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BRIDGING THE ORAL CAVITY AND THE CENTRAL NERVOUS SYSTEM: UNRAVELLING THE ROLE OF PERIODONTAL PATHOGENS IN NEUROINFLAMMATION AND NEURODEGENERATIVE DISEASES

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Abstract:

The oral cavity hosts a diverse microbial ecosystem that plays a crucial role in maintaining oral and systemic health. Disruption of this balanced microbiota results in oral dysbiosis, leading to periodontitis, a chronic inflammatory disease driven by pathogenic bacteria and an exaggerated host immune response. Increasing evidence indicates that periodontal pathogens and their virulence factors contribute to systemic inflammation through recurrent bacteraemia and the release of pro-inflammatory mediators. Recent studies have highlighted the oral–gut–brain axis as a key pathway linking periodontal disease with neuroinflammation and neurodegenerative disorders. Pathogens such as Porphyromonas gingivalis may promote blood–brain barrier disruption, microglial activation, oxidative stress and pathological protein aggregation, thereby contributing to Alzheimer's disease, Parkinson's disease, multiple sclerosis and other neurological conditions. This review summarizes current knowledge on the molecular mechanisms, disease associations, emerging biomarkers and therapeutic strategies, emphasizing periodontal health as a potentially modifiable factor for preventing or delaying neurodegenerative diseases.

Keywords: *Periodontitis, Oral–Gut–Brain Axis, Neuroinflammation, Neurodegenerative Diseases, Porphyromonas Gingivalis, Oral Dysbiosis, Periodontal Pathogens.*

1. Introduction

The oral cavity harbours one of the most diverse microbial ecosystems in the human body, comprising over 700 bacterial species together with fungi, viruses, archaea, and protozoa organized within complex multispecies biofilms (1–3). Under physiological conditions, this microbial community maintains oral homeostasis by regulating host immunity and preventing colonization by pathogenic microorganisms. Disruption of this ecological balance, known as oral dysbiosis, promotes chronic inflammation and is the primary driver of

periodontitis (2–5).

Periodontitis is a chronic multifactorial inflammatory disease characterized by progressive destruction of the periodontal ligament, cementum, and alveolar bone, ultimately leading to tooth loss if left untreated (3,4). The disease results from interactions between a dysbiotic microbial community and an exaggerated host immune response rather than a single pathogenic organism. Keystone pathogens, including *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum*, produce virulence factors such as lipopolysaccharide (LPS), gingipains, fimbriae, and outer membrane vesicles, which promote immune dysregulation, tissue destruction, and persistent inflammation (3–6).

Increasing evidence indicates that periodontitis is not confined to the oral cavity but represents a chronic systemic inflammatory condition. Recurrent bacteraemia originating from inflamed periodontal tissues enables periodontal pathogens and their virulence factors to enter the circulation, while sustained production of inflammatory mediators, including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), contributes to low-grade systemic inflammation (5–7). Consequently, periodontitis has been associated with several systemic diseases, including cardiovascular disease, diabetes mellitus, rheumatoid arthritis, and, more recently, neurodegenerative disorders (5–8).

The oral–gut–brain axis has emerged as a key biological framework linking oral health with neurological function (8–10). Periodontal pathogens and their virulence factors may influence the central nervous system through interconnected mechanisms involving microbial dissemination, gut microbial dysbiosis, systemic inflammation, blood–brain barrier disruption, oxidative stress, and activation of microglia and astrocytes (5–10). These processes have been associated with pathological protein aggregation, neuronal dysfunction, and progressive neuroinflammation, which are characteristic features of several neurodegenerative diseases (6–10).

Growing epidemiological, experimental, and molecular evidence suggests that chronic periodontitis may contribute to the development and progression of Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, stroke, vascular dementia, mild cognitive impairment, and other neurological disorders (6–10). Although a direct causal relationship remains to be established, the available evidence identifies periodontal disease as a potentially modifiable risk factor for neurodegeneration and highlights oral health as an important component of systemic health (5–10).

This review critically summarizes current evidence on the role of periodontal pathogens in neuroinflammation and neurodegenerative diseases through the oral–gut–brain axis. It focuses on the underlying molecular mechanisms, disease-specific associations, emerging biomarkers, therapeutic strategies, and future research directions, emphasizing the importance of periodontal health in preventing or mitigating neurological disorders (5–10).

