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The link between periodontitis and Alzheimer's disease – emerging clinical evidence

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ABSTRACT

Alzheimer's disease (AD) is one of the most prevalent progressive neurodegenerative disorders and among the leading causes of mortality globally. AD is characterized by continued cognitive and behavioral impairments associated with memory loss, difficulty with reasoning, and language impairment. In parallel, periodontal disease (PD) is a prevalent chronic disease, affecting one in two adults, with associations to various systemic disease. Recently, pre-clinical and clinical studies have elucidated associations between PD and AD. The most recent evidence suggests a bi-directional relationship between both disease entities. However, a causal relationship between PD and AD has yet to be established. In this review, we aim to provide an overview of the pathogenesis of PD and AD, and present the main theories behind the link between PD and AD, the role of periodontal pathogenic bacteria on the onset and progression of AD, and emerging clinical evidence on the relationship between PD and AD.

1. Introduction

Alzheimer's Disease (AD), first described in 1906 by the German neuropathologist Alois Alzheimer, is a progressive neurodegenerative disorder characterized by cognitive and behavioral impairments including memory loss, inability to form new memories, difficulty with reasoning and language [1]. As a result, patients experience progressive decrease in quality of life leading to disability, anxiety and depression [2]. AD is one of the leading causes of mortality globally and its prevalence will continue to rise with the aging population [2]. The etiology of AD is multifactorial. Its typical pathological features include neurofibrillary tangle (NFT) formation, and deposition of amyloid-beta (Aβ) plaque [1,2].

Periodontal disease (PD) is a chronic disease that affects one in two adults globally [3–5]. Previous research have demonstrated that PD is associated with systemic diseases including diabetes, cardiovascular diseases, rheumatoid arthritis [6–11]. Recent research reported that oral dysbiosis accelerates the formation of AD pathological hallmarks [12,13]. For instance, certain oral bacteria can reach the brain via cranial nerves or cellular infections, which has been suggested to be associated with an increased risk of developing AD [14,15].

Previous pre-clinical and clinical studies have explored the potential association between oral infection, PD, and AD [2,16]. However, the specific periodontal pathogens and associated mechanisms involved in the pathogenesis of AD and its progression remain largely unknown. In this review, we aim to provide an overview of the main theories linking PD to AD, and summarize emerging preclinical and clinical evidence on the relationship between PD and AD.

2. Pathogenesis

2.1. Pathogenesis of periodontal disease

In periodontitis, dysbiosis triggers exaggerated inflammation in susceptible individuals [13,17,18]. This dysregulation in host immune response leads to destruction of the periodontium, which includes alveolar bone, periodontal ligament, and cementum. A shift in the microbial composition often precedes the clinical signs of periodontitis. A shift in the microbial composition often precedes the clinical signs of periodontitis [17]. In fact, subgingival bacterial species with a higher frequency of periodontal pathogens are associated with refractory and severe forms of periodontitis [19].

Porphyromonas gingivalis (*P. gingivalis*), one of three red complex bacteria, produces lipopolysaccharides (LPS) and gingipains [20–22]. These virulence factors mediate direct tissue destruction, propagate inflamma-

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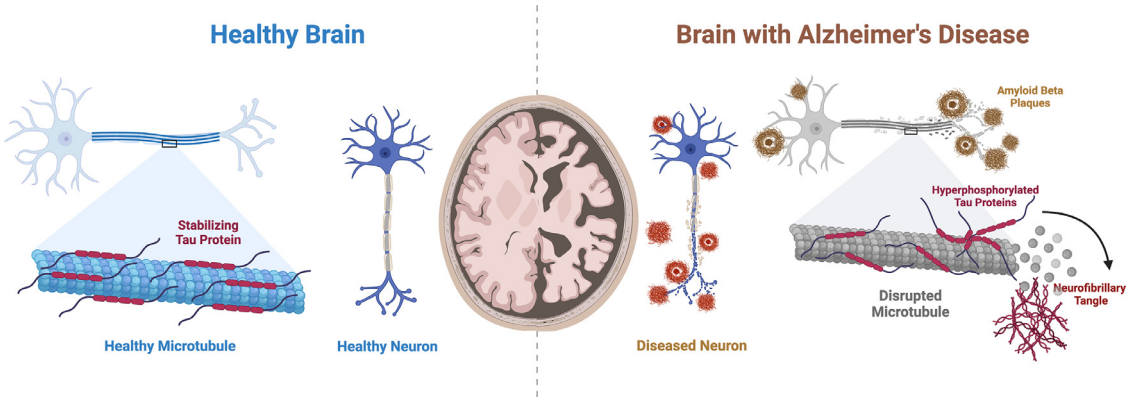

Fig. 1. Schematic of the Human Brain in Health and with Alzheimer's Disease.

tion, and modulate the host immune response during disease progression [23]. For example, gingipains account for 85% of the extracellular proteolytic activity of *P. gingivalis* [24].

