A Deeper Look: Exploring the Relationship between Periodontal Diseases and Cardiovascular Health

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Received: 10 January 2024; Accepted: 12 March 2024; Published: 31 March 2024

Abstract

Aim and objectives: The research extensively explores the link between cardiovascular and periodontal diseases, focusing on the microbial factor, especially plaque, as the main cause of periodontal disease. Other contributing factors include tartar, occlusal trauma, tooth decay, missing teeth, and specific habits. The study aims to discover and understand the genuine links between these two health conditions.

Material and methods: To carry out this review, we studied the scientific basis of Pub Med as well as Google Schooler and periodontal disease, gingivitis, atherosclerosis and cardiovascular disease, hypertension were used as keywords.

Results: The dental management of patients with cardiovascular diseases is one of the essential points in establishing an appropriate treatment plan.

Conclusions: Detailed medical history, signs, symptoms of cardiovascular disease and thorough medical evaluation are essential for the safe delivery of periodontal dental treatments in patients with cardiovascular disease.

Keywords: Periodontal disease, cardiovascular disease, treatment

INTRODUCTION

Periodontal disease is a condition of microbial cause that affects the supporting tissues of the teeth - gingival tissue, alveolar bone, cementum and periodontal ligaments [1]. An imbalance between the subgingival communities and the host immune response characterizes periodontal disorders, which are dysbiotic conditions in the marginal periodontium [2]. Clinical signs and symptoms of periodontal disease can include pain, masticatory impairment, gingival bleeding, halitosis and tooth mobility [3]. Undiagnosed in time and in the absence of an early treatment, periodontal disease can cause the reduction of the bone structure at the level of the alveolar ridges and the avulsion of the teeth [1].

Over the years, several classification systems have been developed to reflect the variety of forms of gingivitis and periodontitis [4]. The most recent classification of periodontal disease was made in 2017 by the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [5]. Gingivitis is an early form of periodontal disease, characterized by gingival inflammation caused by the appearance of bacterial biofilm that accumulates on the teeth and adjacent gums, the condition being reversible, not affecting the bone structures. If left untreated, gingivitis can develop into periodontitis [1,6]. Marginal periodontitis represents an irreversible form of periodontal disease, which generates the loss of the circular gingival tissue of the tooth, the bone support and finally even the loss of the teeth [1].

The term cardiovascular disease (CVD) or heart disease refer to the following four entities that are: coronary artery disease - sometimes referred to as coronary heart disease (CHD) which results from decreased myocardial perfusion that causes angina, myocardial infarction (MI) or heart failure; cerebrovascular disease (CVD) - including stroke and transient ischemic attack; peripheral artery disease - particularly arterial disease involving the limbs that may result in claudication and aortic atherosclerosis - including thoracic and abdominal aneurysms [7]. When we talk about atherosclerotic diseases, we mostly mean peripheral vascular disease, cerebrovascular disease, and coronary heart disease. Chronic inflammatory, infectious, and immunological illnesses such as psoriasis, systemic erythematosus lupus, rheumatoid arthritis and periodontitis are linked to markedly increased chances of severe cardiovascular events [8].

Periodontal disease and cardiovascular disease are covered by Sanz et. al (2020) in the category of non-communicable diseases [9]. Among non-communicable diseases, cardiovascular diseases such as ischemic heart disease, stroke, hypertension, rheumatic heart disease and cardiomyopathy are the most prevalent worldwide, accounting for 45% of total non-communicable disease mortality (NCD) [8,10,11]. At the European level, cardiovascular diseases were found to be responsible for 3.9 million deaths [9]. The World Health Organization estimates that periodontitis affects between 35% and 50% of people worldwide [12], while statistics show that more than 50% of Europeans may have periodontitis in one form or another, and over 10% have the severe form of the condition. The prevalence rises to 70–85% of those in the 60–65 age range [13].

Periodontal disease and cardiovascular diseases are common diseases nowadays, they have in common the aggressive inflammatory response to various stimuli [14]. While periodontal disease is a dysbiotic pathology, in which chronic inflammation is induced and maintained by the multispecies bacterial community accumulated in the subgingival area [6], coronary artery disease is characterized as chronic inflammation that can lead to narrowing and occlusion of blood vessels, causing myocardial infarction (MI) [14].