2. Biological basis of the oral–gut–brain axis

2.1 Oral and gut microbiota in health and disease

The oral cavity and gastrointestinal tract harbour complex microbial communities that play essential roles in maintaining host homeostasis. The oral microbiome comprises more than 700 bacterial species together with fungi, viruses, archaea, and protozoa, which exist as structured multispecies biofilms on teeth and oral mucosal surfaces (11–14). Under healthy conditions, commensal microorganisms such as *Streptococcus*, *Veillonella*, *Actinomyces*, *Neisseria*, and *Rothia* regulate immune responses, inhibit pathogen colonization, and preserve

mucosal integrity. Disturbance of this ecological balance, termed oral dysbiosis, Favors the proliferation of periodontal pathogens, particularly *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum*. These microorganisms' express virulence factors including lipopolysaccharide (LPS), gingipains, fimbriae, and outer membrane vesicles (OMVs), which promote immune dysregulation, tissue destruction, and chronic inflammation, ultimately leading to periodontitis (13–16).

The gut microbiota similarly contributes to nutrient metabolism, immune regulation, epithelial barrier maintenance, and resistance to pathogen colonization. During chronic periodontitis, saliva continuously transports oral microorganisms to the gastrointestinal tract, where certain periodontal pathogens can survive and alter the intestinal microbial community, a phenomenon referred to as oralization of the gut microbiome (17–19). This microbial imbalance reduces beneficial metabolite production, particularly short-chain fatty acids (SCFAs), impairs intestinal barrier integrity, and increases intestinal permeability, allowing bacterial endotoxins and inflammatory mediators to enter the systemic circulation (17–20).

2.2 The oral–gut–brain axis

The oral–gut–brain axis is a bidirectional communication network linking oral and gut microbiota with the central nervous system through immune, neural, endocrine, and metabolic pathways (17–20). Chronic periodontal inflammation initiates systemic immune activation through recurrent bacteraemia and dissemination of microbial products, including LPS and OMVs. These circulating mediators stimulate the release of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), creating a persistent low-grade inflammatory state that affects distant organs, including the brain (15,17–20).

Systemic inflammation together with gut dysbiosis compromises both intestinal and blood–brain barrier integrity, facilitating the entry of microbial components and inflammatory molecules into the central nervous system. Consequently, resident immune cells, particularly microglia and astrocytes, become chronically activated, producing cytokines, reactive oxygen species (ROS), and nitric oxide that amplify neuroinflammation and neuronal injury. Although acute neuroinflammation is protective, persistent activation promotes synaptic dysfunction, mitochondrial impairment, and progressive neuronal loss (18–22).

2.3 Relevance to neurodegeneration

Emerging evidence indicates that periodontal pathogens influence neurodegeneration through multiple interconnected mechanisms rather than direct infection alone. Microbial virulence factors, extracellular vesicles, oxidative stress, and chronic inflammatory signalling promote pathological protein aggregation, including amyloid-β, hyperphosphorylated tau, and α-synuclein, which are characteristic of Alzheimer's disease, Parkinson's disease, and related neurodegenerative disorders. While definitive causality has not yet been established, experimental, clinical, and epidemiological studies consistently support the oral–gut–brain axis as a plausible biological pathway linking chronic periodontitis with neuroinflammation and progressive neurological dysfunction (18–22).

3. Mechanisms underlying periodontal disease–associated neurodegeneration

Periodontal disease may contribute to neurodegeneration through multiple interconnected mechanisms involving microbial dissemination, systemic inflammation, blood–brain barrier (BBB) dysfunction, and chronic neuroimmune activation. Rather than acting independently, these pathways interact to promote neuronal injury and accelerate neurodegenerative processes (23–25).

3.1 Dissemination of periodontal pathogens to the central nervous system

Chronic periodontitis disrupts the gingival epithelium, allowing periodontal pathogens and their virulence factors to enter the bloodstream during routine activities such as mastication, tooth brushing, and dental procedures (24–26). In addition to hematogenous spread, certain microorganisms may migrate through the trigeminal and olfactory nerves, providing a direct route to the brain that partially bypasses the BBB (25–27). Among periodontal pathogens, *Porphyromonas gingivalis* has been most extensively investigated because of its ability to persist within host tissues and disseminate systemically, carrying virulence factors such as lipopolysaccharide (LPS), gingipains, fimbriae, and outer membrane vesicles (OMVs) that initiate inflammatory responses in distant organs (23–27).

3.2 Blood–brain barrier dysfunction and neuroimmune activation

Persistent systemic inflammation associated with periodontitis promotes the release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), together with circulating bacterial endotoxins that compromise BBB integrity (23,25–28). Increased permeability facilitates the entry of microbial products into the central nervous system, where they activate microglia and astrocytes. Sustained glial activation results in excessive production of inflammatory mediators, reactive oxygen species (ROS), and nitric oxide, creating a self-perpetuating inflammatory environment that impairs synaptic function, mitochondrial activity, and neuronal survival (28–30).