In response to the microbial insult, host immune cells express inflammatory cytokines including Tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which contribute to the pathogenesis of periodontitis [25–27]. TNF-α and IL-1β directly stimulate osteoclasts and promote the release of matrix metalloproteinases (MMPs), resulting in the enzymatic breakdown of the periodontium [28]. IL-6 promote bone resorption and drive the maturation of B cells into antibody-secreting plasma cells [29]. Increased concentrations of IL-6 were observed in serum, saliva, and gingival crevicular fluid from periodontitis patients [30–32].

2.2. Pathogenesis of Alzheimer's disease

AD is a progressive neurodegenerative disorder that is primarily characterized by extracellular Aβ peptide deposition, hyperphosphorylation and intracellular aggregation of tau proteins, and microglia-mediated neuroinflammation.

2.2.1. Aβ plaque accumulation

Aβ is normally beneficial and plays key roles in protecting human body from infection, repairing leaks in the blood-brain barrier (BBB), and regulating synaptic function. The amyloid cascade hypothesis establishes excessive Aβ plaque accumulation in the cerebral cortex and hippocampus as the central axis of neurodegeneration in AD development [33–35]. Under normal physiologic conditions, Aβ peptides are phagocytosed and degraded by enzymes in monocytes, macrophages, and neutrophils to be excreted in bile and urine. However, with inefficient clearance and/or overproduction of Aβ, the Aβ proteins accrue extracellularly in the brain to establish senile Aβ plaques (Fig. 1) [36–38]. Excessive Aβ deposition is neurotoxic and induces synapto-toxicity and neuronal cell death, damaging the BBB [38–40]. At lower concentrations of Aβ in the presence of glial cells, Aβ may indirectly cause neuronal damage via reactive gliosis [41–43].

2.2.2. Tau hyperphosphorylation

Tau is a soluble microtubule-associated protein that promotes microtubule assembly and stabilization [44]. Abnormally hyperphosphorylated tau destabilizes tubulin assemblies in neuronal axons and result in the formation of NFTs [45,46]. The progressive hyperphosphorylation and intracellular aggregation of tau correlate with the loss of synapses and decline in cognitive function seen in AD (Fig. 1) [47]. Though NFT aggregation was initially thought to drive neurodegeneration, recent pre-clinical and clinical studies supported that NFTs could be regarded as a marker of neuronal damage and are insufficient to cause cognitive decline or neuronal death [47–50]. AD-related tauopathies were also observed to directly interfere with nucleocytoplasmic transport and induce neurotoxicity [51].

2.2.3. Microglia-mediated neuroinflammation

In addition to the neuronal factors like Aβ and tauopathies, glia-mediated immunological mechanisms are strongly associated with AD progression and severity [43,52,53]. Microglia can remain activated for a long period of time and secrete proinflammatory cytokines and neurotoxic agents that induce and/or exacerbate neurodegeneration [54]. Similar to macrophages in peripheral inflammation, as the inflammatory state and oxidative stress persist in the brain, microglia switch from the alternatively activated M2 phenotype to the classic pro-inflammatory M1 phenotype and release pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α [55–57]. Resident astrocytes are also activated in this process; dysregulated astrocytes potentiate further release of neurotoxic materials such as pro-inflammatory cytokines, nitric oxide, and reactive oxygen species [58–60]. Furthermore, microglial activation has shown to significantly substantiate the potency of Aβ-induced neurotoxicity via production of reactive oxygen species [42]. Together, these molecular events directly and indirectly generate neuro- and synapto-toxicity, constituting the main histopathological markers of neurodegeneration in AD.

3. The link between PD and AD

Previous studies have shown a positive link between periodontitis and AD. It is unclear which comes first as the causal relationship is not established between the two disease entities. Some studies suggest that patients with periodontitis present a risk of developing AD (Fig. 2) [61]. On the other hand, patients with AD or dementia have poor oral hygiene habits as a manifestation of their cognitive decline, thus may be more likely to develop PD. Recent research has shed light on the potential bidirectionality of PD and AD and provide evidence that patients with dementia had a significantly higher risk of developing PD, while those who developed dementia earlier in life had more severe forms of PD (Fig. 2) [62,63].

