NEUROLOGY

Cite as: Archiv EuroMedica. 2026. 16; 2. DOI 10.35630/2026/16/Iss.2.14

Received 24 March 2026;
Accepted 23 April 2026;
Published 28 April 2026

ORAL INFLAMMATION AND ISCHEMIC STROKE: A NARRATIVE REVIEW OF CLINICAL ASSOCIATIONS, SYSTEMIC INFLAMMATION, AND DIFFERENTIAL EVIDENCE FOR PERIODONTITIS AND CHRONIC TONSILLITIS

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ABSTRACT

BACKGROUND

Inflammatory diseases of the oropharynx, in particular chronic tonsillitis, have been investigated as potential contributors to ischemic stroke risk. While epidemiological studies suggest an association, the extent to which oral inflammation independently contributes to cerebrovascular pathology remains insufficiently defined.

AIMS

To evaluate the association between inflammatory diseases of the

oropharynx and ischemic stroke, to analyze underlying pathophysiological mechanisms, and to critically assess the strength and limitations of current clinical and experimental evidence, with attention to differences between periodontitis and other oral inflammatory conditions.

Methods

A narrative review with structured literature search was conducted using PubMed, Embase, and Google Scholar. Studies published between 2000 and 2026 in English were considered. Eligible studies included cohort studies, case control studies, meta-analyses, and experimental research addressing oral inflammation, inflammatory biomarkers, oral microbiota alterations, and ischemic stroke. Selection was based on relevance to the research aims. Due to the narrative design, no quantitative synthesis was performed.

RESULTS

Epidemiological evidence from cohort studies and meta analyses indicates a consistent association between chronic inflammation of the oropharynx and increased risk of ischemic stroke. Elevated inflammatory biomarkers, including C reactive protein, interleukin 6, and fibrinogen, are associated with adverse vascular outcomes, but do not identify the source of inflammation. Experimental studies support several mechanistic pathways, including systemic inflammation, endothelial dysfunction, lipid metabolism dysregulation, plaque instability, and prothrombotic changes. However, most mechanistic data are derived from in vitro and animal models.

CONCLUSIONS

Current evidence supports a reproducible association between inflammation oropharynx and ischemic stroke, with biologically plausible mechanisms. However, the relationship remains non causal due to the predominance of observational data and the absence of interventional studies. Oropharynx inflammation should be interpreted as a component of systemic inflammatory burden rather than an independent causal risk factor. Further well designed clinical studies are required to clarify its role in stroke prevention and to determine the clinical relevance.

Keywords: ischemic stroke, periodontitis, chronic tonsillitis, tonsillar microbiota, oral microbiota, systemic inflammation, endothelial dysfunction, atherosclerosis, inflammatory biomarkers, Fusobacterium nucleatum

1. INTRODUCTION

Infectious and inflammatory processes, particularly chronic tonsillitis, are currently considered an important component in the pathogenesis of ischemic stroke [1, 2, 8, 12]. Despite the well established role of arterial hypertension, diabetes mellitus, dyslipidemia, and smoking, a portion of residual vascular risk remains unexplained even after accounting for the combined effect of traditional risk factors [3, 6].

Epidemiological and clinical data indicate that both acute and chronic infections are associated with an increased risk of cerebrovascular events, with the highest risk observed in the early period following an infectious episode, suggesting a potential role of inflammation as a trigger of acute vascular complications [1, 2, 5, 7].

Systemic inflammation is considered a key link connecting a local infectious focus with vascular injury [8, 9, 10, 11]. Activation of innate immunity, stimulation of Toll like receptor signaling, endothelial activation, increased expression of adhesion molecules, enhancement of procoagulant activity, and progression of atherosclerosis form a unified pathogenic framework in which a chronic inflammatory stimulus may contribute both to the formation of an atherosclerotic plaque and to its destabilization [9, 10, 62, 63, 64, 65, 66, 77]. At the same time, C reactive protein, interleukin 6, and fibrinogen should be regarded as non specific markers of systemic inflammation associated with an increased risk of stroke and adverse vascular outcomes, rather than as independent causal factors [40, 41, 42, 43, 45, 46, 47, 48].

The oropharynx represents one of the potential sources of a persistent inflammatory signal [14, 18, 79].

From a microbiological perspective, the oral microbiota constitutes a complex multispecies biofilm ecosystem composed of aerobic and anaerobic microorganisms that exist in a dynamic equilibrium with the host [19, 14].