3.3 Virulence factors and protein misfolding

Beyond direct bacterial invasion, periodontal pathogens exert pathogenic effects through their virulence factors. Gingipains, LPS, OMVs, and extracellular vesicles transport proteins, toxins, nucleic acids, and regulatory microRNAs that amplify inflammatory signalling and oxidative stress across biological barriers (26,29–32). These processes promote mitochondrial dysfunction, neuronal damage, and abnormal protein aggregation, including amyloid-β, hyperphosphorylated tau, and α-synuclein, which are pathological hallmarks of Alzheimer's disease, Parkinson's disease, and related neurodegenerative disorders (29–32).

Collectively, these mechanisms provide a biologically plausible explanation for the association between chronic periodontitis and neurodegeneration. Although current evidence primarily supports an associative rather than causal relationship, accumulating experimental, molecular, and clinical findings indicate that periodontal inflammation may represent a modifiable contributor to chronic neuroinflammation and neurological disease progression (23–32).

4. Periodontal pathogens in neurodegenerative diseases

4.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia worldwide. It is characterized by progressive cognitive decline associated with extracellular amyloid-β (Aβ) plaques, intracellular hyperphosphorylated tau neurofibrillary tangles, synaptic dysfunction, and neuronal loss. Although aging and genetic predisposition remain the principal risk factors, increasing evidence suggests that chronic systemic inflammation and microbial dysbiosis contribute to disease initiation and progression (33–35).

4.1.1 Evidence linking periodontitis and Alzheimer's disease

Epidemiological and longitudinal studies consistently demonstrate an association between chronic periodontitis and cognitive impairment. Individuals with severe periodontal disease, tooth loss, poor oral hygiene, or elevated antibody titers against periodontal pathogens exhibit an increased risk of Alzheimer's disease and accelerated

cognitive decline compared with periodontally healthy individuals (34–37). While these findings do not establish causality, they identify chronic periodontitis as a plausible and potentially modifiable risk factor for AD.

Among periodontal microorganisms, *Porphyromonas gingivalis* has emerged as the pathogen most strongly associated with Alzheimer's disease. As a keystone periodontal pathogen, *P. gingivalis* promotes microbial dysbiosis and persistent inflammation despite its relatively low abundance within the subgingival biofilm. Importantly, *P. gingivalis* DNA, lipopolysaccharide (LPS), and gingipains have been identified in post-mortem brain tissue from patients with Alzheimer's disease, providing biological evidence supporting a link between chronic periodontal infection and neurodegeneration (35–38).

4.1.2 Pathogenic mechanisms

Rather than direct bacterial invasion alone, periodontal pathogens appear to influence Alzheimer's disease through their virulence factors. Gingipains degrade host proteins, impair immune regulation, and sustain chronic inflammation, whereas outer membrane vesicles (OMVs) transport LPS, proteases, adhesins, and other bacterial components capable of penetrating biological barriers and triggering inflammatory responses within neural tissue (35,38,39).

Experimental studies further demonstrate that exposure to *P. gingivalis*, gingipains, or bacterial LPS enhances amyloid-β production, tau hyperphosphorylation, oxidative stress, and neuronal injury. Animal models have also shown that periodontitis-associated salivary microbiota can alter gut microbial composition and exacerbate Alzheimer's pathology through oral–gut–brain axis interactions. In addition, other periodontal pathogens, including *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum*, may act synergistically within dysbiotic biofilms to amplify systemic inflammation and neurodegenerative processes (35,38–40).

4.1.3 Clinical implications

Current epidemiological, experimental, and molecular evidence supports a significant association between chronic periodontitis and Alzheimer's disease. Although definitive causality remains to be established, periodontal disease represents a potentially modifiable contributor to chronic neuroinflammation and cognitive decline. Maintaining periodontal health may therefore complement strategies aimed at preserving cognitive function and delaying disease progression, although well-designed longitudinal and interventional studies are required to confirm the therapeutic impact of periodontal treatment on Alzheimer's disease outcomes (33–40).

4.2 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of misfolded α-synuclein as Lewy bodies. Clinically, PD presents with resting tremor, bradykinesia, rigidity, postural instability, and a range of non-motor manifestations, including constipation, hyposmia, sleep disturbances, and cognitive impairment. Increasing evidence suggests that chronic inflammation and microbial dysbiosis contribute to PD pathogenesis, highlighting the oral–gut–brain axis as a potential link between periodontitis and neurodegeneration (41–43).

