REVIEW

The Link between Periodontal Disease, Inflammation and Atherosclerosis — an Interdisciplinary Approach

Theodora Benedek

University of Medicine and Pharmacy, Tîrgu Mureș, Romania

CORRESPONDENCE

Theodora Benedek
Str. Gheorghe Marinescu nr. 38
540139 Tîrgu Mureș, Romania
Tel: +40 265 215 551
E-mail: theodora.benedek@gmail.com

ABSTRACT

Periodontal disease is a chronic inflammatory disease that results from the activity of altered oral microbiome, leading to altered immune reaction, destruction of tissues supporting the teeth, and oral bone loss. This disease is particularly associated with an expressed systemic inflammation, being considered nowadays an inflammatory disorder. At the same time, inflammation has been recognized to play a major role in the development of atherosclerotic lesions. Atheromatous plaque formation is triggered by alterations in the structure of the endothelium, which lead to the expression of adhesion molecules and recruitment of immune cells such as macrophages, in the arterial wall. While the association between periodontal disease, inflammation and cardiovascular diseases has been well established, the causality relation between these three entities has not been demonstrated so far. This review presents the most common advances in understanding the complex link between periodontal disease, inflammation and atherosclerosis, as a common pathway leading to increased cardiovascular risk.

Keywords: atherosclerosis, periodontal disease, inflammation

Atherosclerosis remains a major health problem, and atherosclerosis-related diseases continue to represent a significant burden for society. Atherosclerosis is a generalized process that affects the entire arterial system, being characterized by the presence of atheromatous plaques at different locations in the circulation.

According to the location of the atheromatous plaques, the most common presentations of this disease are represented by coronary artery disease (CAD) when the plaques are located in the coronary arteries, peripheral arterial disease (PAD) when the plaques are located in the circulatory system, or ischemic stroke resulting from severe atherosclerotic plaques in the carotid arteries. While the clinical manifestations are different in these three entities, the pathophysiological substrate is common in all clinical forms of atherosclerosis, relying mainly on the mechanisms of plaque formation and associated inflammation.

INFLAMMATION — A COMMON PATHWAY FOR PERIODONTAL DISEASE AND ATHEROSCLEROSIS

Periodontal disease is a chronic inflammatory disease that results from the activity of altered oral microbiome leading to altered immune reaction, destruction of tissues supporting the teeth, and oral bone loss.[1] This disease is particularly associated with an expressed systemic inflammation, being considered nowadays an inflammatory disorder. The activity of sub-gingival microbes accumulated in periodontal disease alters the cytokine and chemokine responses of the host, leading to an exacerbated systemic inflammation.[2] Lu *et al.* demonstrated that human gingiva is one of the sites of C-reactive protein production, proving the significant role of gingiva in the inflammatory pathways.[3]

At the same time, inflammation has been recognized to play a major role in the development of atherosclerotic lesions.[4] Atheromatous plaque formation is triggered by alterations in the structure of the endothelium, which lead to expression of adhesion molecules and recruitment of immune cells such as macrophages, in the arterial wall. Once the endothelial surface is damaged, vascular adhesion molecules (VCAM) and intercellular adhesion molecules (ICAM) are expressed, allowing leucocytes to bind to the endothelium, thus favoring lipid accumulation and the production of chemokines, which in turn promote the accumulation of smooth muscle cells and, as a result of inflammatory stimulation, secretion of metalloproteinases and rupture of the fibrous cap, causing plaque rupture and acute coronary syndromes.[5]

In animal experiments, oral interventions were associated with increased release of biomarkers characterizing atherosclerosis. For instance, in a study by Li *et al.*, oral intervention in mice was associated with increased expression of matrix metalloproteinases in carotid arteries and higher levels of serum interleukin 6, biomarkers traditionally associated with atherosclerosis and, at the same time, powerful inflammatory markers.[6] A case-control study led by Ramirez *et al.* proved that higher plasma levels of cardiovascular biomarkers such as E-selectin and myeloperoxidase were recorded in patients with chronic periodontal disease.[7]

The complex interaction between pro-inflammatory factors released by periodontal microbes and the vascular endothelium represents the pathophysiologic substrate of the link between the atherosclerotic process and periodontal disease (Figure 1). Table 1 presents the results of the main clinical studies that addressed the link between atherosclerosis and periodontal disease.[8,9]

