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# Apical periodontitis and atherosclerosis: Is there a link? Review of the literature and potential mechanism of linkage

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Atherosclerosis is a progressive narrowing of arteries that may lead to occlusion as a consequence of lipid deposition. It underlies coronary heart disease, as well as myocardial and cerebral infarctions. Recent attention has been directed towards the potential contribution of chronic inflammatory processes that may amplify vascular inflammation in atherosclerosis, as it is recognized as a chronic inflammatory disease. In this category are two of the most prevalent oral diseases: periodontal disease and apical periodontitis (AP). There is increasing epidemiologic evidence for a positive association between periodontal disease and cardiovascular disease (CVD) as well as between AP and CVD. A review of the literature, as well as a potential mechanism for the linkage between AP and atherosclerosis, are presented in this article. *(Quintessence Int 2017;48:527–534; doi: 10.3290/j.qi.a38162)*

**Key words:** blood pressure, bone loss, heart disease, plaque

Atherosclerosis is a progressive narrowing of arteries that may lead to occlusion as a consequence of lipid deposition. Atherosclerosis has a multifactorial etiology, and a large majority of cases can be traced to known risk factors. Increased awareness and knowledge of risk factors has played a large part in prevention and reduction of atherosclerosis prevalence and complications.

Recent attention has been directed towards the potential contribution of chronic inflammatory processes that may amplify vascular inflammation in atherosclerosis, as it is recognized as a chronic inflammatory disease. In this category are two of the most prevalent oral diseases: periodontal disease and apical periodontitis (AP). There is increasing epidemiologic evidence for a positive association between periodontal disease and cardiovascular disease (CVD) as well as between AP and CVD. Although a causal effect was demonstrated between periodontal disease and atherosclerosis in mice, no studies evaluating the potential causal relationship between AP and atherosclerosis have been reported. Given the similarity between AP and periodontal disease and the increasing amount of evidence that AP might not be locally limited, research in this area is essential to our understanding of atherosclerosis disease risk. In this article, periodontal disease and AP, and the relationship between each of them and CVD, is discussed, and potential mechanism for the linkage between AP and atherosclerosis is presented.

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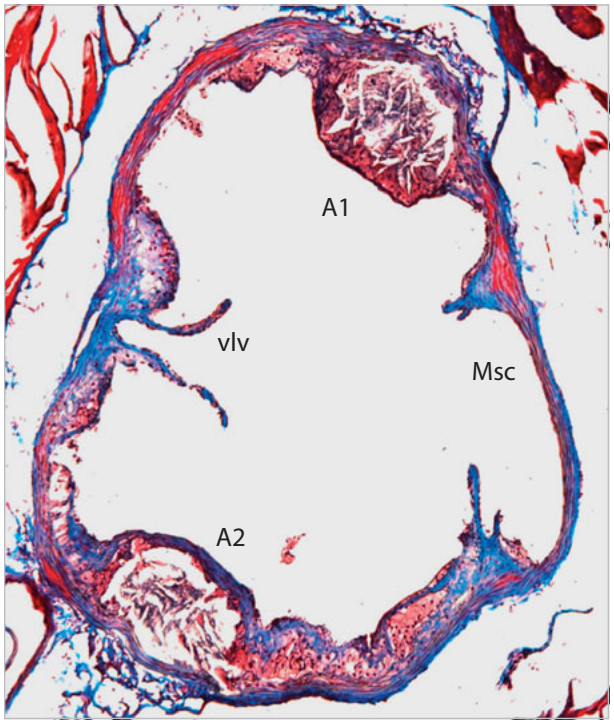



**Fig 1** Atherosclerotic lesions in a mouse aortic sinus. Mouse aortic sinus section cut at the level of the valve leaflets (vlv), stained with Trichrome stain: red, cytoplasm; blue, collagen; purple, nuclei. Msc, normal muscle wall. A1 and A2, atherosclerotic lesions. The atherosclerotic lesions cause narrowing of the arterial space.