The etiology of periodontal disease is closely related to the patients' poor hygiene - the determining factor, to which can be added vicious habits that can influence the disease - the

favoring factors. Factors contributing to periodontal disease include smoking, genetic factors (genetic predisposition, genetic disorders), type 2 diabetes mellitus, unhealthy diet rich in refined carbohydrates and processed foods, stress that contributes to a decrease in the immune system, hematological conditions, neoplastic conditions and immunosuppressants, which can induce periodontal manifestations [1]. Associations of periodontal disease with pregnancy, lung disease and cardiovascular disease have been identified, but the causal relationship between these has not been fully established and understood. Therefore, controlling the bacterial biofilm and risk factors can prevent the onset of periodontal disease, slow down the progressive periodontal disease, and through appropriate treatment can attempt to restore lost tooth support [1,15].

However, since atherosclerosis is a common denominator in the pathophysiology of CVD, addressing risk factors related to its development is crucial [7]. Longitudinal investigations conducted recently have established a strong correlation between periodontal tissue and an increased probability of cardiovascular disease. The incidence of CVD in individuals with periodontal disease has not, however, been thoroughly studied [16,17].

Aim and objectives

The current study is to conduct a mini-review on the effects of periodontal disease on patients with cardiovascular diseases or vice versa. The association between periodontal disease and cardiovascular diseases is not fully understood. The objective of this research is to reveal the links between the two conditions and the way of mutual influence.

MATERIAL AND METHOD

In order to carry out this mini-review, we studied the scientific databases PubMed and Google Schoolar, using keywords such as periodontal disease, gingivitis, periodontitis, cardiovascular diseases, hypertension, coronary disease and atherosclerosis. We reviewed the identified articles, removed duplicates, and selected 55 bibliographic references that we considered eligible for the integrated text.

RESULTS AND DISCUSSIONS

Anaerobic organisms responsible for periodontal disease can colonize in deeper areas of the marginal periodontium where they can perform their destructive action if the patient's oral hygiene is inadequate. To date, nearly 800 different species of bacteria have been identified and characterized in human dental plaque. The main bacteria responsible for periodontal disease *are Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Eubacterium timidum, Parvimonas micra, Prevotella intermedia, Campylobacter rectus, Treponema denticola* and *Tannerella forsythia* [1,18,19].

From a mechanical point of view, infections at the gingival level lead to gingival lesions and subsequently to the contamination of the adjacent tissue [20,21]. The patient's medical history, clinical examination of the oral cavity and close examination of periodontal tissues by periodontal chart are the pillars of diagnosis in periodontal disease [22]. The persistent inflammatory state in periodontal disease can lead to aberrant neutrophil activation and a release of pro-inflammatory mediators, leading to tissue damage, bone resorption and disease progression. The release of inflammatory mediators by neutrophils bridges the gap between local and systemic immunity, thus highlighting neutrophils as key factors in linking periodontal inflammation to chronic conditions, including cardiovascular disease [23].

Ulcerated epithelial tissue becomes the portal of entry of periodontal pathogens and their products into the general circulation, into small and large blood vessels [24]. DeStefano

et al. conducted a prospective cohort research in 1993 and discovered, for the first time, that periodontitis is one of the risk factors for coronary heart disease [25]. Routine dental evaluations are invaluable in recognizing early states of periodontal disease and directing early intervention [26].

Over the past two decades, several studies have shown that people with periodontal disease are at higher risk of cardiovascular events, including myocardial infarction, peripheral arterial disease, stroke, and heart failure [27]. Moderately elevated C-reactive protein (CRP) is a predictor of increased risk of cardiovascular disease [28].

Clinical evidence suggests that periodontal disease affects systemic endothelial function and this in turn could have an impact on hypertension [29]. The presence of the bacterial plaque biofilm can influence cytokines, chemokines, T cells and B cells, which cause vascular inflammation, which are closely related to obesity, stress, lifestyle and diet, generating vascular dysfunction, atherosclerosis and hypertension [29].

