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INVITED REVIEW

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The potential impact of periodontitis on cerebral small vessel disease

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Abstract

Cerebral small vessel disease (CSVD) is a term used to describe abnormalities in the intracranial microvasculature affecting small arteries, arterioles, capillaries, and venules. The etiology of these conditions is not fully understood but inflammation appears to play a significant role. Periodontal diseases have been associated with conditions such as stroke and dementia, which are clinical consequences of CSVD. Periodontitis is a highly prevalent chronic multifactorial inflammatory disease regulated by the host immune response against pathogenic bacterial colonization around the teeth. The inflammatory response and the microbial dysbiosis produce pro-inflammatory cytokines that can reach the brain and promote local changes. This review will explore the potential association between periodontitis and CSVD by assessing the impact of periodontitis-induced inflammation and periodontopathogenic bacteria on the underlying mechanisms leading to CSVD. Given the association of periodontitis with stroke and dementia, which are clinical features of CSVD, it may be possible to suggest a link with CSVD. Current evidence linking periodontitis with neuroimaging findings of CSVD enforces the possible link between these conditions.

KEYWORDS
cerebral small vessel disease, inflammation, periodontitis, vascular endothelial dysfunction

1 | INTRODUCTION

Periodontitis is a highly prevalent chronic inflammatory disease with over 64 million adults over the age of 30 presenting some level of the disease in the United States (Darveau, 2010; Eke et al., 2015). To date, periodontitis has been associated with several systemic diseases, such as diabetes, rheumatoid arthritis, and atherosclerosis, among others. One of the main mechanisms participating in these associations is the low-grade inflammation initiated as a response to a dysbiotic microbial community in the periodontal pocket. This low-grade inflammation, with increased local and systemic levels of pro-inflammatory cytokines, promotes a positive feedback loop in which microbial dysbiosis persists and continues to activate the host immune response, producing pro-inflammatory cytokines that can reach various parts of the body, including the brain (Cecoro et al., 2020). Direct effects of certain periodontopathogens, via virulence factors, have also been reported, where *Porphyromonas gingivalis* gingipains and lipopolysaccharide (LPS) have been linked to alterations in endothelial cells (Bartruff et al., 2005), disruption of the blood-brain barrier (BBB) (Nonaka et al., 2022), and neuroinflammation (Yoshida et al., 2022). Evidence suggests that all these factors could contribute to the progression of cerebrovascular diseases (Aarabi et al., 2019).

Cerebrovascular diseases are a group of disorders in which brain vessels are affected, leading to ischemic and hemorrhagic events. When this condition occurs in cerebral microvessels, it is referred to as cerebral small vessel disease (CSVD). CSVD is a common cause of stroke and cognitive decline, but often starts clinically silent, and only noted upon brain imaging (Debette et al., 2019). Epidemiological

studies have reported an association between stroke and periodontal disease (Jimenez et al., 2009; Leira et al., 2017; Sen et al., 2018) and cognitive impairment, such as Alzheimer's disease (AD) (Dominy et al., 2019). Many risk factors for CSVD are also risk factors for periodontitis, such as age, hypertension, diabetes, hyperlipidemia, and smoking (Genco & Borgnakke, 2013; Wang et al., 2021). However, the impact of periodontitis on the precursor for these diseases, CSVD, is still underreported.

The goal of this manuscript is to review the available literature and attempt to identify an association between periodontitis and CSVD by assessing the impact of periodontitis-induced inflammation on endothelial dysfunction and BBB dysfunction, common underlying mechanisms associated with CSVD, as well as neuroinflammation.

2 | METHODOLOGICAL ASPECTS

This study consisted in a narrative literature review to evaluate the association between periodontitis and CSVD. The searches were performed in the main international databases (PubMed, Web of Science, and Scopus), in addition to a manual search. The search strategy used in all databases included the descriptors and MeSH "(medical subject headings) terms: (periodontal diseases) AND (cerebral small vessels diseases) OR (stroke) OR (dementia)" without study design distinction. No restriction for year or language was used. Observational studies and laboratorial studies were included, and interventional studies were excluded.