4.2.1 Evidence linking periodontitis and Parkinson's disease

Clinical studies indicate that individuals with Parkinson's disease frequently exhibit poorer periodontal health, increased tooth loss, and a higher prevalence of chronic periodontitis than age-matched controls (42–45). While impaired motor function may reduce oral hygiene and contribute to periodontal deterioration, persistent

periodontal inflammation may also increase the systemic inflammatory burden, suggesting a bidirectional relationship between PD and periodontitis (43–45).

Emerging evidence further supports the role of periodontal pathogens in PD. *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* release virulence factors capable of sustaining chronic inflammation and immune dysregulation, processes that have been implicated in dopaminergic neuronal degeneration (42,44–46).

4.2.2 Pathogenic mechanisms

The gastrointestinal tract is increasingly recognized as an important site in Parkinson's disease pathogenesis. According to the Braak hypothesis, pathological α-synuclein aggregation may originate within the enteric nervous system before spreading to the brain through the vagus nerve (41,46). Chronic periodontitis may contribute to this process by altering gut microbial composition, promoting intestinal inflammation, and disrupting epithelial barrier integrity, thereby enhancing systemic exposure to microbial products and inflammatory mediators (43,46,47).

Experimental studies also demonstrate that bacterial virulence factors, particularly lipopolysaccharide (LPS) and gingipains, activate Toll-like receptor signalling, increase oxidative stress, and promote mitochondrial dysfunction, all of which contribute to dopaminergic neuronal injury and α-synuclein pathology (44–47). Although *P. gingivalis* remains the most extensively studied pathogen, the collective effects of polymicrobial dysbiosis are likely to play a more important role than any single bacterial species.

4.2.3 Clinical implications

Current evidence supports a biologically plausible association between chronic periodontitis and Parkinson's disease through mechanisms involving microbial dysbiosis, persistent inflammation, and neuroimmune activation. Although causality has not been established, maintaining periodontal health may reduce systemic inflammatory burden and represent a supportive strategy for preserving neurological function. Future longitudinal studies and interventional clinical trials are required to determine whether periodontal therapy can influence disease progression or improve clinical outcomes in Parkinson's disease (41–47).

4.3 Multiple sclerosis

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system characterized by inflammation, axonal injury, and progressive neurological disability. Although its etiology is multifactorial, involving genetic and environmental factors, increasing evidence suggests that microbial dysbiosis and immune dysregulation contribute to disease development (48–50).

4.3.1 Evidence linking periodontitis and multiple sclerosis

Recent studies indicate that chronic periodontitis may influence MS by maintaining a persistent systemic inflammatory state. Individuals with periodontal disease exhibit elevated circulating inflammatory mediators and altered immune responses, which may exacerbate neuroinflammation and disease progression (48–50). Although epidemiological evidence remains limited, periodontal inflammation has been proposed as a potential modifier of MS severity rather than a primary cause of disease.

Among periodontal pathogens, *Porphyromonas gingivalis* has received particular attention because of its ability to evade host immunity and sustain chronic inflammation. Its virulence factors, including lipopolysaccharide (LPS), gingipains, and outer membrane vesicles (OMVs), activate innate immune pathways and enhance the production

of pro-inflammatory cytokines. Other periodontal bacteria, including *Treponema denticola* and *Tannerella forsythia*, may further amplify systemic immune activation through polymicrobial dysbiosis (48,49).

4.3.2 Pathogenic mechanisms

The oral–gut–brain axis provides a plausible biological link between periodontitis and MS. Continuous swallowing of periodontal pathogens may alter gut microbial composition, leading to intestinal dysbiosis, impaired epithelial barrier integrity, and increased systemic exposure to microbial products (49–51). These alterations influence immune homeostasis by reducing regulatory T-cell (Treg) activity while promoting pro-inflammatory T helper 17 (Th17) responses, both of which are central to MS pathogenesis (49–52).

Experimental autoimmune encephalomyelitis (EAE) models further demonstrate that manipulation of the gut microbiota through antibiotics, probiotics, or fecal microbiota transplantation can modify disease severity, emphasizing the importance of microbial–immune interactions. In addition, reduced production of beneficial short-chain fatty acids (SCFAs) during gut dysbiosis may enhance systemic inflammation and neuroimmune activation, contributing to demyelination and axonal injury (50–53).