Experimental animal evidence points to the immune response to a periodontal pathogen common to periodontal disease and cardiovascular disease: *Porphyromonas gingivalis. Porphyromonas gingivalis* induces increased blood pressure, vascular inflammation and endothelial dysfunction [29]. In vitro studies have shown that *Porphyromonas gingivalis* can penetrate the oral mucosa. Currently, it is unknown how precisely *Porphyromonas gingivalis* actively penetrates tissue barriers. It has been observed that gingipains are essential for the breakdown of tissue barriers when *Porphyromonas gingivalis* is actively invading the host tissue [30].

This periodontopathogen is considered the key etiological agent involved in the occurrence of chronic periodontitis [30]. Jong et al. al (2023) is of the opinion that the oral pathogen *Porphyromonas gingivalis* is not only associated with the appearance of chronic periodontitis, but also with the appearance of systemic diseases at the level of the body [31].

The potential mechanisms of action of *Porphyromonas gingivalis* are:

I. the first mechanism - degradation of adhesion molecules between tissue cells and the extracellular matrix produced by enzymes secreted by *Porphyromonas gingivalis;*
II. the second mechanism - transcytosis: bacteria actively enter tissue cells;
III. the third mechanism - professional phagocytes pick up *Porphyromonas gingivalis* and travel in the bloodstream;
IV. the last mechanism - possibly *Porphyromonas gingivalis* can adhere to hyphae (structured filamentous cells of higher fungi) forming Candida albicans, these hyphae can penetrate the mucosal tissue, which can allow *Porphyromonas gingivalis* to reach deeper structures [31].

Adherence of *Porphyromonas gingivalis* to host cells is multimodal and involves the interaction of bacterial cell surface adhesion with receptors expressed on epithelial cell surfaces [30]. The ability to multiply and activate endothelial cells may be one of the pathogenic mechanisms exerted by *Porphyromonas gingivalis* that may explain the association between it and cardiovascular diseases [32].

Based on the identified scientific results, we consider it necessary to evaluate the interdependence relationship between periodontal disease, cardiovascular diseases and *Porphyromonas gingivalis.*

Porphyromonas gingivalis is an anaerobic, gram-negative bacterium that inhabits the oral cavity. It can become highly damaging and multiply to many cells in periodontal lesions under specific conditions because to virulence factors. Many virulence and pathogenicity factors, including fimbriae, hemolysin, hemagglutinin, capsules, outer membrane vesicles (OMS), lipopolysaccharides, and gingipains, support in *Porphyromonas gingivalis* action [33].

Gram-negative bacteria create outer membrane vesicles (OMVs) at various stages of growth in various environments, such as infected tissues [34]. Gram-negative bacteria develop and continuously release outer membrane vesicles (OMVs), which are double-layer spherical membrane-like structures with a diameter of between 50 and 250 nanometers. These structures preserve the integrity of the membrane during the entire process [35].

The tiny, adherent outer membrane vesicles (OMVs) of *Porphyromonas gingivalis* are more persistent due to their resistance to host-derived proteases [36,37]. Outer membrane vesicles (OMVs) have a greater ability to enter deep tissues and trigger an inflammatory host response as compared to their parent *Porphyromonas gingivalis* [37]. In the form of outer membrane vesicles (OMVs), *Porphyromonas gingivalis* can selectively concentrate significant virulence components and release them into the environment [38]. A proteomics investigation of *Porphyromonas gingivalis* outer membrane vesicles (OMVs) was conducted by Veith et al. (2014), yielding a total of 151 proteins [39,40]. The results reported by Guo et al. (2024) showed that *Porphyromonas gingivalis* outer membrane vesicles (OMVs) promoted pericardial enlargement in zebrafish larvae, raised neutrophil numbers, caused vascular injury, and triggered inflammatory pathways. The immune response and the extracellular matrix-receptor interaction signaling pathway were further identified in this process by transcriptomic analysis [41].

Porphyromonas gingivalis outer membrane vesicles (OMVs) include the majority of the identified adhesins, including FimA and Mfa1. In turn, *Porphyromonas gingivalis* is able to interact with other oral bacteria through outer membrane vesicles (OMVs) [42]. The outer membrane vesicles (OMVs) of *Porphyromonas gingivalis* have the ability to travel to the bloodstream and impact distant organs and tissues [43]. Therefore, systemic illnesses linked to an infection caused by *Porphyromonas gingivalis* may also be impacted by outer membrane vesicles (OMVs) [38].