## ATHEROSCLEROSIS

Cardiovascular disease (CVD) and cerebrovascular disease (stroke, transient ischemic attack) share common mechanisms and often result from atherosclerosis.[1] Atherosclerosis can lead to coronary heart disease, as well as myocardial and cerebral infarctions.[2] Atherosclerosis is a progressive narrowing of arteries that can lead to occlusion due to lipid deposition. According to the World Health Organization, in 2012, CVD accounted for 3 in every 10 deaths despite the prevalence and success of lipid-lowering drugs.[3,4]

Atherosclerotic lesions, or atheromata, are asymmetric focal thickenings of the innermost layer of the artery, which is known as the intima (Fig 1).[5] The intima is in contact with blood and is lined by endothelial cells. Atheromata begin when lipids from high fat diets activate endothelial cells. Increased blood lipids leads to changes in sheer stress, and this is perceived by mechano-sensors on endothelial cells as a danger signal.[6] These blood lipids also accumulate in the space beneath the endothelial cells, known as the sub-intima. Endothelial cells respond to these abnormalities by expressing chemoattractants for monocytes, which are the body's immune surveillance cells.[7] The endothelial cell surface also changes, and expresses receptors, such as a vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), to guide monocyte migration and extravasation to the site of lipid accumulation in the sub-intima.[7] As a result of these signals, monocytes mature into macrophages, which can take up and degrade the lipid. However, this process can be overwhelmed by chronic high fat, leading to entrapment of macrophages within the sub-intima.

The initial lesion of atherosclerosis is known as the fatty streak and consists almost entirely of lipid-engorged macrophages. As the disease progresses, these lesions grow, attract other immune cells and smooth muscle cells, which encapsulate the lesion. Cells die as a result of lipotoxicity, and lipid, cholesterol, and cellular debris accumulate, along with connective tissue elements, as the body attempts to heal this wound.[8] Atherosclerosis plaques may be characterized as stable or unstable, depending upon the strength and thickness of the smooth muscle cell cap.[9] Unstable plaque can rupture, spilling contents that promote blood clotting and occlusion of the vessel.[9] This may result in myocardial infarction or stroke and potential fatal consequences. Atherosclerosis is recognized as a chronic inflammatory disease in that metabolic risk factors, such as hypercholesterolemia and hypertriglyceridemia, lead to an activated endothelium which triggers an immune response, and this initiates, propagates, and activates lesions in the arterial tree.[4,5]

Atherosclerosis has a multifactorial etiology (Fig 2). Major risk factors include unhealthy blood cholesterol and/or triglyceride levels, high blood pressure, smoking, insulin resistance, diabetes, overweight or obesity, lack of physical activity, unhealthy diet, age, gender (male), and family history of early heart disease.[10] High plasma levels of the acute phase response protein,

C-reactive protein (CRP), is a sign of chronic vascular inflammation and correlates with atherosclerosis disease risk.[10] Emerging risk factors include heavy alcohol consumption and sleep apnea.[10-12] Some risk factors are fixed, including family history, age, and gender, but others can be modified by medication (such as controlling blood pressure or cholesterol levels) or by behavioral changes (such as diet and physical activity). Increased knowledge of potential risk factors allows for future prevention and reduction of atherosclerosis.

It is important to note that a substantial proportion of atherosclerotic CVD events occur in individuals without hyperlipidemia.[4] This has turned the attention to other pathophysiologic drivers of atherosclerosis. Because inflammation is involved in all stages of atherosclerosis, interventions modulating systemic or local inflammatory responses have become attractive means to alter CVD risk.[4] Recently, more attention has been directed towards the identification of potential contributors to chronic inflammatory processes that may amplify vascular inflammation in atherosclerosis. In this category are two of the most prevalent oral diseases: periodontal disease (periodontitis) and AP.

## CHRONIC ORAL INFLAMMATORY DISEASES

Periodontal disease and AP share a common bacterial etiology. Bacteria that are normally found in the oral cavity create a pathologic micro-environment in the periodontal pocket or root canal that leads to a continuous host inflammatory reaction. The host tries to eliminate the bacteria, but without success, due to continued bacterial flow (from the oral cavity) and the inability of the immune system to access these two niches. The two diseases are mostly painless and create minimal discomfort to patients, and as a result they may persist unnoticed for years.[13] Periodontal disease and AP can be eliminated by appropriate therapy, which involves removal and prevention of resettlement of the microbial factor.