4.3.3 Clinical implications

Current evidence supports a biologically plausible association between chronic periodontitis and multiple sclerosis through mechanisms involving immune dysregulation, microbial dysbiosis, and persistent neuroinflammation. Although a direct causal relationship has not been established, maintaining periodontal health may help reduce systemic inflammatory burden and complement existing therapeutic strategies. Further longitudinal studies and clinical trials are needed to determine whether periodontal treatment can influence disease activity or improve long-term neurological outcomes (48–53).

4.4 Stroke and cerebrovascular disease

Stroke is a leading cause of mortality and long-term disability worldwide and results from interruption of cerebral blood flow due to ischemic or haemorrhagic events. In addition to established risk factors such as hypertension, diabetes mellitus, smoking, dyslipidaemia, and atrial fibrillation, chronic inflammatory diseases including periodontitis have emerged as potential contributors to cerebrovascular disease through persistent vascular inflammation and endothelial dysfunction (54–56).

4.4.1 Evidence linking periodontitis and stroke

Epidemiological studies consistently report that individuals with moderate-to-severe periodontitis have a higher risk of ischemic stroke than periodontally healthy individuals. Poor periodontal status, tooth loss, elevated serum antibodies against periodontal pathogens, and increased systemic inflammatory biomarkers have also been associated with adverse cerebrovascular outcomes. Although these findings are primarily observational, they suggest that chronic periodontal inflammation may represent a modifiable risk factor for stroke (54–57).

Among periodontal pathogens, *Porphyromonas gingivalis* has been most extensively investigated because of its ability to induce endothelial dysfunction and accelerate atherosclerotic plaque formation. Other organisms, including *Fusobacterium nucleatum*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*, may further contribute to vascular inflammation through polymicrobial interactions (55–58).

4.4.2 Pathogenic mechanisms

Periodontal pathogens and their virulence factors, particularly lipopolysaccharide (LPS), gingipains, fimbriae, and outer membrane vesicles (OMVs), activate vascular endothelial cells and innate immune pathways, promoting

chronic inflammation, oxidative stress, platelet activation, and thrombus formation. These processes accelerate atherosclerosis and increase the susceptibility to ischemic cerebrovascular events (55–58).

In addition, oral dysbiosis may influence cerebrovascular health through the oral–gut–brain axis. Colonization of the gastrointestinal tract by periodontal pathogens can alter gut microbial composition, impair intestinal barrier integrity, and enhance systemic inflammatory signalling. Experimental studies suggest that gut dysbiosis following stroke further amplifies neuroinflammation, delays neurological recovery, and worsens functional outcomes by altering immune responses and reducing beneficial short-chain fatty acid production (56–59).

4.4.3 Clinical implications

Current evidence supports a biological association between chronic periodontitis and stroke through interconnected mechanisms involving vascular inflammation, endothelial dysfunction, atherosclerosis, and microbial dysbiosis. Although causality has not been confirmed, maintenance of periodontal health may contribute to reducing systemic inflammatory burden and improving cerebrovascular health. Prospective clinical studies and randomized intervention trials are required to determine whether periodontal therapy can reduce stroke risk or improve post-stroke recovery (54–60).

4.5 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the selective degeneration of upper and lower motor neurons, leading to progressive muscle weakness, paralysis, respiratory failure, and death. Although approximately 10% of ALS cases are familial, most are sporadic and result from complex interactions between genetic susceptibility and environmental factors. Oxidative stress, mitochondrial dysfunction, protein aggregation, and chronic neuroinflammation are recognized contributors to disease progression (61–63).

4.5.1 Evidence linking periodontitis and ALS

Direct evidence linking periodontitis to ALS remains limited; however, increasing attention has focused on the potential contribution of chronic oral inflammation and microbial dysbiosis to neurodegeneration. Periodontal pathogens, particularly *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum*, release virulence factors that sustain systemic inflammation and may indirectly influence motor neuron degeneration. Current evidence suggests that periodontal disease should be regarded as a potential modifier of inflammatory burden rather than a primary cause of ALS (61–64).

4.5.2 Pathogenic mechanisms

The oral–gut–brain axis provides a plausible biological framework linking periodontal disease with ALS. Persistent oral dysbiosis may alter gut microbial composition, impair intestinal barrier integrity, and reduce the production of beneficial short-chain fatty acids (SCFAs), thereby promoting immune dysregulation and systemic inflammation (62–65). Experimental studies have shown that microbiome modulation can influence disease severity in ALS models, suggesting that microbial composition may affect motor neuron survival. In addition, periodontal virulence factors, including lipopolysaccharide (LPS), gingipains, and extracellular vesicles, may enhance oxidative stress, mitochondrial dysfunction, and neuroimmune activation, increasing the vulnerability of motor neurons to degeneration (63–65).