3 | CEREBRAL SMALL VESSEL DISEASE

CSVD encompasses several abnormalities in the intracranial microvasculature affecting small arteries, arterioles, capillaries, and venules. Given the difficulty in identifying small cerebral vessels in vivo, CSVD is often detected on magnetic resonance imaging (MRI). Common manifestations of CSVD include microinfarcts, small deep infarcts (lacunar infarctions), white matter disease of aging, and cerebral microbleeds (CMBs) (Fang et al., 2023). Many of these observations are incidental as they do not result in symptoms. However, evidence shows that lesion accumulation can lead to an increased risk of stroke (Charidimou et al., 2013) and cognitive impairment (Poels et al., 2010), making CSVD a risk predictor for these diseases (de Havenon et al., 2023).

The two main pathological classifications of CSVD are hypertensive vasculopathy and cerebral amyloid angiopathy (CAA), and these conditions are clinically relevant to stroke and cognitive decline (Jokinen et al., 2020). In hypertensive vasculopathy, which affects mostly the deep penetrating arterioles of the brain, pathologic alterations of the small vessels lead to loss of vessel contractibility. These structural changes are usually associated with endothelial dysfunction, characterized by impaired dilation and a pro-inflammatory phenotype (Schiffrin, 2012). The overall effects of these changes are a reduction in cerebral blood flow and hypoperfusion of the brain tissues (Ter Telgte et al., 2018). It is suggested that dysfunction of the BBB and inflammation can be etiological factors for these changes (Takata et al., 2021).

CAA consists of the accumulation of beta-amyloid protein in cerebral vessel walls. The accumulation of these proteins leads to narrowing of the vessel's lumen thus affecting cerebral blood flow resulting in microbleeds, hypoperfusion, and tissue hypoxia, which could be responsible for intracerebral hemorrhages and cognitive impairment. These pathological changes occur in a different area of the brain (cortical and leptomeningeal arteries), compared to hypertensive vasculopathy.

The underlying mechanism that seems to be related with both hypertensive vasculopathy and CAA is endothelial dysfunction that promotes several changes in the microvasculature of the brain later affecting BBB integrity (Quick et al., 2021). Endothelial cells in the brain are an integral part of the BBB and are joined together by tight junction (TJ) complexes, which act as a protective barrier for the brain parenchyma. With the onset of endothelial dysfunction, a lower expression of TJ proteins is noted, which leads to decreased barrier integrity (BBB dysfunction). With the increased permeability of the BBB, infiltration of blood-borne products triggers activation of glial cells resulting in a positive feedback loop of aggravated brain inflammation and glial activation (Takata et al., 2021).

4 | CSVD AND PERIODONTITIS—MECHANISTIC LINKS

Given that the underlying mechanisms associated with CSVD are endothelial dysfunction and BBB breakdown, which, in themselves, have a relationship with systemic inflammation, it is possible to suggest that the low-grade inflammation induced by periodontitis may play a role in the initiation of CSVD. Besides the effects of inflammation on the initiation of endothelial dysfunction and consequently neuroinflammation, studies have also demonstrated the direct effects of periodontopathogens on endothelial dysfunction and accumulation of beta-amyloid proteins in the brain. We will be discussing these roles separately. The illustration for these links can be better appreciated on Figure 1.

4.1 | Link 1: Low-grade inflammation

4.1.1 | Low-grade inflammation as a result of periodontitis leading to endothelial dysfunction

The activation of the inflammatory response in the periodontal tissues leads to the expression of various pro-inflammatory cytokines that can reach areas further in the body from its origin. Several studies have demonstrated the impact of periodontal pathogens on activation of inflammatory response by endothelial cells (Chhibber-Goel et al., 2016; Schenkein & Loos, 2013).