In the presence of dysbiosis, the composition of the microbial community shifts toward an increased proportion of anaerobic gram negative bacteria, accompanied by alterations in biofilm structure and disruption of symbiotic interactions [19, 18].

These changes are associated with amplification of local inflammation and the establishment of a persistent inflammatory background [14, 18].

The potential systemic effects of the oral microbiota are mediated through several mechanisms [67, 68, 69]. These include transient bacteremia associated with disruption of the mucosal barrier, translocation of bacterial components including lipopolysaccharides, the effects of microbial metabolites, and immune mechanisms involving the development of cross reactivity [57, 67, 68].

These processes may contribute to endothelial activation, impairment of vascular function, and amplification of inflammatory responses associated with atherothrombosis [10, 11, 77].

In recent years, it has been shown that the oral microbiota is associated not only with local inflammation but also with systemic cardiometabolic and neurological effects, including the mouth, gut, brain axis [14, 16, 17, 56]. It should be emphasized that a substantial proportion of mechanistic data has been obtained from in vitro and animal models, which limits the direct clinical interpretation of these mechanisms [50, 51, 53, 54, 59]. In addition, clinical studies of the oral microbiota in patients with stroke have significant limitations, including heterogeneity of sequencing methods, lack of standardization, and the influence of confounding factors such as antibiotic therapy, diet,

and comorbid conditions, which reduce comparability of results [34, 35, 36, 37].

Periodontitis remains the most extensively studied clinical model [12, 22, 26, 27, 28, 29]. Evidence from cohort studies, meta-analyses, and Mendelian randomization demonstrates a consistent association with an increased risk of stroke, predominantly ischemic [22, 24, 25, 26, 27, 28, 29, 38]. At the same time, evidence of a causal relationship remains limited, and the observed association may be partially mediated by systemic inflammation and accompanying risk factors [12, 28, 29, 30].

Alongside periodontitis, increasing attention has been directed toward the role of specific microbial taxa, particularly Fusobacterium nucleatum [49, 50, 51, 52, 53, 54]. Experimental data indicate its potential involvement in processes related to atherogenesis, endothelial dysfunction, and inflammation [49, 50, 51, 53, 54, 59]. However, clinical evidence supporting its role in the development of ischemic stroke remains limited and is largely associative, which does not allow conclusions regarding causal significance [52, 55, 79].

In addition, clinical studies in patients with ischemic stroke have demonstrated alterations in the composition of the oral microbiota associated with disease severity and outcomes, although their pathogenetic interpretation remains uncertain [34, 35, 36, 37, 55].

At the same time, other chronic inflammatory conditions of the oropharynx, including chronic tonsillitis, remain significantly less studied [20, 31, 40]. Despite the presence of data on systemic inflammatory responses and characteristics of tonsillar microbiota, direct clinical evidence linking tonsillar pathology with ischemic stroke is limited [31, 32, 33, 40]. This necessitates considering periodontitis as the primary clinically supported model, while data on chronic tonsillitis and tonsillar microbiota should be regarded as an additional research direction requiring further clinical validation [12, 22, 26, 28].

The relevance of this study is driven by the accumulation of data on the role of infectious-inflammatory processes and systemic inflammation in the development of cerebrovascular risk, as well as the high prevalence of inflammatory diseases of the oropharynx [1, 2, 7, 10, 14, 18].

The scientific novelty of this work lies in the critical integration of clinical epidemiological data, inflammatory biomarkers, and experimental mechanisms with clear differentiation of levels of evidence, as well as in limiting the extrapolation of data from periodontitis to other chronic inflammatory conditions of the oropharynx, including chronic tonsillitis.

AIM

To evaluate the association between inflammatory diseases of the oropharynx, with particular emphasis on periodontitis as the most extensively studied clinical model, and ischemic stroke, taking into account clinical and epidemiological data, systemic inflammatory biomarkers, and pathogenetic mechanisms of atherothrombosis.

RESEARCH OBJECTIVES

1. To analyze clinical and epidemiological data reflecting the association of chronic tonsillitis and other inflammatory diseases of the oropharynx with the risk of ischemic stroke.
2. To assess the role of systemic inflammatory biomarkers, including C reactive protein, interleukin 6, and fibrinogen, as indicators of inflammatory status associated with cerebrovascular risk.
3. To examine the pathogenetic mechanisms of atherothrombosis associated with the oral microbiota, taking into account the limitations of experimental data.
4. To formulate a hypothesis regarding the potential use of periodontitis as a clinical model for interpreting the possible contribution of other chronic inflammatory foci of the oropharynx, including chronic tonsillitis, in view of the limitations of the existing evidence base.