GINGIVAL MICROBIOTA AND ATHEROSCLEROTIC PLAQUE COMPOSITION

Recent evidence suggest that among the multitude of factors involved in the development of atherosclerotic plaques, microbiota and associated inflammation in the periodontium could play a role in the pathophysiology of atheromatous plaque formation, via increasing the inflammatory level in the body of the host. Immune dysregulation mediated by the oral microbiome has been proposed to represent the pathway between periodontitis and chronic inflammation, which in turn triggers and augments the development of the atherosclerotic process.[1] Oral infection leads to an increased release of inflammatory cytokines, which enter the systemic circulation and reach various distant locations, favoring the development of atherosclerosis at these sites.[10] However, the immune mechanisms via which periodontal pathogens exacerbate plaque progression are not elucidated yet. At the same time, Carrion *et al.* demonstrated that blood myeloid DCs
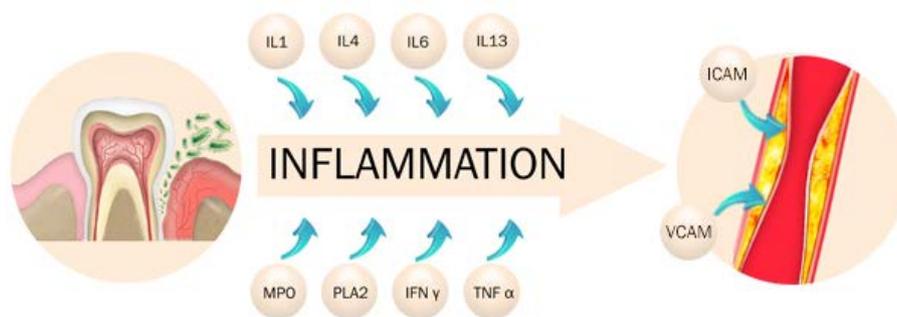
FIGURE 1.   The pathophysiologic substrate of the link between the atherosclerotic process and periodontal disease

TABLE 1. Recent studies on the link between atherosclerosis and periodontal disease

Study	Year	Number of participants	Conclusions
Gomes et al.[32]	2016	278 dental patients	Endodontic burden is an independent predictor of CVD
Bengtsson et al.[35]	2016	499 dental patients	Periodontitis is significantly associated with carotid calcification
Ketabi et al.[34]	2016	59 patients with coronary artery disease 23 patients without coronary obstruction	Periodontal disease and dental parameters correlates with the severity of coronary artery disease
Mahendra et al.[13]	2015	51 patients with CV disease 51 controls	Study lot had higher number of bacteria in the subgingival plaques Number of bacteria in the subgingival plaques correlates with number of bacteria in atherosclerotic plaques
Groves et al.[33]	2015	473 diabetic patients 548 non-diabetic patients	Periodontal disease is a direct predictor of CVD in type 1 diabetic patients
Soder et al.[39]	2015	1676 participants randomly selected	Gingival inflammation correlates with stroke
Ramirez et al.[7]	2014	22 patients with moderate/severe periodontitis 22 controls	E-selectin and myeloperoxidase levels significantly increased in patients with moderate/severe periodontitis
Rathnayake et al.[48]	2015	200 patients with acute myocardial infarction	Salivary levels of Matrix Metalloproteinase-8 and 9 and myeloperoxidase (biomarkers of CV risk) are associated with periodontal status
Gupta et al.[49]	2015	30 patients with severe chronic periodontitis 50 healthy controls	CV risk markers are increased in patients with periodontal disease
Etemadifar et al.[50]	2015	30 patients with severe periodontal disease 30 healthy controls	High levels of C-reactive protein is associated with periodontal disease
Armingohar et al.[47]	2014	40 patients with peripheral arterial disease	Higher bacteria levels in vascular biopsies from patients with periodontal disease
Carrion et al.[11]	2012	40 patients with acute coronary syndrome 25 healthy controls	Blood myeloid DCs play a role in harboring and disseminating oral pathogens to atheromatous plaques
Koren et al.[29]	2011	15 patients with atherosclerosis 15 healthy controls	Levels of plaque, oral and gut microbiota correlate with biomarkers of atherosclerosis
Figuero et al.[38]	2011	42 patients undergoing carotid end-arterectomy	DNA of at least 1 bacteria was present in all 42 samples

play a role in harboring and disseminating oral pathogens to atheromatous plaques, suggesting also a direct effect of bacterial contamination in the determination of athero-sclerotic lesions.[11]