Once endothelial cells develop an inflammatory phenotype, they produce various inflammatory cytokines, including interleukins (IL) as

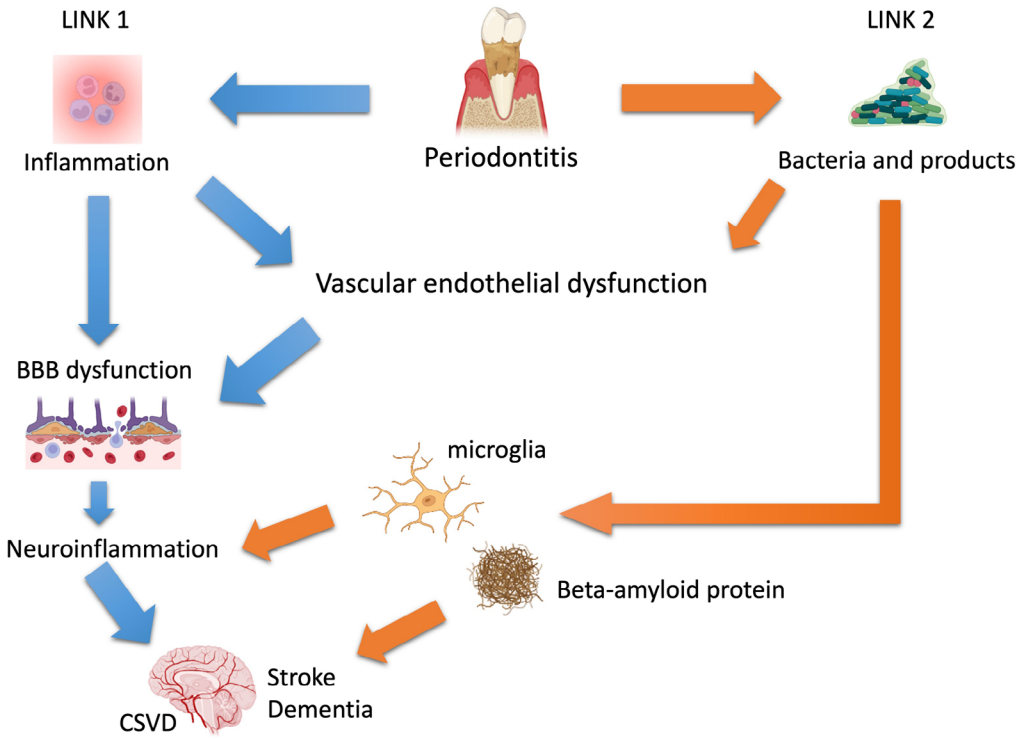

FIGURE 1 Plausible links between periodontitis and cerebral small vessel diseases. The low-grade systemic inflammation elicited during periodontitis, together with periodontopathogens and their products, can have consequences at distant areas from the oral cavity. Inflammation is the main culprit for several of the systemic consequences associated with periodontitis. A plausible mechanism linking periodontitis with CSVD is mediated by systemic low-grade inflammation (Link 1) that impacts the vascular endothelial and the BBB. Disruption of the homeostasis of the vascular endothelial environment has a significant impact on the homeostasis of the BBB. With BBB dysfunction, the increased permeability of this barrier allows circulating pro-inflammatory cytokines, and other products, to reach the brain environment thus promoting neuroinflammation. Periodontopathogens and their products (LPS, etc.) (Link 2) have also been shown to act directly on endothelial cells promoting endothelial dysfunction or acting directly on microglial cells activating an inflammatory profile of these central nervous system (CNS) cells. They have also been implicated in affecting the metabolism of beta-amyloid proteins contributing to their accumulation in the brain.

IL-1, IL-6, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), which will perpetuate the activation of endothelial cells (Moura et al., 2017). If periodontal disease is not treated, the dysbiotic biofilm continues to trigger an immune response, establishing a positive-feedback loop where the constant production of pro-inflammatory cytokines will continue to activate the endothelial cells. This was demonstrated in a clinical study in which treatment of periodontitis resulted in an overall reduction on serum pro-inflammatory markers leading to an improvement in endothelial function (Tonetti et al., 2007).

Another aspect of endothelial dysfunction that has been noted in in vitro and animal studies of experimental periodontitis is the inhibition of nitric oxide (NO) production in endothelial cells via pro-inflammatory cytokines and reactive oxygen species (Parvaneh et al., 2021; Yang et al., 2022). NO is responsible for vasodilation and changes in its production and sensitivity are a sign of endothelial dysfunction (Cyr et al., 2020). The accumulation of reactive oxygen species (ROS) interferes with the NO signaling pathway reducing NO bioavailability, thus affecting endothelial-dependent relaxation (Garcia & Sessa, 2019). Pro-inflammatory cytokines such as IL-6 and TNF-alpha have also been shown to reduce the production of NO (Huang & Vita, 2006).