2. METHODS

This study was conducted as a narrative review with elements of a structured literature search. The applied approach does not represent a systematic review, but includes formalized stages of literature search, selection, and evaluation of sources. The methodology was aimed at the systematic identification and critical analysis of clinical, epidemiological, and experimental data with clear differentiation of levels of evidence.

The literature search was performed using PubMed, Embase, and Google Scholar. The time frame covered the period from 2000 to 2026, with the inclusion of earlier studies when considered pathogenetically relevant. The final search update was conducted in February 2026. In addition, a manual search of reference lists from selected publications was performed.

Combinations of the following search terms were used: periodontitis, oral microbiota, oral microbiome, ischemic stroke, cerebrovascular disease, inflammation, C reactive protein, interleukin 6, fibrinogen, atherosclerosis, thrombosis, Fusobacterium nucleatum. Search queries were constructed by combining terms describing inflammatory diseases of the oral cavity using the OR operator, followed by their combination with terms related to ischemic stroke and cerebrovascular diseases using the AND operator. The primary search strategy included the following combination: (periodontitis OR oral microbiota OR oral microbiome) AND (ischemic stroke OR cerebrovascular disease) AND (inflammation OR C reactive protein OR interleukin 6 OR fibrinogen OR atherosclerosis OR thrombosis OR Fusobacterium nucleatum).

Only publications in English were included in the analysis.

Inclusion criteria comprised original clinical studies, including cohort, prospective, and case control designs, in which the association between inflammatory diseases of the oropharynx and ischemic stroke or cerebrovascular events was evaluated, as well as experimental studies aimed at investigating pathogenetic mechanisms. Review articles were used selectively for the interpretation of mechanistic aspects.

Exclusion criteria included review articles without primary data when analyzing clinical associations, studies lacking clearly defined outcomes, and studies with insufficient methodological transparency.

The selection of publications was carried out in two stages. The first stage involved screening of titles and abstracts. The second stage consisted of full text assessment with evaluation of compliance with inclusion and exclusion criteria. Study selection and evaluation were performed by two independent reviewers. Disagreements were resolved through discussion with the achievement of consensus.

A total of 102 publications were identified. After applying the inclusion and exclusion criteria, 79 studies were included in the final analysis.

The assessment of the quality of evidence was conducted descriptively, taking into account study design, the presence of prospective data, reproducibility of results, and consistency across studies. Cohort and prospective studies were considered to provide a higher level of evidence compared to case control and experimental studies. Limitations of observational designs were taken into account, including the risk of confounding and the inability to establish causal relationships.

Data analysis was performed in three domains: clinical epidemiology, systemic inflammatory biomarkers, and pathogenetic mechanisms of atherothrombosis. For each domain, study design, consistency of results, and limitations of interpretation were evaluated.

3. RESULTS

3.1. CLINICAL EPIDEMIOLOGY OF ORAL INFLAMMATORY DISEASES AND ISCHEMIC STROKE

Clinical and epidemiological data indicate that inflammatory diseases of the oropharynx are associated with an increased risk of ischemic stroke. The most consistent evidence has been obtained from cohort and prospective studies, demonstrating that the presence of chronic inflammation of the oropharynx is associated with a higher incidence of cerebrovascular events even after adjustment for traditional vascular risk factors [27, 28, 38, 39]. These findings are consistent with broader observations on the contribution of infectious and inflammatory conditions to residual vascular risk [1, 2, 7].

The table below summarizes key clinical studies evaluating the association between periodontitis and ischemic stroke.

Table 1. Clinical studies on the association between periodontitis and ischemic stroke

Author, year	Study design	Population	Exposure	Outcome	Main finding	Limitations
Hsu et al., 2022 [38]	Cohort study	Patients from the Taiwan National Health Insurance Research	Periodontitis	Stroke	Increased risk of stroke in patients with periodontitis	Observational design, potential residual confounding