One hypothesis is that periodontal pathogens can enter the brain through different paths and directly cause damage to the CNS. In order to access the brain from the bloodstream, pathogens must break through the BBB. Previous studies have reported reduced BBB integrity in both mice infected with *P. gingivalis* and elderly AD patients [64]. An alternate hypothesis is that cytokines and pro-inflammatory factors released in response to periodontal pathogens trigger systemic inflammation which induces neuroinflammation, neurodegenerative changes, and cognitive impairment consequently [2]. Interestingly, a recent study by Kantarci et al. explored the microglial response to experimental periodontitis in a murine model of AD [65]. The study demonstrated that

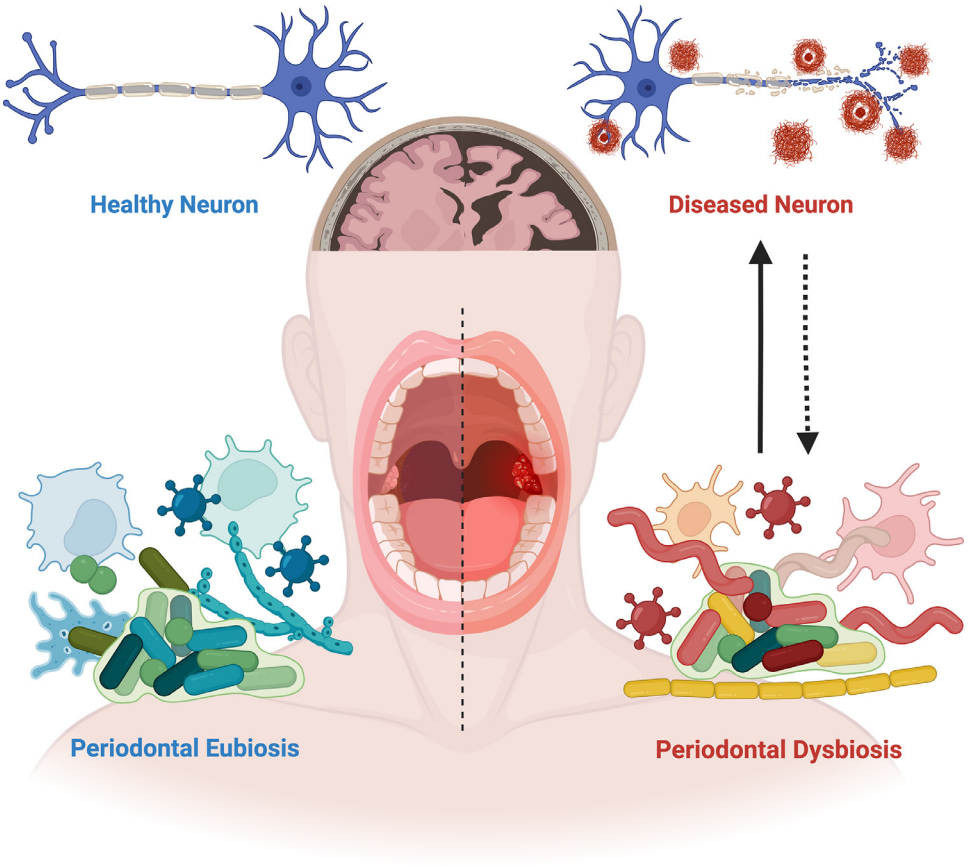

Fig. 2. The Bidirectional Relationship Between Periodontitis and Alzheimer's Disease.

PD increases neuroinflammation in wild-type mice and disrupts the neuroinflammatory response in 5XFAD mice, and AD-like pathology alone leads to periodontal bone loss [65]. Their results suggest that the mechanisms of microglial cell activation and neuroinflammation are important links between PD and AD [65].