4.1.2 | Low-grade inflammation as a result of periodontitis inducing neuroinflammation

Neuroinflammation is an inflammatory response within the brain or the spinal cord, which is mediated by cytokines, chemokines and other mediators produced by glial cells, endothelial cells as well as peripherally derived immune cells (DiSabato et al., 2016). As noted previously, periodontal disease induces a low-grade level of systemic inflammation that is confirmed by increased serum levels of CRP. The heightened systemic inflammatory burden increases the permeability of the BBB allowing pro-inflammatory cytokines to reach the brain and trigger activation of microglia, the immune surveillance cells of the central nervous system (CNS), to produce brain-derived inflammatory cytokines. In the presence of low-grade inflammatory signals such as in periodontitis, the chronic activation of the microglial cells can lead to detrimental changes in the CNS (Norden & Godbout, 2013).

Animal studies have also demonstrated that ligature-induced periodontitis can trigger the immune response in the brain, via an increase in circulating pro-inflammatory cytokines, thus affecting microglial

cells directly, which suggests a direct role of periodontitis-induced inflammation on neuroinflammation (Almarhoumi et al., 2023; Kantarci et al., 2020).

4.2 | Link 2: Direct effects of periodontopathogens

4.2.1 | Effects of periodontopathogens on endothelial dysfunction

In vitro studies show the direct effect of *P. gingivalis* on vascular endothelial cells, with upregulation of pro-inflammatory cytokines such as TNF-alpha and IL-6, along with increased matrix metalloproteinase 2 (MMP2) among others (Moura et al., 2017). *P. gingivalis* gingipains have also been shown to increase vascular permeability via cleavage of platelet endothelial cell adhesion molecule 1 (PECAM-1) (Farrugia et al., 2020; Zhang et al., 2021). *P. gingivalis* LPS also induced cleavage of adherens junction proteins leading to an increase in vascular permeability (Ding et al., 2020). Besides, this pathogen can spread from cell to cell in the vascular tissue and it is suggested that the entry of *P. gingivalis* into the brain happens in a similar manner via peripheral nerves (Kamer et al., 2015).

It has also been demonstrated that certain periodontopathogens can invade endothelial cells and persist intracellularly, which contributes to the activation of the inflammatory response in these cells. Even though the consequence on endothelial dysfunction is mediated by the inflammatory response, *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* via direct invasion of endothelial cells, can lead to a dysfunctional phenotype of the endothelial cells.

4.2.2 | Effects of periodontopathogens on neuroinflammation and beta-amyloid accumulation

It has been demonstrated that periodontopathogenic bacteria such as *P. gingivalis* can affect the accumulation of beta-amyloid via virulence factors such as gingipains, outer membrane vesicles, and LPS (Leira, Iglesias-Rey, et al., 2019). These virulence factors have also been implicated in the disruption of the BBB via destruction of the TJs between neurovascular endothelial cells (Nonaka et al., 2022; Pritchard et al., 2022), and perpetuation of neuroinflammation via activation of microglial cells (Yoshida et al., 2022).

Beta-amyloid peptides play a protective role in the body; however, local vascular disturbances affect the clearance of these peptides leading to their accumulation in the brain parenchyma and vasculature. In vitro and animal studies have also demonstrated the effects of *P. gingivalis* on the clearance rate of beta-amyloid from the brain and increased activation of microglia (Liu et al., 2017; Olsen et al., 2016).

Overall, the data available point to the impact of periodontitis-induced inflammation on endothelial dysfunction, neuroinflammation, and alterations in the metabolism of beta-amyloid, which could be considered potential links in the association between periodontal disease and CSVD.

5 | CSVD AND PERIODONTITIS—CLINICAL ASSOCIATIONS

Many epidemiological studies evaluating the association between periodontitis and stroke and AD are available in the literature. However, only few studies have explored the association between periodontitis and CSVD, which is responsible for 25% of ischemic strokes, most hemorrhagic strokes, and 45% of case of dementia (Singh et al., 2023). Given that CSVD is an underlying condition in the development of strokes and dementia, and the underlying mechanisms associated with their development stem from systemic inflammation, it is important to investigate the impact of periodontitis on CSVD.