		Database				
Zheng et al., 2023 [27]	Observational study	Adult participants	Periodontitis	Stroke	Association between periodontitis and stroke, stronger with greater disease severity	Does not establish causality
Ling et al., 2026 [28]	Observational study	Adult participants	Periodontal disease	Stroke	Association between periodontal disease and increased stroke risk, partially mediated by inflammation	Limited detail on study design based on available data
Ma et al., 2023 [29]	Mendelian randomization study	Genetic association data	Genetic predisposition to periodontitis	Ischemic stroke and subtypes	Evidence supporting a possible causal relationship	Limitations inherent to Mendelian randomization
Sen et al., 2023 [30]	Randomized clinical trial	Patients after stroke or transient ischemic attack with periodontitis	Periodontal treatment	Vascular outcomes	Demonstrated clinical relevance of periodontal treatment	Does not address primary prevention
Wood et al., 2025 [39]	Observational study	Adult participants	Periodontal disease and dental caries	Ischemic stroke	Possible cumulative effect of oral diseases on stroke risk	Limited detail on population and study design

Additional support for this association is provided by meta analyses in which periodontitis is consistently associated with a higher risk of stroke, predominantly ischemic [22, 24, 25, 26]. At the same time, the results for hemorrhagic stroke appear less consistent and less robust, highlighting the need to differentiate stroke subtypes when interpreting the data [23]. A Mendelian randomization study also suggests a possible causal relationship between periodontitis and stroke; however, it does not eliminate the limitations of observational epidemiology and does not establish clinical causality [29].

Observational studies overall confirm the presence of an association, but are characterized by variability in effect estimates, which is related to differences in the diagnosis of chronic inflammation of the oropharynx, inclusion criteria, the degree of adjustment for confounding factors, and methods of stroke verification [27, 28, 38]. An important additional observation is that the coexistence of chronic inflammatory conditions of the oropharynx may be associated with a higher risk of ischemic stroke, suggesting a possible cumulative effect of chronic oral inflammatory burden [39].

Interventional data remain limited. The PREMIERS study demonstrated the clinical relevance of chronic inflammation of the oropharynx in patients after stroke or transient ischemic attack, however the available data are insufficient to conclude that treatment of chronic inflammation of the oropharynx reduces the risk of primary stroke [30].

Thus, data from cohort and other observational studies form the main empirical basis, but heterogeneity of study designs, differences in the definition of exposure, and the predominance of observational models limit interpretation in terms of causal relationships [22, 24, 25, 26, 27, 28, 29, 38, 39].

With regard to other inflammatory conditions of the oropharynx, the evidence base is considerably weaker. For chronic tonsillitis, there are no cohort studies evaluating the risk of ischemic stroke. Only indirect clinical

observations, isolated case reports, and data on systemic inflammatory responses are available, which do not allow extrapolation to a level comparable with periodontitis [20, 31, 32, 33, 40].

3.2 INFLAMMATORY BIOMARKERS AND SYSTEMIC RESPONSE

Systemic inflammatory biomarkers, primarily C reactive protein, interleukin 6 and fibrinogen, are consistently associated with an increased risk of stroke, vascular recurrence and adverse outcomes [41, 42, 43, 44, 45, 46, 47, 48]. These markers should be interpreted as indicators of systemic inflammatory status rather than as specific markers of oral inflammation. Nevertheless, they reflect the pathogenic pathway through which chronic inflammatory processes may be linked to vascular risk [9, 10, 11, 77].

Table 2 lists key studies on inflammatory biomarkers and stroke risk.

Table 2. Inflammatory biomarkers and stroke risk

Author, year	Design	Biomarker	Population	Outcome	Main finding	Limitations
Nordestgaard et al., 2025 [41]	Prospective longitudinal cohort study	High sensitivity C reactive protein	Initially healthy women	Stroke	Elevated hs CRP was associated with long term stroke risk	Association does not prove causality
Ling et al., 2025 [42]	Prospective cohort study	C reactive protein change	Adult participants from UK Biobank	Stroke	Change in CRP was associated with stroke risk	Observational design
McCabe et al., 2021 [43]	Systematic review and meta analysis	Interleukin 6, C reactive protein, fibrinogen	Patients after ischemic stroke or transient ischemic attack	Recurrence, major vascular events	Higher biomarker levels were associated with recurrent vascular events	Heterogeneity of included studies
Wu et al., 2025 [45]	Observational study	Routine inflammatory biomarkers	Patients with non valvular atrial fibrillation	Stroke, all cause mortality	Inflammatory biomarkers showed prognostic value for stroke and mortality	Small and specific study population
Jiang et al., 2024 [48]	Observational study	Interleukin 6	Patients with acute ischemic stroke	Recurrence	Elevated IL 6 was associated with stroke recurrence	Limited sample size and short follow up

For C reactive protein, both baseline levels and their dynamics have been shown to be associated with the risk of stroke and other cardiovascular events [41, 42]. Interleukin 6 is considered one of the key indicators of inflammatory activation associated with recurrent stroke and vascular complications [43, 44, 48]. Fibrinogen, in turn, reflects not only inflammation but also a prothrombotic shift, which is particularly relevant in the context of atherothrombosis [43, 66]. In patients with atrial fibrillation, inflammation related biomarkers also demonstrate prognostic significance, highlighting the systemic vascular nature of the inflammatory response [45, 47].