4.5.3 Clinical implications

Although current evidence does not establish a causal relationship between periodontitis and ALS, chronic

periodontal inflammation may contribute to disease progression by amplifying systemic inflammatory responses. Maintaining periodontal and gut microbial health may therefore represent a supportive strategy for reducing inflammatory burden. Future longitudinal studies and clinical trials are required to clarify whether periodontal therapy or microbiome-targeted interventions can influence ALS progression or improve patient outcomes (61–65).

4.6 Mild cognitive impairment

Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive aging and dementia, characterized by measurable deficits in memory and other cognitive domains while preserving functional independence. Individuals with MCI are at increased risk of progressing to Alzheimer's disease, making the identification of modifiable risk factors an important research priority (66–68).

4.6.1 Evidence linking periodontitis and MCI

Emerging clinical evidence indicates that poor periodontal health, tooth loss, and chronic oral inflammation are associated with impaired cognitive performance and an increased risk of MCI. Although these associations are largely observational, they suggest that persistent periodontal inflammation may contribute to early cognitive decline through sustained systemic immune activation (66–69).

4.6.2 Pathogenic mechanisms

Periodontal pathogens, particularly *Porphyromonas gingivalis*, release virulence factors capable of promoting chronic inflammation and microbial dysbiosis. Alterations in the oral microbiota may extend to the gastrointestinal tract through the oral–gut–brain axis, leading to intestinal dysbiosis, impaired barrier function, and reduced production of neuroprotective short-chain fatty acids (SCFAs). These changes may enhance neuroinflammation, impair synaptic function, and accelerate early cognitive decline. Although the precise mechanisms remain under investigation, microbial dysbiosis and persistent inflammation are considered key contributors to MCI progression (67–70).

4.6.3 Clinical implications

Current evidence supports an association between chronic periodontitis and mild cognitive impairment, although causality has not been established. Periodontal health may therefore represent a modifiable factor for preserving cognitive function during aging. Well-designed prospective studies and randomized clinical trials are needed to determine whether periodontal treatment can delay cognitive decline or reduce progression from MCI to Alzheimer's disease (66–70).

4.7 Depression and anxiety

Depression and anxiety are multifactorial psychiatric disorders influenced by genetic, environmental, immune, and microbial factors. Increasing evidence suggests that chronic systemic inflammation and disruption of the oral–gut–brain axis contribute to altered mood regulation and psychological disorders (71–73).

4.7.1 Evidence linking periodontitis and mood disorders

Clinical studies have reported a higher prevalence of depression and anxiety among individuals with chronic periodontitis. Conversely, psychiatric disorders may worsen periodontal health by impairing oral hygiene, dietary habits, and treatment adherence, suggesting a bidirectional relationship (72–74).

4.7.2 Pathogenic mechanisms

Periodontal pathogens, particularly *Porphyromonas gingivalis*, release virulence factors including

lipopolysaccharide (LPS), gingipains, and extracellular vesicles that promote systemic inflammation. Through the oral–gut–brain axis, periodontal dysbiosis may alter gut microbial composition, reduce beneficial short-chain fatty acid (SCFA) production, activate the hypothalamic–pituitary–adrenal (HPA) axis, and stimulate microglial activation. These mechanisms contribute to neuroinflammation, altered neurotransmitter signalling, and impaired stress responses associated with depression and anxiety (71–75).

4.7.3 Clinical implications

Although causality remains unproven, chronic periodontal inflammation may contribute to mood disorders by increasing systemic inflammatory burden. Maintaining periodontal health may therefore provide supportive benefits for psychological well-being, although prospective clinical trials are needed to determine whether periodontal therapy improves psychiatric outcomes (72–75).

4.8 Vascular dementia

Vascular dementia (VaD) is the second most common form of dementia and results from cerebrovascular injury, impaired cerebral perfusion, and chronic vascular inflammation. Endothelial dysfunction, oxidative stress, and blood–brain barrier disruption are central features of disease progression (76–78).

4.8.1 Evidence linking periodontitis and vascular dementia

Epidemiological studies associate periodontitis, tooth loss, and elevated systemic inflammatory markers with an increased risk of vascular cognitive impairment and dementia (76–79). Although these associations do not establish causality, they suggest that periodontal disease may contribute to cerebrovascular pathology.

4.8.2 Pathogenic mechanisms

Periodontal pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* promote endothelial dysfunction through chronic inflammatory signalling and release of virulence factors including LPS and gingipains. Oral dysbiosis may also alter gut microbial composition, increasing systemic inflammation and blood–brain barrier dysfunction through the oral–gut–brain axis. Collectively, these processes may accelerate vascular injury and cognitive decline (77–80).