**Fig 2** Atherosclerosis risk factors. Atherosclerosis is a chronic inflammatory condition with a multifactorial etiology.

### Periodontal disease

Periodontal disease is inflammation of the tissues surrounding the tooth, including the periodontal ligament, cementum, and alveolar bone. It develops as a response to (mostly) gram-negative, anaerobic bacteria, which originate in the oral cavity and accumulate on the tooth surface as dental plaque.[2,14] The host mounts an inflammatory response to the bacteria in plaque. Whether acute or chronic, the inflammation can eventually lead to loss of bone supporting the tooth structures. Severe periodontal disease is found in 15% to 20% of middle-aged (35 to 44 years) adults. More than 70% of adults 65 and older have moderate to severe periodontal disease.[15]

The association between periodontal disease and CVD has been widely investigated and a positive association has been reported in a systematic review and meta-analysis of observational studies.[16] The meta-analysis concluded that periodontal disease is associated with a 19% increase in the risk of future coronary heart disease.[16] Furthermore, the increase in relative risk was more prominent (44%) in persons aged 65 years and

older.[16] A cross-sectional human study found that levels of triglycerides were higher in periodontitis patients compared to subjects without periodontitis (178 mg/dL vs 165 mg/dL; $P < .05$), and levels of high-density lipoproteins were lower (44 mg/dL vs 50 mg/dL; $P < .05$).[17] This lipid profile is consistent with greater potential for CVD. Several basic science studies have shown a causative association between atherosclerosis and periodontal disease.[18,19] A recent study, using a genetically engineered atherosclerosis mouse model, identified CD36 as essential to host inflammatory signaling in response to the gram-negative bacteria, *Porphyromonas gingivalis*, which is a known perio-pathogen (and also found in infected root canals in AP) and suggested CD36-dependent interleukin 1 beta (IL-1β) generation as a link between periodontal disease and CVD.[19]

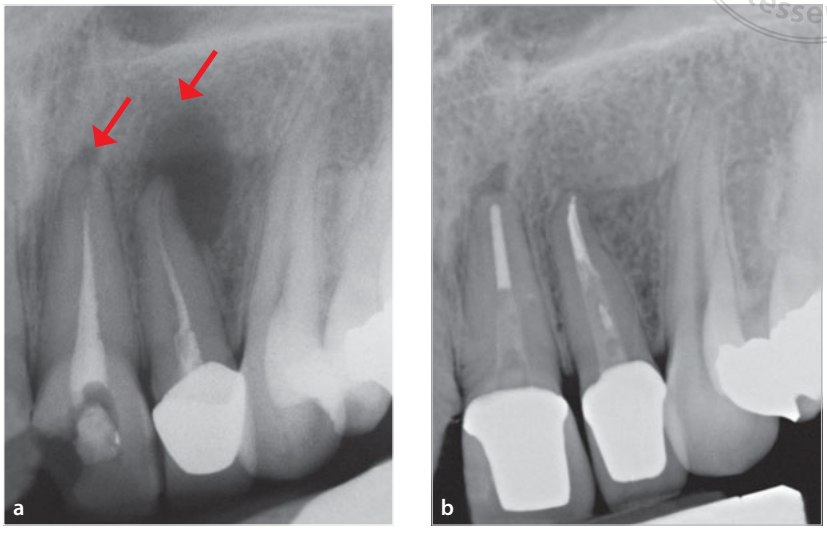
### Apical periodontits (AP)

The term "apical periodontitis" describes inflammation in the alveolar bone, adjacent to the apical opening of an infected root canal, in reaction to infection harbored in the root canal system. This infection, similar to periodontal disease, consists primarily of gram-negative anaerobic bacteria. AP may be detected radiographically as a radiolucent lesion in the surrounding alveolar bone adjacent to the apical part of the infected tooth, and is then referred to as a periapical lesion (PAL) (Fig 3). PALs are highly prevalent, occurring in 34% to 61% of patients.[20-22] Five percent of all teeth without root canal treatment (RCT) and 25% with RCT present with PALs.[23] These numbers are likely an underestimation, due to the limited sensitivity of radiographs. Because PALs are usually not painful, they may go undetected and remain chronic and untreated for years.[24] In a recent publication, the long-term (at least 4 years) dynamics of PALs were evaluated and described.[25] In this study, 51% of the PALs worsened, 28.5% of PALs remained unchanged, and 20% improved over time. The authors concluded that further endodontic treatment was indicated in non-healed cases, those with poor root fillings or poor coronal restorations, because of the likelihood for the lesions to worsen.[25] The treatment of choice, tooth retention or extraction, should be evidence-based, taking into account the various factors and related treatment outcomes, as well as some perceptions based on clinical experience.[26]