Oral inflammation may contribute to the systemic inflammatory background through chronic antigenic stimulation, transient bacteremia and the release of bacterial components into the systemic circulation [14, 16, 18, 19, 57, 67,

68, 70]. In the case of chronic inflammation of the oropharynx, this mechanism is considered the most plausible biological link between local inflammation and vascular outcomes [8, 12, 18, 27, 28, 57]. Additional support comes from studies showing that the association between periodontal disease and stroke may be partially mediated by inflammation [28].

The relationship between inflammatory biomarkers, endothelial dysfunction and thrombosis is biologically plausible. Chronic inflammation is associated with endothelial activation, increased expression of adhesion molecules, enhanced coagulation potential and impaired vascular reactivity [10, 11, 66, 77]. In this context, oral inflammation should be regarded as a potential source of systemic inflammatory signaling capable of sustaining a proatherogenic and prothrombotic state, but not as a proven independent causal factor of stroke [8, 12, 18, 28, 57].

3.3 MECHANISTIC PATHWAYS OF ATHEROTHROMBOSIS

Mechanistic evidence suggests that oral dysbiosis may be associated with processes related to atherothrombosis, however the majority of these data have been obtained from experimental models and require cautious clinical interpretation [16, 49, 50, 51, 79]. The most extensively studied bacterial factor is Fusobacterium nucleatum, which is considered a potential contributor to systemic inflammation, endothelial dysfunction and the progression of atherosclerosis [49, 50, 51, 52, 53, 54, 59].

The following table summarizes key mechanistic studies on the role of oral microbiota in atherothrombosis.

Table 3. Mechanistic studies on the role of oral microbiota in atherothrombosis

Author, year	Study type	Factor	Mechanism	Main finding	Limitations
Zhou et al., 2023 [50]	Experimental study	Fusobacterium nucleatum	Hepatic glycolysis and lipogenesis	Promotion of atherogenesis and lipid metabolism dysregulation	Experimental model
Wu et al., 2026 [51]	In vitro study	F. nucleatum	NOX4/NRF2 imbalance	Endothelial senescence and oxidative stress	No clinical validation
Shen et al., 2024 [53]	Cell model	F. nucleatum	PI3K AKT, MAPK, NF κB signaling	Increased lipid accumulation in macrophages	Limited clinical translatability
Farrugia et al., 2022 [59]	In vitro study	F. nucleatum	Endothelial damage and permeability	Increased endothelial permeability and damage	No clinical validation
Aoki et al., 2025 [52]	Observational study	F. nucleatum	Association with cerebral small vessel disease	Association of oral F. nucleatum with vascular changes in ischemic stroke patients	Association does not imply causation

The first mechanism is related to the induction of systemic inflammation. Bacterial components, including lipopolysaccharides, can activate innate immunity through TLR dependent pathways and enhance the production of proinflammatory cytokines [10, 11, 49, 57]. This creates conditions for sustained activation of the vascular wall and immune cells involved in atherogenesis [10, 11, 57, 67]. The concepts of the oral gut axis and the oral gut brain axis further expand the understanding of systemic effects of oral dysbiosis, although their clinical relevance in relation to ischemic stroke remains under investigation [13, 14, 15, 16, 17, 56, 68, 69, 70].

Table 4 outlines key mechanisms linking oral dysbiosis to systemic inflammation.

