tooth loss leads to diminished proprioceptive feedback due to the loss of periodontal proprioceptive nerve endings.[7] Periodontitis and impaired mastication have been shown to independently result in microglia activation, the release of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, and neurodegeneration in the hippocampus and other brain regions involved in cognitive function, which are hallmarks in AD progression.[30,56,57] abbreviations: IL-1β: interleukin 1-β, TNF-α: tumor necrosis factor α, IL-6: interleukin 6, AD: Alzheimer's disease.

inflammation and loss of masticatory function regardless of etiology individually affect cognitive function while also considering the potential combined effect of the two diseases on cognitive decline. In conclusion, the evidence supporting the bi-directional relationships between both periodontal disease and tooth loss with cognitive decline is growing and continues to highlight the importance of overall oral health and preventative care.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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