Most radiographically detected PALs (97.2%) represented lesions of endodontic origin and included periapical granulomas (60%), radicular cysts (36.7%), periapical fibrous scars (0.27%) and periapical abscesses (0.23%).[13] High-quality endodontic treatment or retreatment led to PAL resolution in 80% of cases.[27] A small subset (2.8%) of PALs represent a group of lesions of non-endodontic origin.[13] These lesions require a different and more radical treatment, including surgical intervention, due to their aggressive behavior, tendency to recur, and risk of malignancy; they should not be left untreated. Therefore, in cases when there is no resolution/healing despite intervention, a biopsy is required for further diagnosis and reevaluation. The potential histopathologic diagnoses of these lesions include odontogenic keratosis, benign fibro-osseous lesions, ameloblastoma, Langerhans cell disease, and central giant cell granuloma or malignancy.[13] In addition to the fact that long-standing, unhealed PALs raise suspicion for one of these different diagnoses, the chronic inflammatory process may, like periodontal disease, have systemic influence.

## EPIDEMIOLOGIC EVIDENCE FOR LINKAGE BETWEEN AP AND CVD

New studies continue to emerge regarding the epidemiologic evidence for the association between AP and CVD, and this area of research draws interest within the dental research community.[28-31] A recent systematic review identified 19 epidemiologic studies in humans (4 cohort, 5 cross-sectional, and 10 case-control) that examined the association between radiographically detected AP and CVD.[28] Of these, 13 showed a significant positive association between AP and CVD, although two lost significance after multivariable analysis. It was concluded that evidence exists for a positive association between AP and CVD; however, the level was moderate to low, and no causal relationship could be established.[28] Since that analysis, new epidemiologic evi-




**Figs 3a and 3b** Radiolucent periapical lesions (PALs)/apical periodontitis (AP). *(a)* Radiolucent PALs (red arrows) associated maxillary left incisors, poor endodontic treatments, and poor restorations. *(b)* One year following endodontic retreatment and new restorations in the maxillary left incisors; maxillary left lateral incisor with a healed PAL; maxillary left central incisor with an unchanged PAL.

dence supporting the positive association between AP and CVD has emerged, including a study, with 364 participants, that found that the likelihood of subjects with radiographically detected AP to also have CVD was 5.3-fold higher compared with subjects without AP.[29]

Evaluation of the influence of AP as a separate risk factor for CVD is challenging for several reasons. First, many factors contribute to the risk of atherosclerosis, as it is known to have a multifactorial etiology (Fig 2).[10] These factors can be addressed during study design and analysis as potential confounders, but based on previous publications, these factors are not always easily controlled.[28] Another challenge is the method used in the studies to measure outcome (CVD) and level of exposure (AP). For example, different radiographic methods are used to evaluate for the presence of AP, including periapical radiographs, panoramic radiographs, cone beam computed tomography (CBCT), and whole body CT.[28] The variation in method is significant because the type of radiograph influences the ability to detect a PAL. The specificity and sensitivity for detection of a PAL varies among panoramic radiographs, periapical radiographs, and CBCT images: sensitivity 0.28, 0.55, 0.91 to 0.98, respectively; and specificity 1, 0.98, and 0.73, respectively.[32,33] This means that when a panoramic radiograph is used for screening only 28% of PALs would be detected. Some studies have used patients' self-report of having a RCT in the past as an indicator of AP, without a complementary radiographic evaluation.[34-36] This method would be considered the least reliable. For these reasons, studying the direct association between CVD and AP is challenging in an experimental setting that involves humans, and a causal relationship between the two has not yet been established.