Jia et al. al (2015) closely studied the bidirectional relationship between outer membrane vesicles (OMVs) of *Porphyromonas gingivalis* and cardiovascular diseases and concluded that these nanosized particles can promote epithelial dysfunction [44], while Yang et. al (2016) believe that outer membrane vesicles (OMVs) of *Porphyromonas gingivalis* promote the calcification of vascular smooth muscle cells, a hallmark of atherosclerosis [45]. In vitro and in vivo research demonstrates the significant increase in vascular permeability and vascular edema by cleavage of endothelial cell connexins due to the presence of outer membrane vesicles (OMVs) of Porphyromonas gingivalis and proteolytic damage in blood vessels, where the parent bacteria cannot gain access [46]. These investigations highlight that outer membrane vesicles (OMVs) are as important as the parent periodontopathogenic bacteria [38,46].

While findings reported by Zaremba et al. (2007) support the idea that periodontitis-related bacteria may also infiltrate coronary vessels, Geerts et al. (2002) proposed that oral pathogens and their pathogenic factors may enter the bloodstream through tooth brushing, chewing, debridement, or scaling [47,48].

One of the most prevalent forms of cardiovascular disease, atherosclerosis, was first thought to be caused by the buildup of lipids and fibrous debris. But these days, an increasing number of scientists consider it to be a chronic inflammatory illness. Atherogenic disease risk is associated with infectious diseases like periodontitis. One of the most prevalent bacteria in stomatology, *Porphyromonas gingivalis*, is typically found in patients' atherosclerotic plaque. Moreover, *Porphyromonas gingivalis* has been shown to accelerate the development of atherosclerosis [49]. Data from experiments and epidemiology point to *Porphyromonas gingivalis* infection as worsening the development of atherosclerosis. Rodrigues et al. (2012) demonstrated that the virulence mechanisms of different strains of *Porphyromonas gingivalis* are diverse, and the pathogenic mechanisms identified for one strain are not necessarily

applicable to other strains [50]. Periodontal bacteria present in the bloodstream or in situ in vascular lesions are associated by Salhi et. al (2019) with the development of aneurysmal disease [51]. Recently, several researchers identified *Porphyromonas gingivalis* in atheroma plaques and pointed out the significance of *Porphyromonas gingivalis* type II FimA [52–54].

Numerous investigations have revealed a strong correlation between vascular endothelial homeostasis and periodontal infections, particularly *Porphyromonas gingivalis*. However, the underlying processes and function of *Porphyromonas gingivalis* remain unclear. According to studies conducted by Xie et al. (2020), *Porphyromonas gingivalis* can damage endothelial integrity by preventing cell division, causing endothelial mesenchymal transition, and causing endothelial cells to undergo apoptosis. These processes lower cell counts and weaken the endothelium's capacity for self-healing. Based to a mechanistic analysis, *Porphyromonas gingivalis* can severely degrade endothelium integrity. However, TLR-NF-κB signaling can significantly restore this integrity, indicating that TLR-NF-κB signalling is essential for maintaining vascular endothelial homeostasis. These findings point to a possible course of action for treating and preventing cardiovascular disease [55].

CONCLUSIONS

Periodontal disease could be associated with an increased risk of cardiovascular disease, and its management could influence the treatment of cardiovascular disease. Through this article I have tried to highlight a potential for improvement of cardiovascular diseases through a strict approach to oral hygiene. Periodic professional hygiene reduces the microbial load, including gram-negative flora well represented by *Porphyromonas gingivalis*.

Investigating the correlation between these pathologies is complex, requires a longer period of time and in-depth studies to determine if periodontal treatment can lead to a decrease in morbidity and mortality from cardiovascular diseases induced by *Porphyromonas gingivalis.*

