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# FROM GINGIVA TO GRAY MATTER: EXPLORING THE PATHOPHYSIOLOGICAL CONNECTION BETWEEN PERIODONTITIS AND ALZHEIMER'S DISEASE- A REVIEW

Periodontology

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## ABSTRACT

Periodontitis, a chronic inflammatory disease of the tooth-supporting tissues, has been linked to an increased risk of Alzheimer's disease (AD) through shared inflammatory, vascular, and microbial pathways. Evidence indicates that Porphyromonas gingivalis and its gingipains can invade the brain, promote amyloid-β and tau pathology, and trigger neuroinflammation. Epidemiological studies consistently show a higher dementia risk among individuals with severe periodontitis or tooth loss, while limited trials suggest that periodontal therapy reduces systemic inflammation and may modestly improve cognition. Overall, growing evidence supports a biologically plausible connection between periodontitis and AD, underscoring the importance of oral health in dementia prevention.

## KEYWORDS

Periodontitis; Alzheimer's disease; Porphyromonas gingivalis; Oral–brain axis; Neuroinflammation; Blood–brain barrier; Cognitive decline; Dementia; Gingipains; Systemic inflammation

## INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 55 million individuals worldwide and imposing a significant public health burden. Traditionally characterized by memory loss, cognitive decline, and neuropathological hallmarks—amyloid-β plaques and neurofibrillary tangles—AD is now recognized as multifactorial disease involving genetic, vascular, metabolic, and inflammatory contributors.(1)

Periodontitis is a chronic inflammatory disease driven by dysbiotic subgingival biofilm and dysregulated host immune response, leading to destruction of tooth-supporting structures. Beyond oral morbidity, periodontitis contributes to systemic inflammation. Over the last two decades, research has increasingly investigated its role in neurodegenerative disease, particularly AD.(2)

The "oral–brain axis" concept proposes that chronic oral infection and inflammation influence CNS health. Porphyromonas gingivalis, a keystone periodontal pathogen, has been detected in AD brains, and its virulence factors—gingipains. Epidemiological studies similarly associate periodontitis and tooth loss with increased dementia risk.

### 2. Epidemiological Evidence

Epidemiological research spanning multiple populations and study designs supports an association between periodontitis and Alzheimer's disease (AD), Case–control and cross-sectional analyses further reinforce these findings, though they may be more susceptible to reverse causation and residual confounding. Table 1 shows human studies which links between periodontitis and AD.(3–6)

### 3. Mechanistic Links Between Periodontitis And Alzheimer's Disease

The association between periodontitis and Alzheimer's disease (AD) is supported by converging mechanistic evidence spanning microbiological, immunological, vascular, and histopathological domains. These pathways are not mutually exclusive and likely act synergistically to promote neurodegeneration.

### 3.1 Direct Microbial Invasion Of The Brain

Porphyromonas gingivalis (P. gingivalis), a keystone pathogen in chronic periodontitis, has been detected in human AD brain tissue through polymerase chain reaction (PCR), immunoblotting, and immunohistochemistry.

- **Hematogenous spread** following bacteremia during mastication or dental procedures.
- **Neural routes** via the trigeminal and olfactory nerves.
- **Infected monocyte trafficking** across the blood–brain barrier (BBB).

In vitro, P. gingivalis can invade neuronal cells and induce cytotoxicity, further supporting its pathogenic potential within the CNS. (7)

### 3.2 Histopathological Evidence

Histologic studies provide some of the most direct evidence of an oral–brain connection:

- **Human Postmortem Findings:** Brain tissue from AD patients frequently shows P. gingivalis antigens and DNA within the hippocampus and cerebral cortex. Gingipains have been localized to neurons, astrocytes, and microglia, often adjacent to amyloid-β deposits. (8) (9)
- **Amyloid And Tau Changes:** In murine models orally infected with P. gingivalis, hippocampal histology reveals increased amyloid-β42 deposition, hyperphosphorylated tau, and activated microglia. These changes recapitulate hallmark AD neuropathology.(10)
- **Neuroinflammation Markers:** Immunohistochemistry shows elevated IL-1β, TNF-α, and IL-6 in brains from AD patients with a history of severe periodontitis. Complement activation products (C1q, C3) are found in close proximity to bacterial antigen deposits. (11)
- **BBB Disruption:** Tight junction proteins (claudin-5, occludin) show reduced staining in infected mouse models, accompanied by perivascular inflammation and microhemorrhages in hippocampal tissue. (12)
- **Confocal Microscopy Localization:** Gingipain antigens co-localize with neuronal nuclei markers (NeuN) and microglial markers (Iba1), suggesting direct bacterial-host cell interactions. (13)

### 3.3 Systemic Inflammation And Neuroimmune Crosstalk

Chronic periodontitis drives persistent systemic inflammation, characterized by elevated circulating C-reactive protein (CRP), IL-6, and TNF-α. These pro-inflammatory mediators can cross or signal across the BBB, activating microglia and astrocytes. Activated glial cells, in turn, secrete neurotoxic cytokines, reactive oxygen species, and nitric oxide, exacerbating amyloid and tau pathology. (14) (15) (16)

### 3.4. Blood–brain Barrier Disruption

LPS from periodontal bacteria increases endothelial permeability by downregulating tight junction proteins (occludin, claudin-5), facilitating entry of both pathogens and peripheral inflammatory mediators into the CNS. Animal studies show that gingipain inhibitors can attenuate BBB leakage and reduce amyloid deposition. (9,17)

### 3.5. Vascular And Metabolic Effects

Periodontitis is associated with endothelial dysfunction, arterial stiffness, and increased carotid intima–media thickness, all of which impair cerebral perfusion. Chronic low-grade bacteremia can contribute to cerebral small vessel disease — a recognized co-pathology in AD — and exacerbate cognitive decline.(18)

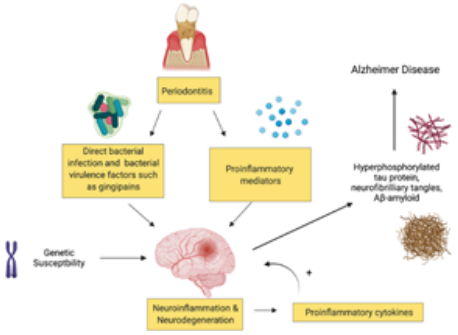


**Fig 1:** Possible mechanism linking periodontitis and Alzheimer's disease.

## 4. Interventional And Translational Research

Despite growing evidence linking periodontitis and Alzheimer's disease, interventional studies are limited, mostly examining whether periodontal therapy lowers systemic inflammation or improves cognition in early or at-risk patients.

### 4.1. Periodontal Treatment And Systemic Inflammation

- **Scaling And Root Planing (SRP) —** Multiple small randomized controlled trials (RCTs) have shown that SRP, with or without adjunctive antibiotics, significantly reduces serum CRP, IL-6, and TNF-α levels over 3–6 months in older adults with moderate to severe periodontitis.(19)
- **Impact On Vascular Function —** Some studies report improvements in endothelial-dependent flow-mediated dilation after periodontal therapy, suggesting potential indirect benefits on cerebral perfusion.(20) (21)

### 4.2. Cognitive Outcomes Following Periodontal Therapy

- **Pilot Studies In MCI (Mild Cognitive Impairment)** — One Japanese RCT found that 6 months of intensive periodontal treatment in MCI patients improved Mini-Mental State Examination (MMSE) scores by ~1.5 points compared with standard care, alongside reductions in serum pro-inflammatory cytokines. (22)

### 4.3. Translational And Experimental Interventions

- **Gingipain Inhibitors** — COR388 (atuzaginstat), a small-molecule gingipain inhibitor, has shown promise in reducing P. gingivalis brain load and amyloid production in murine models. A phase 2/3 human trial in mild-to-moderate AD suggested a trend toward slower cognitive decline in subgroups with high baseline P. gingivalis levels, although the primary endpoint was not met. (23)
- **Microbiome Modulation** — Probiotic and prebiotic interventions aimed at restoring oral and gut microbial balance are under investigation, with early data suggesting reductions in systemic inflammatory load.