## Possible underlying mechanism of the association between AP and CVD

Although periapical infections cause a number of local tissue responses that limit the spread of infectious elements, AP may not be an exclusively local phenomenon.[37] Results from a meta-analysis by Gomes et al[38] show that the presence of AP is associated with a systemic increase in inflammatory markers including C-reactive protein (CRP), IL-1, IL-2, IL-6, asymmetric dimethylarginine (ADMA), and immunoglobulins (IgA, IgG, and IgM) in humans.[38] Overall those findings suggest that AP contributes to a systemic immune response that may mediate accelerated atherosclerosis.[38] The potential role of these inflammatory mediators is as follows:

- CRP, which is increased in patients with AP,[38] is a marker associated with atherosclerotic cardiovascular disease, independent of traditional risk factors for CVD.[4,39]
- It is known that endothelial cells can undergo a dramatic modulation in their functional phenotype in response to certain bacterial products, such as gram-negative endotoxins, and other pathogen-associated molecular patterns (PAMPs) or cytokines, such as IL-1, tumor necrosis factor (TNF), and interferon-gamma (INF-γ).[40,41]
- ADMA, an endogenous inhibitor of the endothelial enzyme nitric oxide (NO) synthase, is a cardiovascular risk marker.[42] Low levels of NO are associated with endothelial dysfunction.
- Endotoxin or lipopolysaccharide (LPS) is an important gram-negative bacteria virulence factor. After its release from bacteria, LPS initially binds to a plasma protein called LPS-binding protein and then is delivered to the cell receptor for LPS, CD14, which is expressed primarily on the surface of macrophages.[43] In most situations, CD14 facilitates signaling by the innate immune receptor, Toll-like receptor 4 (TLR4), leading to the host response, which includes activation of the transcription factor nuclear factor kappa B (NF-κB) and consequent expression of pro-inflammatory cytokines and chemokines.[43]

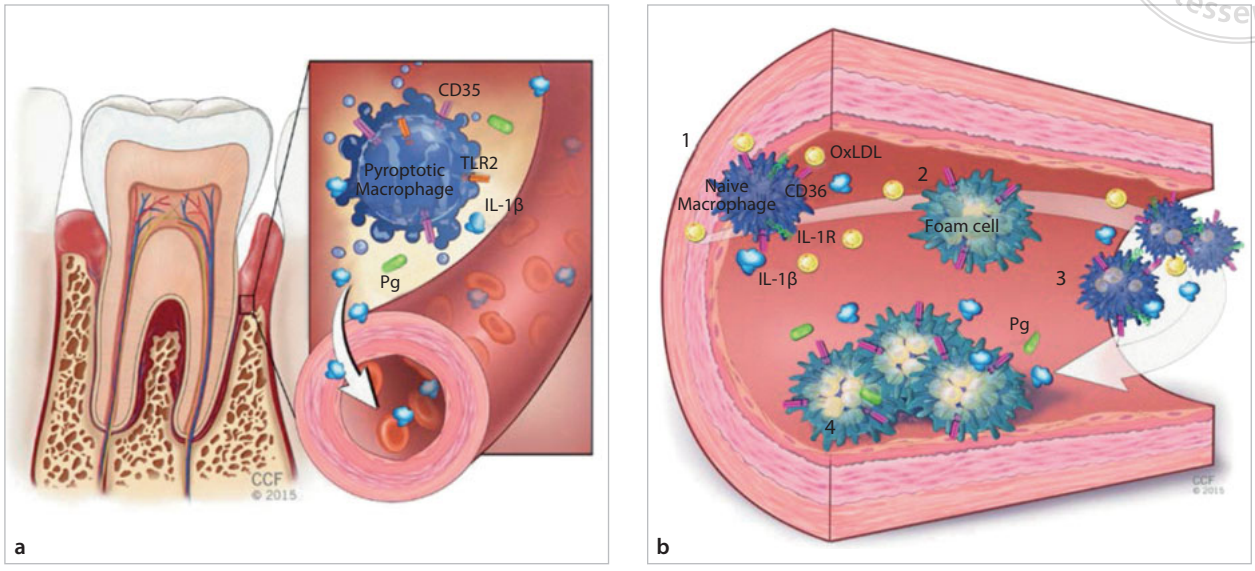
Interestingly, LPS from a major causative pathogen in periodontal disease and AP, the anaerobic gram-negative bacteria *P gingivalis*, has been found to activate macrophages through an alternative TLR, TLR2.[44] Bacterial activation of this inflammatory cascade may underlie the association between periodontitis (and potentially AP) with CVD; locally released cytokines may gain access to the systemic circulation, inducing or perpetuating an elevated chronic systemic inflammatory status.[45] Indeed, a recent study, using a mouse model of *P gingivalis*-induced periodontal disease found evidence for a systemic pro-inflammatory effect, through increasing overall oxidative stress and levels of IL-1β.[19] This study implicated the macrophage receptor CD36, as essential to *P gingivalis*-induced TLR2 signaling and cytokine production, which provides a new target for therapeutic strategies (Fig 4).[19]