REFERENCES

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. The Lancet 2005; 366:1809–20. https://doi.org/10.1016/S0140-6736(05)67728-8.
2. Abusleme L, Dupuy AK, Dutzan N, Silva N, Burleson JA, Strausbaugh LD, et al. The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation. ISME J 2013; 7:1016–25. https://doi.org/10.1038/ismej.2012.174.
3. Hung H, Douglass CW. Meta-analysis of the effect of scaling and root planing, surgical treatment and antibiotic therapies on periodontal probing depth and attachment loss. J Clin Periodontol 2002; 29:975–86. https://doi.org/10.1034/j.1600-051X.2002.291102.x.
4. Classification of Periodontal Diseases. Dent Pract Educ Res Unit Univ Adel n.d. https://health.adelaide.edu.au/arcpoh/dperu/colgate-periodontal-education-program/classification-of-periodontal-diseases (accessed February 16, 2024).
5. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. J Periodontol 2018;89. https://doi.org/10.1002/JPER.18-0157.
6. Hoare A, Soto C, Rojas-Celis V, Bravo D. Chronic Inflammation as a Link between Periodontitis and Carcinogenesis. Mediators Inflamm 2019; 2019:1–14. https://doi.org/10.1155/2019/1029857.
7. Olvera Lopez E, Ballard BD, Jan A. Cardiovascular Disease. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024.

8. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. N Engl J Med 2015; 372:1333–41. https://doi.org/10.1056/NEJMoa1406656.
9. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol 2020; 47:268–88. https://doi.org/10.1111/jcpe.13189.
10. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol 2017; 70:1–25. https://doi.org/10.1016/j.jacc.2017.04.052.
11. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics 2017. Brussels: European Heart Network; 2017.
12. Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. Periodontol 2000 2012; 60:15–39. https://doi.org/10.1111/j.1600-0757.2011.00425.x.
13. EU OHP. The State of Oral Health in Europe - Oral Health Platform. Oral Health Platf EU n.d. http://www.oralhealthplatform.eu/our-work/the-state-of-oral-health-in-europe/ (accessed February 16, 2024).
14. Aarabi G, Zeller T, Seedorf H, Reissmann DR, Heydecke G, Schaefer AS, et al. Genetic Susceptibility Contributing to Periodontal and Cardiovascular Disease. J Dent Res 2017; 96:610–7. https://doi.org/10.1177/0022034517699786.
15. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primer 2017; 3:17038. https://doi.org/10.1038/nrdp.2017.38.
16. Khan SS, Beach LB, Yancy CW. Sex-Based Differences in Heart Failure. J Am Coll Cardiol 2022; 79:1530–41. https://doi.org/10.1016/j.jacc.2022.02.013.
17. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure with Preserved Ejection Fraction. Circulation 2018; 138:198–205. https://doi.org/10.1161/CIRCULATIONAHA.118.034271.
18. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci 2017; 11:72–80.
19. Lourenço TGB, Heller D, Silva-Boghossian CM, Cotton SL, Paster BJ, Colombo APV. Microbial signature profiles of periodontally healthy and diseased patients. J Clin Periodontol 2014; 41:1027–36. https://doi.org/10.1111/jcpe.12302.
20. Sudhakara P, Gupta A, Bhardwaj A, Wilson A. Oral Dysbiotic Communities and Their Implications in Systemic Diseases. Dent J 2018; 6:10. https://doi.org/10.3390/dj6020010.
21. Darveau RP. Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol 2010; 8:481–90. https://doi.org/10.1038/nrmicro2337.
22. Cai R, Wang L, Zhang W, Liu B, Wu Y, Pang J, et al. The role of extracellular vesicles in periodontitis: pathogenesis, diagnosis, and therapy. Front Immunol 2023; 14:1151322. https://doi.org/10.3389/fimmu.2023.1151322.
23. Bassani B, Cucchiara M, Butera A, Kayali O, Chiesa A, Palano MT, et al. Neutrophils' Contribution to Periodontitis and Periodontitis-Associated Cardiovascular Diseases. Int J Mol Sci 2023; 24:15370. https://doi.org/10.3390/ijms242015370.
24. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL. Microbial complexes in subgingival plaque. J Clin Periodontol 1998; 25:134–44. https://doi.org/10.1111/j.1600-051X.1998.tb02419.x.
25. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. BMJ 1993; 306:688–91. https://doi.org/10.1136/bmj.306.6879.688.
26. Mehrotra N, Singh S. Periodontitis. StatPearls, Treasure Island (FL): StatPearls Publishing; 2024.
27. Liccardo D, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, et al. Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. Int J Mol Sci 2019; 20:1414. https://doi.org/10.3390/ijms20061414.
28. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal Infections Contribute to Elevated Systemic C-Reactive Protein Level. J Periodontol 2001; 72:1221–7. https://doi.org/10.1902/jop.2000.72.9.1221.

29. Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, et al. Th1-type immune responses to Porphyromonas gingivalis antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. Br J Pharmacol 2019; 176:1922–31. https://doi.org/10.1111/bph.14536.
30. Andrian E, Grenier D, Rouabhia M. Porphyromonas gingivalis -Epithelial Cell Interactions in Periodontitis. J Dent Res 2006; 85:392–403. https://doi.org/10.1177/154405910608500502.
31. De Jongh CA, De Vries TJ, Bikker FJ, Gibbs S, Krom BP. Mechanisms of Porphyromonas gingivalis to translocate over the oral mucosa and other tissue barriers. J Oral Microbiol 2023; 15:2205291. https://doi.org/10.1080/20002297.2023.2205291.
32. Deshpande RG, Khan M, Genco CA. Invasion Strategies of the Oral Pathogen Porphyromonas gingivalis: Implications for Cardiovascular Disease. Invasion Metastasis 1998; 18:57–69. https://doi.org/10.1159/000024499.
33. Aleksijević LH, Aleksijević M, Škrlec I, Šram M, Šram M, Talapko J. Porphyromonas gingivalis Virulence Factors and Clinical Significance in Periodontal Disease and Coronary Artery Diseases. Pathogens 2022; 11:1173. https://doi.org/10.3390/pathogens11101173.
34. Ellis TN, Kuehn MJ. Virulence and Immunomodulatory Roles of Bacterial Outer Membrane Vesicles. Microbiol Mol Biol Rev 2010; 74:81–94. https://doi.org/10.1128/MMBR.00031-09.
35. Beveridge TJ. Structures of Gram-Negative Cell Walls and Their Derived Membrane Vesicles. J Bacteriol 1999; 181:4725–33. https://doi.org/10.1128/JB.181.16.4725-4733.1999.
36. Cecil JD, O'Brien-Simpson NM, Lenzo JC, Holden JA, Singleton W, Perez-Gonzalez A, et al. Outer Membrane Vesicles Prime and Activate Macrophage Inflammasomes and Cytokine Secretion In Vitro and In Vivo. Front Immunol 2017; 8:1017. https://doi.org/10.3389/fimmu.2017.01017.
37. O'Brien-Simpson NM, Pathirana RD, Walker GD, Reynolds EC. Porphyromonas gingivalis RgpA-Kgp Proteinase-Adhesin Complexes Penetrate Gingival Tissue and Induce Proinflammatory Cytokines or Apoptosis in a Concentration-Dependent Manner. Infect Immun 2009; 77:1246–61. https://doi.org/10.1128/IAI.01038-08.
38. Zhang Z, Liu D, Liu S, Zhang S, Pan Y. The Role of Porphyromonas gingivalis Outer Membrane Vesicles in Periodontal Disease and Related Systemic Diseases. Front Cell Infect Microbiol 2021; 10:585917. https://doi.org/10.3389/fcimb.2020.585917.
39. Veith PD, Chen Y-Y, Gorasia DG, Chen D, Glew MD, O'Brien-Simpson NM, et al. Porphyromonas gingivalis Outer Membrane Vesicles Exclusively Contain Outer Membrane and Periplasmic Proteins and Carry a Cargo Enriched with Virulence Factors. J Proteome Res 2014; 13:2420–32. https://doi.org/10.1021/pr401227e.
40. Grenier D. Porphyromonas gingivalis Outer Membrane Vesicles Mediate Coaggregation and Piggybacking of Treponema denticola and Lachnoanaerobaculum saburreum. Int J Dent 2013; 2013:1–4. https://doi.org/10.1155/2013/305476.
41. Guo J, Lin K, Wang S, He X, Huang Z, Zheng M. Effects and mechanisms of Porphyromonas gingivalis outer membrane vesicles induced cardiovascular injury. BMC Oral Health 2024; 24:112. https://doi.org/10.1186/s12903-024-03886-7.
42. Ho M-H, Chen C-H, Goodwin JS, Wang B-Y, Xie H. Functional Advantages of Porphyromonas gingivalis Vesicles. PLOS ONE 2015;10:e0123448. https://doi.org/10.1371/journal.pone.0123448.
43. Aguayo S, Schuh CMAP, Vicente B, Aguayo LG. Association between Alzheimer's Disease and Oral and Gut Microbiota: Are Pore Forming Proteins the Missing Link? J Alzheimers Dis 2018; 65:29–46. https://doi.org/10.3233/JAD-180319.
44. Jia Y, Guo B, Yang W, Zhao Q, Jia W, Wu Y. Rho kinase mediates Porphyromonas gingivalis outer membrane vesicle-induced suppression of endothelial nitric oxide synthase through ERK1/2 and p38 MAPK. Arch Oral Biol 2015; 60:488–95. https://doi.org/10.1016/j.archoralbio.2014.12.009.
45. Yang WW, Guo B, Jia WY, Jia Y. Porphyromonas gingivalis -derived outer membrane vesicles promote calcification of vascular smooth muscle cells through ERK 1/2- RUNX 2. FEBS Open Bio 2016; 6:1310–9. https://doi.org/10.1002/2211-5463.12151.
46. Farrugia C, Stafford GP, Murdoch C. Porphyromonas gingivalis Outer Membrane Vesicles Increase Vascular Permeability. J Dent Res 2020; 99:1494–501. https://doi.org/10.1177/0022034520943187.