4. Role of periodontal pathogens in AD – preclinical evidence

The connection between periodontal disease bacteria and the pathogenesis of Alzheimer's disease is frequently discussed in the literature. A subset of bacteria in the oral microbiome are pathogenic and can lead to periodontitis [66,67]. These microbes produce toxins that stimulate a chronic inflammatory response and periodontal tissue destruction. *P. gingivalis* and *Treponema* species have been demonstrated potential to directly or indirectly (via virulence factors) invade the CNS and have been detected centrally in both living animals and tissue sections of AD patients [68,69]. Furthermore, recent evidence suggests that *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) and *Fusobacterium nucleatum* (*F. nucleatum*) may also be involved in the pathogenesis of AD [70–72]

4.1. P. gingivalis

P. gingivalis infections and its virulence factors seem to be closely associated with the development of the sporadic variant of AD. Animal studies have routinely demonstrated intracerebral localization and increased expression of inflammatory mediators in the CNS following chronic oral administration of *P. gingivalis* [14,73–75]. In addition, LPS and gingipain are virulence factors of *P. gingivalis* and have demonstrated potential to mediate direct tissue destruction, propagate inflammation, and modulate the host immune response during the progression from acute to chronic periodontitis [23].

4.1.1. Gingipain

Intracerebral localization of *P. gingivalis* and gingipain has been demonstrated in frontotemporal lobe and hippocampal tissue sections following chronic oral infection of mice with *P. gingivalis* [14,15,37]. Further, *P. gingivalis* and gingipain were localized in astrocytes, microglia, and neurons indicating that they mediate their neuroinflammatory activity through glial and neuronal cells [14]. Additionally, studies demonstrated that gingipain promotes microglial migration and release of proinflammatory mediators thereby promoting neuroinflammation [75,76]. Gingipain is capable of directly invading endothelial cells and initiating physical injury to the cerebral microvasculature which may lead to degeneration of the endothelial tight junctions and increased permeability of the BBB [77]. Singhrao et al. introduced the concept of 10-year lag phase for chronic periodontitis to become a risk factor for the development of AD [15,37]. They postulated that the initial weakening of the BBB through aging may allow easier access for periodontal bacteria to enter the brain, which then can further damage the BBB and allow more circulating periodontal bacteria and virulence factors to enter the CNS [15,37]. Dominiy et al. showed direct evidence that oral administration of small-molecule inhibitors targeting gingipains blocked gingipain-induced neurodegeneration in murine models of AD [73]. Gingipain inhibitors also significantly reduce the bacterial load of *P. gingivalis* in the mouse brain, decrease the host response to *P. gingivalis* brain infection, rescue hippocampal neurons, and block Aβ1–42 production which is a hallmark of AD [73].

4.1.2. P. gingivalis*-derived LPS*

P. gingivalis-LPS-mediated neuroinflammation emerge as a key potential contributor to neurodegeneration. *P. gingivalis* appears to mediate its effects through pattern recognition receptors (PRR), such as Toll-like receptors (TLR), which are G-protein-coupled receptors selectively expressed by microglia. These receptors recognize and bind pathogen-

associated molecular patterns (PAMPs), such as LPS, to activate an inflammatory response in glial cells [78,79]. In addition, a recent study indicated intrasulcular LPS can translocate to the CNS and produce neuroinflammation via TLR4 receptor and the NF-κB signaling pathway on microglia [80]. Mice supplemented with LPS experienced spatial learning and memory deficits in the Morris Water Maze Test and impaired passive avoidance compared to control. These effects were significantly prevented by concomitant administration of TAK-242 indicating the involvement NF-κB signaling pathway with memory deficits in mice [81].

4.2. Treponema *species*

Treponema species have a known ability to invade the CNS and produce amyloid [68]. Foschi and colleagues used PCR detection of the 16S rRNA gene of severe combined immunodeficient (SCID) mice infected with *Treponema denticola* to show evidenced of dissemination to the spleen and CNS [82].

4.3. *A. actinomycetemcomitans*

Recently, it was demonstrated that serotype b LPS from *A. actinomycetemcomitans* triggered the secretion of proinflammatory cytokines by microglia, induced neurite shrinking, and increased the level of extracellular Aβ, all features strongly associated with the etiology of AD [83].

4.4. *F. nucleatum*

F. nucleatum is a common pathogen that significantly overgrows in periodontitis and linked to microbiome-associated systemic diseases [84–87]. An earlier study reported that antibodies to *F. nucleatum* can be detected in the serum of patients with AD or cognitive impairment [71]. A recent study demonstrated, *F. nucleatum* can activate microglial cells causing morphological changes, accelerated proliferation and enhanced expression of TNF-α and IL-1β in microglial cells [72]. In addition, *F. nucleatum*-induced periodontitis can lead to the worsening of Alzheimer's symptoms in 5XFAD mice, a mouse model which recapitulates major features of AD. Symptoms included increased cognitive impairment, beta-amyloid accumulation and Tau protein phosphorylation in the mouse cerebrum. This study may suggest a possible link between a periodontal pathogen and AD. *F. nucleatum* may be a risk factor in the AD pathogenesis.