Table 4. Mechanisms of systemic inflammation in oral dysbiosis

Component	Biological factor	Mechanism	Main effect	Evidence base	Limitations
Bacterial components	Lipopolysaccharides	Activation of innate immunity via TLR dependent pathways	Increased production of proinflammatory cytokines	Experimental and review data [10, 11, 49]	Lack of direct clinical evidence for ischemic stroke
Systemic inflammatory response	Cytokines	Maintenance of chronic inflammation	Activation of the vascular wall and immune cells involved in atherogenesis	Review and pathophysiological data [10, 11, 57, 67]	Nonspecific nature of inflammatory markers
Interorgan interactions	Oral gut axis	Signaling between microbiome compartments	Potential amplification of systemic inflammation	Conceptual and review data [14, 16, 68, 69, 70]	Limited clinical validation
Neuroimmune interactions	Oral gut brain axis	Microbiota mediated modulation of neuroinflammatory pathways	Possible involvement in cerebrovascular pathology	Review and conceptual data [13, 15, 17, 56]	Hypothetical nature in the context of stroke

The second mechanism concerns endothelial dysfunction. Experimental studies indicate that Fusobacterium nucleatum may increase endothelial permeability, disrupt redox balance and activate signaling pathways associated with endothelial cell aging [51, 59]. These findings are consistent with the broader framework of inflammatory mechanisms of endothelial dysfunction, well described in vascular pathology in general [75, 76, 77, 78]. Clinically, this aligns with observations that in patients with ischemic stroke, alterations in the oral microbiome are associated with greater disease severity and worse outcomes, although the causal nature of these associations has not been established [34, 35, 36, 52, 55].

Table 5 presents mechanisms linking oral microbiota to endothelial dysfunction.

Table 5. Mechanisms of endothelial dysfunction associated with oral microbiota

Component	Factor	Mechanism	Main effect	Evidence base	Limitations
Endothelial barrier dysfunction	Fusobacterium nucleatum	Direct interaction with endothelial cells, increased permeability	Disruption of endothelial barrier function	Experimental data [59]	No direct clinical confirmation
Oxidative stress	Fusobacterium nucleatum	NOX4 NRF2 imbalance	Oxidative damage and endothelial cell senescence	In vitro data [51]	Limited translational relevance

Cellular senescence	Fusobacterium nucleatum	Activation of senescence related signaling pathways	Endothelial dysfunction	Experimental data [51]	Lack of clinical validation
Systemic inflammation	Circulating inflammatory cytokines	Endothelial activation in systemic inflammatory conditions	Enhanced vascular injury	Review and pathophysiological data [77]	Nonspecific mechanisms
Clinical evidence	Oral microbiome dysbiosis	Association with stroke severity and outcomes	Worse functional outcomes	Observational studies [34, 35, 36, 52, 55]	No evidence of causality

The third mechanism involves dysregulation of lipid metabolism leading to foam cell formation. Fusobacterium nucleatum has been shown to enhance hepatic glycolysis and lipogenesis, as well as to promote lipid accumulation in macrophages through PI3K AKT, MAPK and NF κB dependent pathways [50, 53]. These processes are consistent with the current model of inflammation associated atherosclerosis, in which infectious stimuli may contribute to the progression of plaque formation [10, 18, 57, 63, 65, 67].

Table below summarizes mechanisms linking oral microbiota to lipid metabolism and foam cell formation.

Table 6. Mechanisms linking oral microbiota to lipid metabolism dysregulation and foam cell formation

Component	Factor	Mechanism	Main effect	Evidence base	Limitations
Hepatic lipid metabolism dysregulation	Fusobacterium nucleatum	Increased hepatic glycolysis and lipogenesis	Elevated systemic lipid burden contributing to atherogenesis	Experimental data [50]	No clinical validation
Macrophage lipid accumulation	Fusobacterium nucleatum	Activation of PI3K AKT MAPK NF κB signaling pathways promoting lipid uptake and retention	Intracellular lipid accumulation in macrophages	Cellular models [53]	Limited translational relevance
Foam cell formation	Lipid overloaded macrophages	Imbalance between lipid uptake and efflux	Formation of foam cells and early atherosclerotic lesions	Experimental and pathophysiological data [18, 57]	No direct clinical evidence
Inflammatory amplification of atherogenesis	Infection related inflammatory stimuli	Chronic inflammation enhancing lipid accumulation and plaque progression	Progression of atherosclerosis	Review and pathophysiological data [10, 63, 65, 67]	Nonspecific mechanisms

The fourth mechanism concerns the formation and instability of the atherosclerotic plaque. Experimental and review data indicate that bacterial factors may enhance inflammation within the plaque microenvironment, promote expansion of the necrotic core, weaken the fibrous cap and activate matrix remodeling [54, 61, 62, 63, 64, 65, 67].

Additional interest arises from the detection of oral bacteria and bacterial genetic material in atherosclerotic plaques, including within carotid vessels, which supports the biological plausibility of hematogenous dissemination [71, 72, 73, 74].