47. Zaremba M, Górska R, Suwalski P, Kowalski J. Evaluation of the Incidence of Periodontitis-Associated Bacteria in the Atherosclerotic Plaque of Coronary Blood Vessels. J Periodontol 2007; 78:322–7. https://doi.org/10.1902/jop.2006.060081.
48. Geerts SO, Nys M, De Mol P, Charpentier J, Albert A, Legrand V, et al. Systemic Release of Endotoxins Induced by Gentle Mastication: Association with Periodontitis Severity. J Periodontol 2002; 73:73–8. https://doi.org/10.1902/jop.2002.73.1.73.
49. Zhang J, Xie M, Huang X, Chen G, Yin Y, Lu X, et al. The Effects of Porphyromonas gingivalis on Atherosclerosis-Related Cells. Front Immunol 2021; 12:766560. https://doi.org/10.3389/fimmu.2021.766560.
50. Rodrigues PH, Reyes L, Chadda AS, Bélanger M, Wallet SM, Akin D, et al. Porphyromonas gingivalis Strain Specific Interactions with Human Coronary Artery Endothelial Cells: A Comparative Study. PLoS ONE 2012; 7:e52606. https://doi.org/10.1371/journal.pone.0052606.
51. Salhi L, Rompen E, Sakalihasan N, Laleman I, Teughels W, Michel J-B, et al. Can Periodontitis Influence the Progression of Abdominal Aortic Aneurysm? A Systematic Review. Angiology 2019; 70:479–91. https://doi.org/10.1177/0003319718821243.
52. Figuero E, Sánchez-Beltrán M, Cuesta-Frechoso S, Tejerina JM, Del Castro JA, Gutiérrez JM, et al. Detection of Periodontal Bacteria in Atheromatous Plaque by Nested Polymerase Chain Reaction. J Periodontol 2011; 82:1469–77. https://doi.org/10.1902/jop.2011.100719.
53. Szulc M, Kustrzycki W, Janczak D, Michalowska D, Baczynska D, Radwan-Oczko M. Presence of Periodontopathic Bacteria DNA in Atheromatous Plaques from Coronary and Carotid Arteries. BioMed Res Int 2015; 2015:1–6. https://doi.org/10.1155/2015/825397.
54. Mahalakshmi K, Krishnan P, Arumugam SB. "Association of periodontopathic anaerobic bacterial co-occurrence to atherosclerosis" – A cross-sectional study. Anaerobe 2017; 44:66–72. https://doi.org/10.1016/j.anaerobe.2017.02.003.
55. Xie M, Tang Q, Yu S, Sun J, Mei F, Zhao J, et al. Porphyromonas gingivalis disrupts vascular endothelial homeostasis in a TLR-NF-κB axis dependent manner. Int J Oral Sci 2020; 12:28. https://doi.org/10.1038/s41368-020-00096-z.