5. Human studies on PD and AD

5.1. *Effects of PD on neuroinflammation*

One hypothesis that explains the relationship between PD and AD is that periodontal inflammation and infections contribute to the risk, onset and/or progression of AD by increasing the peripheral inflammatory burden which then can trigger and/or exacerbate neuroinflammation. In both animal and experimental human studies, the peripheral presence of low-grade inflammation has been observed to have a significant impact on the pathophysiology of AD via cross-talk between peripheral and central immune cells [88–91].

It is largely unknown which stage of AD development is affected by peripheral inflammation and infections like periodontitis. Kamer and colleagues demonstrated, for the first time in humans, a positive association between chronic periodontal disease and brain Aβ load by utilizing positron emission tomography imaging [92]. After adjusting for confounders of age, medical conditions, smoking, oral hygiene behaviors, tooth loss, memory, and apolipoprotein E (ApoE) genotype, the inflammatory insults from periodontal infections remained sufficient to produce Aβ accumulation [92]. These associations were found not secondary to cognitive impairment.

Additionally, in a Taiwanese retrospective matched-cohort study with a 10-year follow-up, patients with a 10-year exposure to low-grade inflammation caused by chronic periodontitis showed a 1.7-fold increased risk of developing AD, regardless of AD-related co-morbidities such as hypertension, hyperlipidemia, chronic kidney disease, depression, stroke, diabetes mellitus, traumatic brain injury [93].

5.2. *Cytokine profiles of PD and AD*

Production of pro-inflammatory cytokines by peripheral blood mononuclear cells has been proposed to be predictors of future risk of AD in older adults with intact cognitive performance [94]. The primary mechanism is that the systemic inflammatory signals and antigens prime the central microglial cells which then express an aggressive pro-inflammatory phenotype and aggravate neuroinflammation and neurodegeneration in AD. In chronic periodontitis patients, the local oral inflammation induces a low-grade systemic inflammation which can be observed in elevated serum levels of C-reactive protein (CRP), pro-inflammatory cytokines and antibodies against bacterial antigens (i.e. LPS) [7,25–27]. Increased levels of plasma TNFα, IL-1 and IL-6 were observed in AD patients compared to normal patients [94–96]. Moreover, CRP has been detected within amyloid plaques and neurofibrillary tau tangles in AD patients [97–99]. High serum levels of CRP are associated with increased risk of developing cognitive decline and AD, up to 3 folds [97,100].

5.3. *Periodontopathic bacteria and virulence factors*

In addition to the host immune response to bacterial challenges in peripheral inflammation/infections, virulence factors produced by pathogenic bacteria have been observed to breach the BBB and directly contribute to pathophysiology of AD [69,73,89,101–103]. The role of LPS in AD has been suggested to result in progression of AD by acting on leukocyte and microglial toll-like receptor complexes. Zhan et al. found significantly higher levels of LPS and *E coli* in human and mouse AD brains compared to control/normal-aging brains [101]. Based on the findings of LPS colocalization with Aβ in amyloid plaques and peri-vascular amyloid in every tested AD brain, Zhan et al. suggested that systemic presence of LPS and gram-negative bacteria is associated with neuropathology in AD [101,104]. This is pertinent to periodontal diseases in that approximately 85% of the bacterial composition of subgingival biofilm are gram-negative bacteria with marked LPS expression [22]. Statistically significant amounts of *P. gingivalis*-derived LPS were detected in the brains of AD patients postmortem, indicating that virulence factors of oral pathogens are capable of penetrating central compartments and that chronic infection of periodontal pathogens contributes to the inflammatory pathology of AD [69].

Gingipains is another virulence factor of *P. gingivalis* that was detected in AD patients. Both *P. gingivalis* and gingipains were exclusively detected in CSF of AD patients with mild to moderate cognitive impairment [73]. Gingipains were also identified to colocalize with tau tangles and intraneuronal Aβ in mice brain tissue affected by AD and to cleave within the Tau-5 antibody epitope leading to tau truncation and fragmentation. These findings support the hypothesis of PD directly contributing to main pathologic processes in AD by inducing formation of Aβ plaques and insoluble and hyperphosphorylated tau [34,105,106]. The evidence of oral *P. gingivalis* in CSF also supports that pathogens causing periodontitis are capable of invading the central system and thus directly causing neuroinflammation.