4.8.3 Clinical implications

Current evidence supports a biological association between chronic periodontitis and vascular dementia, although direct causality remains uncertain. Effective periodontal care may help reduce systemic inflammatory burden and improve vascular health; however, randomized clinical studies are required to confirm its role in dementia prevention (76–80).

4.9 Lewy body dementia

Lewy body dementia (LBD) is a progressive neurodegenerative disorder characterized by cognitive decline, visual hallucinations, fluctuating attention, and parkinsonism. The pathological hallmark is the accumulation of misfolded α-synuclein within neurons, accompanied by chronic neuroinflammation (81–83).

4.9.1 Evidence linking periodontitis and LBD

Direct evidence linking periodontal disease to LBD remains limited. However, shared mechanisms involving chronic inflammation, microbial dysbiosis, and α-synuclein pathology suggest a plausible biological association (81–84).

4.9.2 Pathogenic mechanisms

Periodontal pathogens, particularly *Porphyromonas gingivalis*, release LPS, gingipains, and outer membrane

vesicles that promote systemic inflammation and microglial activation. Through the oral–gut–brain axis, dysbiosis may influence α-synuclein aggregation, immune regulation, and oxidative stress. Experimental findings from Parkinson's disease models support the contribution of gut microbial imbalance to α-synuclein-mediated neurodegeneration (82–85).

4.9.3 Clinical implications

Although direct clinical evidence is scarce, current data support periodontal inflammation as a potential modifier of neurodegenerative processes rather than a direct cause of LBD. Further longitudinal and mechanistic studies are required to determine whether periodontal treatment can influence disease progression (81–85).

5. Clinical significance: Periodontitis as a modifiable risk factor for neurodegeneration

Periodontitis shares several pathogenic mechanisms with established risk factors for neurodegenerative diseases, including chronic systemic inflammation, oxidative stress, endothelial dysfunction, and immune dysregulation (86–89). Unlike non-modifiable factors such as age or genetic susceptibility, periodontal disease is preventable, detectable during routine dental examinations, and effectively managed through evidence-based therapy. These characteristics make periodontitis a potential modifiable risk factor for neurodegenerative disorders (86,90).

Successful periodontal treatment has been associated with reductions in systemic inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), suggesting that improving periodontal health may reduce inflammatory pathways implicated in neurodegeneration (87–90). Although direct evidence that periodontal therapy prevents neurological disease is still limited, maintaining periodontal health represents a practical and cost-effective strategy that may complement existing preventive measures.

Interdisciplinary collaboration among dentists, neurologists, geriatricians, and primary care physicians may facilitate early identification of individuals at risk and promote integrated management of oral and neurological health. Large prospective studies and randomized clinical trials are required to determine whether periodontal intervention can modify disease onset or progression (89–91).

Table 1: Association between periodontal pathogens and neurodegenerative diseases

Diseases	Major Pathogens	Main Mechanism	Key Outcome
Alzheimer's	*P. gingivalis*	Gingipains, Aβ deposition	Cognitive declines
Parkinson's	*P. gingivalis*	α-Synuclein, gut dysbiosis	Dopaminergic loss
Multiple Sclerosis	Mixed pathogens	Th17 activation	Demyelination
Stroke	*P. gingivalis*	Endothelial dysfunction	Ischemic
ALS	Mixed pathogens	Oxidative stress	Motor neuron loss
MCI	Mixed pathogens	Neuroinflammation	Early cognitive decline
Depression	Mixed pathogens	HPA-axis activation	Mood Disorders
Vascular Dementia	*P. gingivalis*	Vascular inflammation	Cognitive impairment
Lewy body Dementia	Mixed pathogens	α-Synuclein pathology	Dementia

6. Emerging therapeutic strategies targeting the oral–gut–brain axis

Growing recognition of the oral–gut–brain axis has prompted the development of therapeutic strategies aimed at reducing oral dysbiosis, restoring microbial balance, and limiting neuroinflammation (92–95). While current evidence remains largely experimental, these approaches may complement conventional periodontal care in

reducing systemic inflammatory burden (92–95).

6.1 Conventional periodontal therapy

Scaling and root planning (SRP) remains the gold standard for periodontal treatment. By reducing pathogenic biofilms and local inflammation, SRP also lowers systemic inflammatory biomarkers such as CRP and IL-6, potentially influencing pathways involved in neurodegeneration. Long-term periodontal maintenance is essential to prevent recolonization and sustained inflammation (95,96).