Since the etiology and the pathophysiology of periodontal disease and AP are similar, there may also be similar underlying mechanisms for systemic effects from these chronic oral infections. This area remains to be further investigated. A summary of the suggested mechanism of association between AP and atherosclerosis, based on the studies uncovered, is presented in Fig 5. Briefly, it is known that AP is a local inflammatory reaction, but systemic influence has been demonstrated.[38] Chronic inflammatory mediators may be carried via the circulation to various areas in the body. In those areas with a pre-existing atherosclerotic lesion, this could enhance the immune reaction at that site. This may potentially result in acceleration of the pre-existing atherosclerosis process.

## CONCLUSION

Although there is epidemiologic evidence for an association between AP and CVD, a recent systematic review concluded that the level of evidence was moderate to low.[28] Atherosclerosis has a multifactorial etiology and AP may potentially contribute to atherosclerotic lesion development in certain subjects, similar to periodontal disease. Since the etiology and the pathophysiology of periodontal disease and AP are similar, it is reasonable to hypothesize that similar underlying mechanisms could be responsible for a link between AP and CVD, but this remains an area that needs further study. The question of causality also remains unanswered.

In addition to these questions, there are also other important issues that need to be considered: is there a critical periapical lesion number/size that determines systemic influence? Is the length of time with an AP important? Can AP lead to CVD in the absence of hyperlipidemia or other more traditional risk factors of CVD? Given the number of patients with AP and the potential impact, further longitudinal study is warranted, with better control of confounders, and investigation of mechanisms of linkage. Mechanistic understanding of how a chronic long-term inflammatory




**Figs 4a and 4b** Inflammation: From the tooth to the arteries. (a) Activation of macrophages by periodontal disease bacteria (*Porphyromonas gingivalis*, Pg) in the oral cavity is mediated by CD36 and TLR2 and leads to systemic release of pro-atherosclerotic IL1β. *(b)* Systemic IL1β activates naive (to Pg) vascular macrophages to secrete IL1β (1), and promotes CD36-mediated uptake of lipid (2) and enhanced atherosclerosis (3). Although it is controversial as to whether Pg/PgLPS is found in the vasculature, the presence of lipid would promote the development of greater atherosclerotic plaque (4). Reproduced with permission from Brown et al.[19]

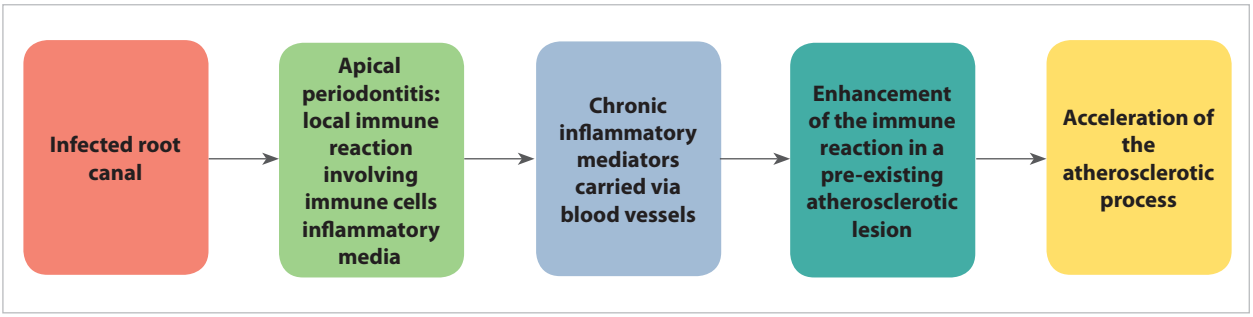



**Fig 5** Suggested potential biologic mechanism for linkage between AP and atherosclerosis.

condition, such as AP, increases risk of atherosclerosis may be applicable to other conditions, including rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease, etc. Overall, there is a need for more research to fill the gaps in our knowledge.