Furthermore, using PCR and immunohistochemical staining, common oral *Treponema* species were detected in the trigeminal nerve and trigeminal neuronal cell bodies, pons, hippocampus and frontal lobe cortex in humans postmortem; higher prevalence and numbers of *Treponema* species were seen in AD-affected brains [68].

5.4. Antibody markers of PD as predictors of AD

Several clinical studies have supported the hypothesis that certain serological markers of PD can be predictors of incident cognitive impairment of older adults [107–111]. In a longitudinal study of older adults by Noble et al., a significant association was found between high serum immunoglobulin G (IgG) titer against *Actinomyces naeslundii* (*A. naeslundii*) and increased risk of developing incident AD [112]. *A. naeslundii* is a gram-positive oral pathogen crucial in early dental plaque formation, and development of gingivitis and dental caries. This association was found to be strong even after adjusting for AD-related comorbidities [112].

In another investigation of biomarkers of periodontitis in AD patients, elevated IgG levels against common periodontopathic pathogens including *A. actinomycetemcomitans, P. gingivalis and Tannerella forsythia*, and high were independently associated with incident AD [96]. Sparks et al. demonstrated that baseline levels of IgG against to *F. nucleatum* and *Prevotella intermedia* were significantly higher in subjects that later developed AD and MCI subjects [113]. These results suggest that periodontal disease may contribute to the risk of AD onset and/or progression.

5.5. Population-based data on association between PD and cognitive decline

No definitive conclusions on a causal relationship or the directionality of the association between periodontitis and impaired cognition could be discerned from these population-based studies [108,109,114–118,107]. The following section elucidates results from these studies.

5.5.1. NHANES-III analysis

To evaluate cognitive function, NHANES-III used the Neurobehavioral Evaluation System 2 (NES2) which aims to measure neurocognitive function and reflect an individual's psychomotor speed and control, learning, and attention [109,111]. It has three computer-assisted components: (1) simple reaction time test (SRTT); (2) the symbol digit substitution test (SDST); and (3) the serial digit learning test (SDLT). Higher scores indicate decreased cognitive function.

Sung et al. analyzed 4633 participants of ages 20 to 59 years that underwent a full-mouth periodontal examination and the NES2 cognitive test [114]. The subjects with mild and moderate to severe periodontitis scored higher on SDST and SDLT; after adjusting for demographic, medical and psychosocial factors, periodontitis remained to be significantly correlated with higher SDST and SDLT scores [114]. These results were consistent with earlier findings by Stewart et al. in their analysis of NHANES-III data relating to oral health and cognitive function [109]. With a full adjustment for covariates (i.e. demographics, cardiovascular and metabolic disorders, smoking), gingival bleeding and periodontal attachment loss remained associated with relative impairment on SDST and SDLT scores [109].

During the second phase of enrollment into NHANES-III (1991–1994), sera from 9371 participants were collected to be analyzed for antibody levels of *P. gingivalis* [107]. Of these participants, 2355 adults of older than 59 years were also evaluated for cognitive function. The administered cognitive test had three parts: (1) an immediate and delayed logical verbal memory test (East Boston Memory Test); (2) a three-word registration and memory recall test; (3) five serial subtractions by intervals of three. Noble et al. analyzed this subgroup ($n = 2355$) and delineated dose-dependent relationships with poor scores on verbal recall and serial subtractions in individuals with the highest serum *P. gingivalis* IgG levels [107]. This is consistent with later studies that explore serological markers in PD correlating to AD [96,112,113].

5.5.2. Tooth loss and cognitive function

Saito et al. investigated tooth loss in association with cognitive function among Japanese community-dwelling individuals ($N = 462$) and reported that lower remaining teeth number (10 or fewer) may be an independent risk factor for cognitive decline [116]. Though limited by lack of data on socioeconomic status and longitudinal evaluations, the results showed subjects with poor cognition were significantly older, less educated and intellectually active, and had fewer remaining teeth [116] .

Minn et al. reported similar results among Korean community-dwelling adults without a history of strokes or dementia in that severe tooth loss could be a predictor for developing silent cerebral infarcts and cerebral white matter changes [117]. This remained statistically significant when adjusting for age, education, hypertension, diabetes mellitus, hyperlipidemia, and smoking [117].