6.2 Microbiome-based therapies

Probiotics, prebiotics, and synbiotics have shown promise in restoring oral and gut microbial balance, enhancing short-chain fatty acid (SCFA) production, and modulating immune responses. Dietary interventions, particularly Mediterranean-style diets rich in fiber and polyphenols, may further support microbial diversity and reduce systemic inflammation. However, evidence for neurological benefits remains limited (94–97).

6.3 Targeted antimicrobial strategies

Selective antimicrobial approaches, including gingipain inhibitors targeting *Porphyromonas gingivalis*, pathogen-specific therapies, and bacteriophage treatment, aim to eliminate periodontal pathogens while preserving beneficial microbiota. Although preclinical findings are encouraging, clinical evidence remains insufficient (96–99).

6.4 Future precision therapies

Emerging technologies such as microbiome engineering, CRISPR-based microbial editing, engineered probiotics, and fecal microbiota transplantation (FMT) offer opportunities for personalized modulation of the oral and gut microbiome. These approaches remain investigational but may provide future strategies for reducing neuroinflammation and disease progression (98–101).

Key Takeaway

Targeting the oral–gut–brain axis extends beyond conventional periodontal therapy and represents a promising direction for preventing or reducing neuroinflammation. While periodontal treatment remains the cornerstone of care, microbiome-based therapies and precision antimicrobial approaches may provide additional benefits. However, robust longitudinal studies and randomized clinical trials are still required before these interventions can be recommended for preventing or modifying neurodegenerative diseases (92–101).

7. Bridging current evidence gaps

Despite growing evidence supporting the oral–gut–brain axis, several important knowledge gaps remain. Most available data are derived from observational studies and experimental models, limiting the ability to establish a direct causal relationship between periodontal disease and neurodegeneration (102–104). In addition, variability in microbiome sampling, sequencing technologies, and analytical methods reduces the reproducibility and comparability of published findings (103,105). Future research should focus on standardized methodologies, validated salivary and microbial biomarkers, multicentre longitudinal cohorts, and randomized clinical trials to determine whether periodontal therapy can modify neurological outcomes (102,104–106).

Table 2: Current limitations and future research priorities

Current limitations	Future direction
Predominantly observational evidence	Longitudinal cohort studies
Limited randomized clinical trials	Interventional studies
Variable microbiome methodologies	Standardized protocols
Lack of validation biomarkers	Salivary and microbial biomarkers validation
Limited mechanism evidence	Multi-omics research
Poor clinical translation	Precision medicine approaches

8. Future perspectives

Rapid advances in microbiome science, multi-omics technologies, and precision medicine are expanding opportunities for early diagnosis and personalized management of neurodegenerative diseases (106–108). Emerging approaches, including salivary biomarker discovery, microbiome profiling, probiotics, prebiotics, synbiotics, bacteriophage therapy, and fecal microbiota transplantation, may help restore microbial homeostasis and reduce neuroinflammation, although robust clinical validation is still required (107–109).

Future progress will rely on close collaboration among dentists, neurologists, microbiologists, immunologists, and other healthcare professionals to translate these discoveries into effective preventive and therapeutic strategies (106,108,109).

Conclusion

The oral–gut–brain axis has emerged as an important biological framework linking periodontal health with neurological function. Current evidence suggests that chronic periodontitis and oral dysbiosis may contribute to neurodegenerative diseases through interconnected mechanisms involving microbial dissemination, systemic inflammation, immune dysregulation, oxidative stress, blood–brain barrier dysfunction, and neuroinflammation. These pathways collectively highlight the potential influence of oral health on disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, stroke, mild cognitive impairment, vascular dementia, Lewy body dementia, and mood disorders.

Although the available evidence strongly supports an association between periodontal disease and neurodegeneration, a definitive causal relationship has not yet been established. Further well-designed longitudinal studies, mechanistic investigations, and randomized clinical trials are required to determine whether periodontal therapy and microbiome-targeted interventions can prevent, delay, or modify the progression of neurological disorders.

From a clinical perspective, periodontal disease represents a readily identifiable, preventable, and treatable condition that may serve as a modifiable risk factor for systemic and neurological health. Integrating periodontal assessment into multidisciplinary healthcare and promoting preventive oral care may help reduce systemic inflammatory burden while supporting healthy ageing. Continued advances in microbiome research, biomarker discovery, and precision medicine are expected to further clarify the therapeutic potential of the oral–gut–brain axis and strengthen the integration of oral health into comprehensive neurological care.

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