## REFERENCES

1. Adams RJ, Chimowitz MI, Alpert JS, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: A scientific statement for healthcare professionals from the stroke council and the council on clinical cardiology of the American Heart Association/American Stroke Association. Circulation 2003;108:1278–1290.
2. Beck JD, Slade G, Offenbacher S. Oral disease, cardiovascular disease and systemic inflammation. Periodontology 2000 2000;23:110–120.
3. World Health Organization. Factsheet: The top 10 causes of death. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 5 October 2014.
4. Shapiro MD, Fazio S. From lipids to inflammation: New approaches to reducing atherosclerotic risk. Circ Res 2016;118:732–749.

5. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–1695.
6. Chien S. Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell. Am J Physiol Heart Circ Physiol 2007;292:H1209–H1224.
7. Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol 2009;78:539–552.
8. Stary H, Chandler A, Dinsmore R, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the committee on vascular lesions of the council on arteriosclerosis, American Heart Association. Circulation 1995;92:1355–1374.
9. van der Wal AC, Becker AE. Atherosclerotic plaque rupture: pathologic basis of plaque stability and instability. Cardiovasc Res 1999;41:334–344.
10. National Heart, Lung, and Blood Institute; National Institutes of Health. Who Is at Risk for Atherosclerosis? Available at: https://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis/atrisk. Accessed 22 June 2016.
11. Gupta A, Tripathi A, Trivedi C, Sharma P, Mishra A. A study to evaluate the effect of different mandibular horizontal and vertical jaw positions on sleep parameters in patients with obstructive sleep apnea. Quintessence Int 2016;47:661–666.
12. Santander P, Sievers D, Moser N. Sleep-related breathing disorders and dentistry: what is the relationship? Quintessence Int 2016;47:617–621.
13. Sullivan M, Gallagher G, Noonan V. The root of the problem: occurrence of typical and atypical periapical pathoses. J Am Dent Assoc 2016;147:646–649.
14. Clark D, Febbraio M, Levin L. Aggressive periodontitis: the unsolved mystery. Quintessence Int 2017;48:103–111.
15. World Health Organization. Fact sheet no. 318: Oral health. Available at: http://www.who.int/mediacentre/factsheets/fs318/en/. Accessed 7 March 2012.
16. Blaizot A, Vergnes J, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J 2009;59:197–209.
17. Ardila CM, Olarte-Sossa M, Ariza-Garces AA. Association between the presence of *Treponema denticola* and reduced levels of antiatherogenic high density lipoprotein in periodontitis. Quintessence Int 2015;46:207–215.
18. Velsko IM, Chukkapalli SS, Rivera-Kweh MF, et al. Periodontal pathogens invade gingiva and aortic adventitia and elicit inflammasome activation in alphavbeta6 integrin-deficient mice. Infect Immun 2015;83:4582–4593.
19. Brown PM, Kennedy DJ, Morton RE, Febbraio M. CD36/SR-B2-TLR2 dependent pathways enhance *Porphyromonas gingivalis* mediated atherosclerosis in the ldlr KO mouse model. PLoS ONE 2015;10:e0125126.
20. Lopez-Lopez J, Jane-Salas E, Estrugo-Devesa A, et al. Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. Int Dent J 2012;62:40–46.
21. Jimenez-Pinzon A, Segura-Egea JJ, Poyato-Ferrera M, Velasco-Ortega E, Rios-Santos JV. Prevalence of apical periodontitis and frequency of root-filled teeth in an adult Spanish population. Int Endod J 2004;37:167–173.
22. Dugas NN, Lawrence HP, Teplitsky PE, Pharoah MJ, Friedman S. Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. Int Endod J 2003;36:181–192.