Kaye et al. prospectively followed 597 male subjects of ages ranging from 28 to 70 years over 32 years with approximately 3-year recall visits and reported that the risk of cognitive decline was higher in men with increased number of tooth loss, progressive alveolar bone loss around remaining teeth, and older age than 45.5 years [119]. Both periodontal disease and dental caries were primarily responsible for the tooth loss. The Nun Study by Stein et al. evaluated 144 female participants for a decade and reported that those with fewer than 10 teeth at baseline and without ApoE4 genotype were more likely to have dementia at baseline or later develop dementia during the study [108]. In a German population-based study of 1336 male and female subjects, a significant association between tooth loss and cognitive impairment was found in females when fully adjusted for age, medical and psychosocial parameters [118].

Gil-Montoya et al. conducted a case-control study of 409 dentate adults (180 subjects with cognitive impairment and 229 control subjects) who underwent a Phototest cognitive test and periodontal examination measuring tooth loss, plaque and bleeding indices, probing depths, and clinical attachment loss [115]. In contrast to the population-based studies that support a significant association between tooth loss and cognitive decline [108,116–119], this study found no significant association with tooth loss [115]. However, the risk of cognitive impairment was more than three times higher in patients with severe PD than patients with no or mild PD [115].

Despite the strength of the association between tooth loss and impaired cognition, researchers agreed that PD is a major contributor to tooth loss and that PD may potentially be a modifiable risk factor for the onset and/or progression of cognitive decline or dementia.

5.5.3. Effect of AD on periodontal health

Patients with AD or cognitive impairment, especially older adults, are more prone to developing chronic oral disease due to poor oral hygiene adherence [120–123]. Martande et al. conducted a cross-sectional study that assesses the effect of progression of AD on periodontal health by comparing periodontal status in patients with ($n = 58$) and without AD ($n = 60$) [122]. Significantly greater breakdown in clinical periodontal parameters including gingival and plaque indices, pocket depth, and bleeding on probing (%) were observed in the AD group than in healthy controls [122]. Within the AD group, subjects were separated into three groups (mild, moderate, and severe AD) based on their diagnosis and scores on the Mini-Mental State Examination. Severity of PD worsened with AD severity as intergroup comparisons showed statistically significant increases in the mentioned periodontal variables [122]. However, the directionality of PD/AD associations were not clear in this cross-sectional study due to its insufficient sample sizes and time-dependent variables.

The question of bidirectionality was most recently investigated and elucidated by Ma et al. in a retrospective longitudinal cohort study which aimed to identify the longitudinal risk of developing PD in a cohort of patients with dementia and AD who did not show any signs of PD at baseline [62]. The results from the most recent population-based study suggested a cumulative and detrimental effect of dementia on periodontal health in that patients with dementia had a significantly higher risk of developing PD, while those who developed dementia earlier in

life had more severe forms of PD [62]. Moreover, within the dementia group, AD had more significant effects on periodontal health, and the effect of dementia/PD were stronger in patients with concomitant hyperlipidemia. The associations remained significant after adjusting for confounding factors such as diabetes, cardiovascular disease, metabolic syndrome, diabetes mellitus, rheumatoid arthritis, pulmonary diseases, and low oral health awareness [62].

6. Conclusion

In conclusion, current clinical evidence shows an association between PD and AD. The latest evidence suggests that there is a bidirectional relationship between PD and AD. On one hand, patients with chronic periodontitis may be in a state of systemic inflammation, which may involve neuroinflammation. In addition, periodontal pathogenic bacteria and their virulence factors may further contribute to AD pathogenesis and progression. On the other hand, patient who had developed dementia earlier in life had higher risk of developing PD and more severe PD. Further studies are needed to elucidate the pathogenesis mechanisms and potential causality between the two disease entities. In terms of clinical relevance, it is paramount for clinicians to emphasize and implement prevention strategies for PD including promotion of oral health practices to prevent or manage periodontal disease to reduce its potential effect on the onset and progression of AD.

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Declaration of Competing Interest

The authors have no conflict of interest to declared.

CRediT authorship contribution statement

David T. Wu: Conceptualization, Writing – original draft. **Ye Won Cho:** Conceptualization, Writing – original draft. **Mark Bishara:** Conceptualization, Writing – original draft. **Thomas T. Nguyen:** Conceptualization, Writing – original draft.

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