Before looking into the available evidence investigating the association between periodontitis and CSVD, it is important to briefly discuss the clinical outcomes of these conditions, stroke and dementia, and their reported association with periodontitis.

5.1 | Stroke

Stroke is the clinical manifestation of an abrupt interruption of blood floor to the brain that causes loss of neurological function. In 2017, stroke was the third-leading cause of death and disability combined and the second-leading cause of death in the world, leading to a substantial physical, psychological, and economic burden (Krishnamurthi et al., 2020; Kyu et al., 2018).

Strokes can be divided into two major categories: hemorrhagic and ischemic. Hemorrhagic strokes occur by the rupture of a blood vessel resulting in bleeding into the brain. High rates of severe morbidity and mortality have been demonstrated in hemorrhagic stroke (Van Asch et al., 2010). Ischemic strokes are caused by interruption of blood supply to a part of the brain. The prevalences of the various types of stroke are: ischemic stroke accounts for 87% of cases, intracerebral hemorrhage accounts for 10%, and only 3% of cases are due to subarachnoid hemorrhage (Tsao et al., 2023).

Epidemiological studies report common risk factors between stroke and periodontitis such as hypertension, diabetes, smoking, and advanced age (Kelly et al., 2007). In addition, studies have sugested periodontal disease as a risk factor for stroke, two meta-analyses reporting that patients presenting with periodontitis have a relative risks between 1.88- and 2.52-fold risk of developing ischemic stroke (Leira et al., 2017; Fagundes et al., 2019) according to cohort studies included in these meta-analysis.

The biological plausibility for this association is multifaceted. A systemic inflammatory host response to periodontitis is suggested to mediate this relationship (Kamer et al., 2008). Inflammatory process may induce a state through mechanisms that include dissemination of pro-inflammatory cytokine and periodontopathogens in the systemic circulation (Hajishengallis, 2015). Systemic inflammation can increase the risk of stroke episodes in chronic phases, and inflammatory markers such as CRP and IL-6 were pointed as indicators of increased stroke risk and are also identified as biomarkers for periodontitis (Jimenez et al., 2009). A systemic inflammation process was also linked to changes

in microglia. It was suggested that this process could lead to alterations in the phenotype, resulting in increased neuroinflammation and neurodegeneration (Perry & Teeling, 2013) .

Although several studies showed association between periodontitis and stroke, the mechanisms behind this relationship still need to be further elucidated. In addition, differences between the studies should be noted (Fagundes et al., 2019; Leira et al., 2017). The use of different criteria for periodontitis diagnosis (full mouth exam, self-report, or partial exam) and differences in criteria user for diagnosing stroke could overestimate or underestimate this association (Kingman et al., 2008). Most studies evaluating the association between periodontitis and stroke are focused on ischemic stroke due to its higher prevalence compared to hemorrhagic (Fagundes et al., 2019; Leira et al., 2017). Future investigations should consider the time between stroke and periodontal evaluation, and employ current criteria to diagnose periodontitis and stroke, use a representative sample, have calibrated examiners , and statistical analysis with adjustment for confounding factors.

5.2 | Dementia

Dementia is an umbrella term that includes several conditions, among them AD. It is characterized by functional incapacitation and progressive cognitive decline. It has been demonstrated that CAA, one of the pathological alterations noted in CSVD, has been associated with cognitive decline and also noted in patients with AD (Brenowitz et al., 2015); however, these two conditions show different clinical presentation, even though both are associated with the accumulation of beta-amyloid.

In CAA, beta-amyloid accumulation occurs in the walls of the arteries and arterioles within the cortex and leptomeninges, with a preference noted for occipital cortex followed by frontal, temporal, and parietal cortices (Magaki et al., 2018). The brain injuries observed with CAA are associated with blood vessel dysfunction, either due to loss of vessel integrity or loss of normal blood supply, and the clinical presentation can be in the form of a stroke or cognitive decline (Greenberg et al., 2020; Smith, 2018). The effects of beta-amyloid on AD are noted in the brain parenchyma and seem to be associated with loss of synapses and neurons and tau deposition (Greenberg et al., 2020).