### 4.4. Limitations Of Current Interventional Research

- **Small sample sizes and short duration** limit statistical power and the ability to detect meaningful cognitive changes.
- **Heterogeneous definitions of periodontitis** make cross-trial comparisons difficult.
- **Lack of longitudinal mechanistic monitoring** — Few studies track changes in brain imaging, cerebrospinal fluid biomarkers, or microbial DNA in response to periodontal therapy.

### 4.5. Future Directions

- Large-scale, multi-center RCTs with standardized periodontal and cognitive assessment protocols.
- Integration of neuroimaging (MRI, PET) and molecular biomarkers to establish causal links.
- Exploration of combination therapies — periodontal treatment plus vascular and lifestyle interventions — for synergistic benefit in dementia prevention.

## 5. Critical Appraisal of Current Evidence

While the association between periodontitis and AD is supported by multiple lines of evidence, several methodological limitations must be considered:

**A) Reverse Causality-** AD can impair oral hygiene through cognitive decline and reduced motor skills, potentially leading to secondary periodontitis.

**B) Limited Mechanistic Endpoints In Clinical Research-**Few human trials assess brain imaging, cerebrospinal fluid biomarkers, or microbial DNA load in response to periodontal therapy. This limits causal inference.

**C) Small-scale Intervention Studies-** Most RCTs are underpowered, with follow-up durations too short to capture meaningful dementia outcomes.

## 6. CONCLUSIONS

The accumulating evidence from epidemiological, mechanistic, histologic, and limited interventional studies supports a **biologically plausible** and **epidemiologically consistent** link between periodontitis and Alzheimer's disease (AD). Chronic periodontal infection, particularly by Porphyromonas gingivalis and its gingipain proteases, can promote systemic inflammation, compromise the blood–brain barrier, and contribute to amyloid-β deposition, tau hyperphosphorylation, and neurodegeneration.

**Table 1. Representative Human Studies Examining The Association Between Periodontitis/tooth Loss And Alzheimer's Disease Or Dementia**

| Year | Country / Region | Study Design | Population (n) | Exposure Definition | Outcome | Follow-up | Effect Estimate (95% CI) | Key Adjustments |
|---|---|---|---|---|---|---|---|---|
| 2017 | Taiwan | Nationwide cohort | 9,291 | Chronic periodontitis (ICD codes) | AD diagnosis | 10 years | HR 1.70 (1.16–2.48) | Age, sex, comorbidities, socioeconomic status |
| 2018 | South Korea | Cohort (NHIS) | 262,349 | Tooth loss ≥10 | Dementia diagnosis | 9 years | HR 1.16 (1.06–1.27) | Age, sex, BMI, smoking, income |
| 2020 | Sweden | Case–control | 4,505 | Severe periodontitis (clinical) | AD diagnosis | — | OR 1.65 (1.15–2.37) | Age, sex, education, APOE ε4 |
| 2016 | USA | Prospective cohort (ARIC) | 8,275 | Clinical attachment loss ≥5 mm | Dementia hospitalization | 20 years | HR 1.22 (1.03–1.45) | Vascular risk factors, smoking |
| 2021 | Japan | Cohort | 4,425 | Tooth loss ≥20 | Incident dementia | 4 years | HR 1.55 (1.18–2.03) | Age, sex, diet, exercise |
| 2022 | USA | Cohort (NHANES linked mortality) | 6,836 | Severe periodontitis | AD-related mortality | 17 years | HR 1.31 (1.04–1.65) | Age, sex, BMI, smoking |
| 2023 | China | Cohort | 12,765 | Periodontitis (self-report) | Dementia diagnosis | 7 years | HR 1.19 (1.05–1.34) | Age, sex, urban/rural, comorbidities |
| 2015 | Israel | Case–control | 1,003 | Tooth loss ≥15 | AD diagnosis | — | OR 1.54 (1.11–2.13) | Education, cardiovascular risk factors |

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