23. Pak JG, Fayazi S, White SN. Prevalence of periapical radiolucency and root canal treatment: a systematic review of cross-sectional studies. J Endod 2012;38:1170–1176.
24. Yu VS, Messer HH, Yee R, Shen L. Incidence and impact of painful exacerbations in a cohort with post-treatment persistent endodontic lesions. J Endod 2012;38:41–46.
25. Tsesis I, Goldberger T, Taschieri S, Seifan M, Tamse A, Rosen E. The dynamics of periapical lesions in endodontically treated teeth that are left without intervention: a longitudinal study. J Endod 2013;39:1510–1515.
26. Baba NZ, Goodacre CJ, Kattadiyil MT. Tooth retention through root canal treatment or tooth extraction and implant placement: a prosthodontic perspective. Quintessence Int 2014;45:405–416.
27. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of nonsurgical root canal treatment: Part 1: Periapical health. Int Endod J 2011;44:583–609.
28. Berlin-Broner Y, Febbraio M, Levin L. Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature (Epub ahead of print, 21 Oct 2016). Int Endod J. doi: 10.1111/iej.12710.
29. An GK, Morse DE, Kunin M, Goldberger RS, Psoter WJ. Association of radiographically diagnosed apical periodontitis and cardiovascular disease: a hospital records-based study. J Endod 2016;42:916–920.
30. Garg P, Chaman C. Apical periodontitis: is it accountable for cardiovascular diseases? J Clin Diagn Res 2016;10:ZE08–ZE12.
31. Liljestrand JM, Mantyla P, Paju S, et al. Association of endodontic lesions with coronary artery disease. J Dent Res 2016;95:1358–1365.
32. Petersson A, Axelsson S, Davidson T, et al. Radiological diagnosis of periapical bone tissue lesions in endodontics: a systematic review. Int Endod J 2012;45:783–801.
33. Lennon S, Patel S, Foschi F, Wilson R, Davies J, Mannocci F. Diagnostic accuracy of limited-volume cone-beam computed tomography in the detection of periapical bone loss: 360° scans versus 180° scans. Int Endod J 2011;44:1118–1127.
34. Joshipura KJ, Pitiphat W, Hung H, Willett WC, Colditz GA, Douglass CW. Pulpal inflammation and incidence of coronary heart disease. J Endod 2006;32:99–103.
35. Caplan DJ, Pankow JS, Cai J, Offenbacher S, Beck JD. The relationship between self-reported history of endodontic therapy and coronary heart disease in the atherosclerosis risk in communities study. J Am Dent Assoc 2009;140:1004–1012.
36. Arroll B, Dhar D, Cullinan M. Relationship of root canal treatment to C-reactive protein as an inflammatory marker for cardiovascular disease. J Primary Health Care 2010;2:11–15.
37. Segura-Egea JJ, Martin-Gonzalez J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. Int Endod J 2015;48:933–951.
38. Gomes MS, Blattner TC, Sant'Ana Filho M, et al. Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis. J Endod 2013;39:1205–1217.
39. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–140.
40. Gimbrone MA Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118:620–636.
41. Pober JS, Cotran RS. Cytokines and endothelial cell biology. Physiol Rev 1990;70:427–451.
42. Hsu C, Zhao J, Lin S, et al. Asymmetric dimethylarginine limits the efficacy of simvastatin activating endothelial nitric oxide synthase. J Am Heart Assoc 2016;5:e003327.
43. Rocas IN, Siqueira JF Jr, Del Aguila CA, Provenzano JC, Guilherme BP, Goncalves LS. Polymorphism of the CD14 and TLR4 genes and post-treatment apical periodontitis. J Endod 2014;40:168–172.
44. Bainbridge BW, Darveau RP. *Porphyromonas gingivalis* lipopolysaccharide: an unusual pattern recognition receptor ligand for the innate host defense system. Acta Odontol Scand 2001;59:131–138.
45. Caplan DJ, Chasen JB, Krall EA, et al. Lesions of endodontic origin and risk of coronary heart disease. J Dent Res 2006;85:996–1000.