The following table summarizes mechanisms linking oral microbiota to plaque formation and instability.

Table 7. Mechanisms of atherosclerotic plaque formation and instability associated with oral microbiota

Component	Factor	Mechanism	Main effect	Evidence base	Limitations
Plaque inflammation	Bacterial and inflammatory signals	Increased inflammation within the plaque microenvironment	Progression of atherosclerotic plaque	Experimental and review data [54, 61, 63, 65, 67]	Lack of direct clinical evidence of causality
Necrotic core formation	Inflammatory plaque microenvironment	Processes associated with cellular injury and plaque destabilization	Expansion of the necrotic core	Pathophysiological and review data [62, 63, 64]	Limited specificity for oral microbiota
Fibrous cap integrity	Inflammatory mediators	Matrix remodeling and weakening of the fibrous cap	Increased plaque vulnerability	Review and pathophysiological data [61, 63, 65]	Mechanisms are not specific to oral bacteria
Bacterial dissemination	Oral bacteria and bacterial genetic material	Hematogenous translocation and presence in the vascular wall	Detection of bacteria or bacterial material in atherosclerotic plaques	Clinical, microbiological and review data [71, 72, 73, 74]	Association does not establish causality

The fifth mechanism is related to activation of coagulation and thrombus formation. Chronic inflammation and endothelial activation contribute to the transition of the vascular wall to a prothrombotic state [10, 66, 77]. In this context, bacterially induced inflammation may further increase the propensity for thrombosis, particularly in the presence of an unstable atherosclerotic plaque. However, it should be emphasized that for oral microbiota, and especially for chronic tonsillitis, this part of the model remains largely hypothetical and is mainly based on extrapolation from data on periodontitis, experimental vascular biology and general mechanisms of infection associated atherothrombosis [10, 11, 18, 20, 40, 57, 67, 79].

Table 8 presents mechanisms linking inflammation to coagulation activation and thrombus formation.

Table 8. Mechanisms linking oral microbiota to coagulation activation and thrombus formation

Component	Factor	Mechanism	Main effect	Evidence base	Limitations
Chronic systemic inflammation	Circulating inflammatory cytokines	Activation of the coagulation cascade and procoagulant pathways	Prothrombotic state	Pathophysiological and review data [10, 66, 77]	Nonspecific mechanism
Endothelial activation and dysfunction	Endothelial injury and inflammatory signals	Loss of anticoagulant properties and increased expression of procoagulant	Increased thrombogenicity	Experimental and review data [10, 77]	Limited direct clinical validation

		factors			
Coagulation system activation	Inflammatory and infection related stimuli	Amplification of coagulation pathways and thrombin generation	Increased thrombus formation potential	Experimental and conceptual data [10, 11, 18, 57, 67, 79]	Lack of direct clinical evidence for oral microbiota
Atherosclerotic plaque instability	Unstable atherosclerotic plaque	Plaque rupture and exposure of thrombogenic material	Acute thrombus formation and vascular events	Pathophysiological data [63, 65, 66]	Indirect link to oral microbiota
Systemic inflammatory effects of oral microbiota	Periodontitis and chronic tonsillitis	Induction of systemic inflammation contributing to prothrombotic state	Potential enhancement of thrombosis risk	Review and conceptual data [18, 20, 40, 57, 67, 79]	Largely hypothetical, based on extrapolation

4. DISCUSSION

The presented data indicate that inflammatory diseases of the oral cavity, including chronic tonsillitis, are associated with an increased risk of ischemic stroke, however the nature of this relationship remains predominantly observational [22, 24, 25, 26, 27, 28, 38]. The most consistent results have been obtained in cohort and prospective studies and are supported by meta analyses, allowing this association to be considered reproducible at the epidemiological level [22, 24, 25, 26]. At the same time, the absence of randomized studies on primary prevention and the limited availability of interventional data do not allow this relationship to be interpreted as causal [30].

A key pathogenic link connecting local inflammation with vascular risk is the systemic inflammatory response [10, 43, 46]. Elevated levels of C reactive protein, interleukin 6 and fibrinogen are consistently associated with adverse vascular outcomes, including stroke and its recurrence [41, 42, 43, 48]. At the same time, these biomarkers reflect nonspecific inflammatory activation and do not allow identification of the source of inflammation [43, 46]. Oral inflammation is considered one of the potential contributors to the overall inflammatory background [12, 18, 57, 67, 79], however its relative contribution to vascular risk remains insufficiently defined.