It has been suggested that vascular changes associated with the accumulation of beta-amyloid can result in hemorrhagic or ischemic brain injuries reflective of CSVD such as microbleed and white-matter hyperintensities (WMH), and can eventually lead to cognitive impairment (Smith, 2018). This theory has been suggested after findings showed CAA to be a predictor of cognitive decline and increased risk for dementia when results were controlled for AD pathology (Smith, 2018).

The current studies available in the literature have attempted to investigate the association between AD and periodontitis and have made significant strides in understanding the underlying mechanisms associated with these two conditions (Ryder, 2022). Other studies have also investigated the association between dementia and cognitive decline with periodontitis, suggesting the role of neuroinflammation as the intermediary between the two conditions (Asher et al., 2022). The study designs, however, must be carefully considered as categorizing periodontal disease and cognitive decline can have a significant impact on the findings.

As studies suggest the underlying cause of cognitive decline/dementia to be CAA, it is important to investigate the potential association between periodontitis and this condition. Available evidence demonstrates a link between periodontitis and accumulation of beta-amyloid plaques and neuroinflammation, it is possible to suggest that the same mechanisms could contribute to alterations noted in CAA.

6 | CSVD NEUROIMAGING FINDINGS AND PERIODONTITIS

In order to explore the current evidence attempting to associate periodontitis with various presentations of CVSD, we will be discussing them according to their imaging presentation.

6.1 | Lacunar infarcts

Most of the evidence available investigating the association between periodontitis and CSVD is related to lacunar infarcts. Lacunar infarcts cause approximately 25% of the cases of ischemic stroke (Singh et al., 2023). In order for CSVD to be considered the underlying cause of ischemic stroke, patients must undergo brain imaging via MRI, given that these lesions are small and challenging to be identified via other methods.

Studies have investigated the association between periodontitis and lacunar infarcts in different populations and have obtained varying results (Adam et al., 2022; Ito et al., 2022; Leira et al., 2016; Leira, Rodriguez-Yanez, et al., 2019a; Taguchi et al., 2013). Most studies have noted a positive association between the presence of periodontitis and lacunar infarcts (Ito et al., 2022; Leira et al., 2016; Leira, Rodriguez-Yanez, et al., 2019a; Taguchi et al., 2013), whereas Adam et al (2022) could not identify such association. These differences between studies are associated with several factors including the type of population included in the study, how periodontal disease was defined and assessed, the sample size, among others.

The severity of periodontitis was associated with the number of lacunar infarctions (Taguchi et al., 2013) and poor functional outcomes at 3 months (Leira, Rodriguez-Yanez, et al., 2019a). These results corroborate the data presented by Leira et al., which suggested a correlation between systemic inflammation and endothelial dysfunction triggered by periodontitis in a cohort of patients with lacunar infarct (Leira, Rodriguez-Yanez, et al., 2019b).

Given the nature of these studies' design, it is difficult to assess the causality between periodontitis and pathogenesis of lacunar infarcts. It is also important to consider confounding factors that can play a role in the etiopathogenesis of both conditions. Multiple risk factors for cerebrovascular disease, such as smoking, diabetes, obesity,

hypertension, and advanced age, are also risk factors or risk indicators for periodontitis (Fang et al., 2023; Genco & Borgnakke, 2013). Hence, it is uncertain whether these factors could just behave as comorbidities or whether there are specific mechanisms and pathological pathways linking CSVD and periodontitis (Genco & Borgnakke, 2013; Jimenez et al., 2009). All these conditions should be considered and properly analyzed.

6.2 | White matter hyperintensities

WMH, another marker of CSVD, occurs with increasing age and share common risk factors with periodontitis such as smoking and diabetes. It has been associated with cognitive impairment, triple the risk for stroke, and double the risk for dementia (Wardlaw et al., 2015). Only three studies have investigated the correlation of white matter hyperintensity (WMH) and periodontal disease (Hada et al., 2020; Mayer et al., 2023; Minn et al., 2013).