Mechanistic data provide biological plausibility for the observed clinical associations [10, 11, 16, 49, 50, 51, 57, 67, 79]. Experimental studies demonstrate that bacterial components are capable of activating innate immunity, increasing the production of proinflammatory cytokines, impairing endothelial function and promoting atherogenesis [10, 11, 49, 57, 59, 67]. Specific microbial taxa, most notably Fusobacterium nucleatum, have been shown to influence lipid metabolism, redox balance and cellular signaling pathways associated with inflammation and endothelial aging [49, 50, 51, 53, 54, 59]. However, these findings are derived predominantly from in vitro and animal models, which substantially limits their direct clinical interpretation [50, 51, 53, 54, 58, 59].

The association between oral microbiota and structural changes in the vascular wall is also supported by the detection of bacterial genetic material in atherosclerotic plaques [71, 72, 73, 74]. This observation supports the hypothesis of hematogenous dissemination and local microbial effects within the vascular wall. Nevertheless, such data remain associative and do not demonstrate a functional role of bacteria in plaque formation or destabilization.

Particular attention should be paid to the issue of data extrapolation. In this work, periodontitis is considered the most extensively studied clinical model of oral inflammatory disease [12, 22, 26, 27, 28, 38]. In contrast, for other chronic inflammatory conditions of the oropharynx, including chronic tonsillitis, the evidence base remains substantially limited [20, 31, 32, 33, 40].

A significant limitation of the entire field is the heterogeneity of methodological approaches. Clinical studies use different diagnostic criteria for chronic inflammation of the oropharynx, heterogeneous populations and varying degrees of adjustment for confounding risk factors [22, 24, 25, 26, 27, 28, 38]. Studies of oral microbiota lack standardization of sequencing and analytical methods, which complicates comparison of results [16, 34, 35, 36, 55]. Additional influences include factors such as antibacterial therapy, diet and comorbid conditions, which are rarely fully controlled [34, 35, 36, 55].

Another limitation is the predominance of observational study designs. Even with the use of Mendelian randomization,

it is not possible to fully exclude the influence of residual confounding and pleiotropy [29].

From a clinical perspective, the available data allow oral inflammation to be considered a potential modifiable risk factor within a comprehensive approach to vascular prevention [3, 7, 12, 18, 22, 26, 67, 79]. However, at the current stage, this should be interpreted as a hypothesis requiring confirmation in well designed interventional studies. Of particular importance are studies capable of demonstrating a reduction in vascular risk following treatment of inflammatory diseases of the oral cavity.

Thus, the existing body of evidence supports a coherent model in which oral inflammation, systemic inflammatory response and vascular pathology are linked within a unified pathogenic framework [10, 11, 12, 18, 22, 26, 43, 57, 67, 79]. At the same time, clinical data remain limited to associations, while mechanistic studies provide biological plausibility without establishing causality. This necessitates cautious interpretation of the findings and a clear distinction between levels of evidence.

5. CONCLUSIONS

Inflammatory diseases of the oropharynx, including chronic tonsillitis, are associated with an increased risk of ischemic stroke based on observational data, including cohort studies and meta analyses. This association is reproducible, however it remains observational and does not establish causality.

Systemic inflammatory biomarkers, including C reactive protein, interleukin 6 and fibrinogen, are consistently associated with vascular risk and adverse outcomes in stroke. They reflect overall inflammatory status and do not allow identification of the source of inflammation, including the contribution of oral inflammation.

Mechanistic data suggest a potential role of oral microbiota in processes related to atherothrombosis, including systemic inflammation, endothelial dysfunction, dysregulation of lipid metabolism, atherosclerotic plaque instability and activation of coagulation. These findings provide biological plausibility for the observed associations, however they are derived predominantly from experimental models and do not establish clinical causality.

The evidence base remains limited and does not allow direct extrapolation.

The available data support the consideration of chronic tonsillitis as a potential source of systemic inflammatory signaling associated with vascular risk.

6. DISCLOSURE

The authors declare no competing financial or personal interests that could have influenced the preparation of this manuscript. No external funding or sponsorship was received for the conduct of this review or for the preparation of the article.

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The authors acknowledge that OpenAI's ChatGPT was used solely for language refinement, formatting uniformity, and organization of the manuscript. All scientific content, data interpretation, study design, and final approval were performed exclusively by the authors, guaranteeing that the intellectual responsibility and scholarly integrity of the work remain entirely their own.

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