The study of the Korean cohort investigated the association of tooth loss and the presence of computerized tomography (CT) images of WMH and silent infarcts in 438 subjects (Minn et al., 2013). The study demonstrated an association between CT images of WMH and tooth loss, and even suggested that tooth loss may be a predictor of WMH. It is important to look at these results carefully as one cannot extrapolate the conclusion that periodontal disease and WMH are associated, given that the reason for tooth loss was not recorded in this study.

In the Japanese cohort, 444 patients were included, and severity of periodontal disease was based on a partial mouth assessment using the community periodontal index (CPI) that assesses patient's periodontal condition on 10 teeth (Hada et al., 2020). Periodontal disease was also defined as the presence of pocket depths (PDs) greater than or equal to 4 mm, with PD 4–5 mm being moderate disease and PD $\geq$ 6 mm being severe disease. The results indicated that severe periodontitis (PD $\geq$ 6 mm) increased the risk for WMH, with an adjusted odds ratio of 1.948 (95% CI: 1.132–3.354, $p < 0.016$). The partial periodontal assessment could have led to an overestimation of periodontitis in this cohort, as pointed out by the authors that these patients presented a prevalence of periodontitis compared to other studies investigating similar ethnic groups.

In the German cohort, a total of 1622 subjects were included and underwent a full mouth periodontal assessment, where clinical attachment loss (CAL) was derived (Mayer et al., 2023). The study reported that CAL greater than 3 mm was associated with WMH load, where subjects with higher loads presented more CAL, but was not associated with microstructural white matter integrity. It is important to note that when controlling the analysis for risk factors such as smoking and diabetes, CAL did not show an association with outcomes studied, which suggests that other comorbidities were contributing to the association.

As noted above, these studies were conducted in different populations and characterized periodontal disease in different ways (CPI, CAL, or tooth loss). As it is noted, comparison of these results is difficult given the differences in periodontal parameters assessed. As also pointed out in the studies evaluating the association with lacunar infarcts, some methodological differences should be carefully noted when studying the brain images, as two studies used MRI imaging (Hada et al., 2020; Mayer et al., 2023), whereas the other used CT imaging (Minn et al., 2013), which has a much lower resolution.

6.3 | Cerebral microbleeds

CMBs are focal accumulation of blood products in brain tissue and are typically identified in MRI as small ovoid lesions (Haller et al., 2018; Lee et al., 2018). Presence of CMBs signals small vessel diseases that can lead to ischemic and hemorrhagic stroke (Lee et al., 2018) and are located in deeper regions of the brain (deep white matter, basal ganglia, thalamus, brainstem, cerebellum). CMBs identified in cortical areas of the brain (cortical–subcortical regions of brain lobes) are associated with CAA. The presence of CMB has been associated with elevated circulating levels of inflammatory markers such as CRP (Shoamanesh et al., 2015; Wang et al., 2021).

Only one study is available investigating the association between CMBs, observed in acute stroke patients, and periodontal disease (Shiga et al., 2020). This cohort included 639 patients who were admitted to the hospital due to acute stroke. These patients did not undergo periodontal assessment; therefore, a clinical diagnosis of periodontitis was not stablished. Presence of periodontal disease was inferred by measuring serum antibody titers against periodontal pathogens. A correlation between positive serum antibody titers for *Campylobacter rectus* and the presence of CMBs was noted; however, it was not associated with multiple CMB lesions. Given the study design, it is important to consider the limitations associated with the lack of clinical periodontal assessment as well as the small number of patients who did not present with acute stroke.

7 | CONCLUSIONS

In summary, it is suggested that periodontitis may be a risk factor for CSVD, and that systemic inflammatory mechanisms and the effects of periodontopathogens may mediate this association. The clinical manifestations of CSVD can have serious consequences, such as stroke and dementia. Additional studies analyzing the relationship of periodontitis with CSVD, and their underlying mechanisms are required. Moreover, observational and interventional studies assessing both conditions are needed to determine whether a causal relationship exists between these conditions. Despite the lack of direct evidence, these emerging areas of research highlight the important role of the oral health professional in the prevention and treatment of periodontal diseases to prevent or minimize the poor outcomes associated with CSVD.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable

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PEER REVIEW

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