In the Oral Infection and Vascular Disease Epidemiology Study, 4,561 biofilm samples were collected from 593 patients for the assessment of bacterial species and found significantly increased levels of secretory phospholipase A2 and lipoprotein-associated PLA2, two inflammatory enzymes associated with atherosclerosis.[12] At the same time, Mahendra et al. proved that patients with cardiovascular diseases (CVD) exhibit higher levels of periodontal pathogens in subgingival biofilms, and that the amount of subgingival bacteria was significantly associated with the amount of bacteria identified in the atherosclerotic plaques.[13]

Various pathogens such as *Chlamidia pneumoniae, Porphyromonas gingivalis* or *Helicobacter pylori* were identified in human atheromatous plaques, suggesting that infectious agents present in the systemic circulation could penetrate the vascular endothelium and accumulate within the atheromatous plaques, favoring plaque progression.[1,14–21] Table 2 presents the main types of bacteria from oral microbiota, identified by different studies as related to atheromatous plaque formation. In a study on 91 patients with carotid artery disease, the DNA of atheromatous plaques was assessed following carotid or coronary atherectomy (an interventional technique used for in vivo plaque removal using a cutting device introduced percutaneously via the femoral artery and guided under fluoroscopic control to the site of the carotid or coronary plaque). This technique succeeded to identify the DNA of *Porphyromonas gingivalis* in atheromatous plaques of patients with periodontitis.[22,23]

Filardo *et al.* isolated a *Chlamidia pneumoniae* strain from the gingival cervical fluids and demonstrated that this isolate significantly increased the number of foam cells

TABLE 2. Main types of bacteria from oral microbiota identified by different studies as related to atheromatous plaque formation

Study	Year	Bacteria
Haraszthy et al.[16]	2000	Porphyromonas gingivalis
		Tannerella forsythensis
		Proteolla intermedia
Figuero et al.[37]	2011	Porphyromonas gingivalis
		Aggregatibacter actinomycetemcomitans
		Tannerella forsythensis
		Eikenella corrodens
		Fusobacterium nucleatum
		Campylobacter rectus
Koren et al.[28]	2011	Chryseomonas
		Veillonella
		Streptococcus
Carrion et al.[10]	2012	Porphyromonas gingivalis
		Burkholderia cepacia
Szulc et al.[21]	2015	Porphyromonas gingivalis
Fak et al.[27]	2015	Anaeroglobus
		Parvimonas
		Catonella
		Lactobacillus
		Capnocytophaga
Filardo et al.[23]	2015	Chlamydia pneumonie
Chukkapalli et al.[24]	2015	Porphyromonas gingivalis
		Treponema denticola
		Tannerealla forsythis
		Fusobacterium nucleatum

and the levels of interleukin-1 and interleukin-6, all these factors playing major roles in the development of atherosclerotic plaques.24

In a study by Chukkapali et al., the oral cavity of ApoE^{null} mice was infected with various microbial species such as *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nucleatum* and *Tannerealla forsythia*, agents that have been identified in the atherosclerotic plaques collected from humans. The study demonstrated an increased release of inflammatory cytokines such as IL-13, IFN gamma and IL-4 at 24 weeks after infection. At the same time, polybacterial infection was associated with altered lipid profiles and increased plaque formation in the aorta, proving that these oral cavity infections could induce atherosclerosis via inflammatory pathways.[25,26]

In a study on pigs exposed orally to *P. gingivalis*, Paquette *et al.* demonstrated that exposed pigs exhibited higher levels of systemic C-reactive protein (a strong inflammatory marker) and increased atheroma burden as compared to controls.[27] In humans, Fak *et al.* proved that atherosclerotic patients had higher levels of *Anaeroglobus*

as compared to controls, and that the presence of *Lactobacillus*, *Catonella* and *Capnocytophaga* in the periodontal space was associated with elevated levels of serum lipids.[28] Other bacteria isolated from atherosclerotic plaques were *Chryseomonas*, *Veillonella* and *Streptococcus*.[29]

PERIODONTAL DISEASE AND CARDIOVASCULAR RISK

The association between periodontitis and CVD has been recognized for many years, and since then, many studies tried to elucidate the role of periodontal disease as a cardiovascular risk factor. Buhlin *et al.*, using a nationwide questionnaire in Sweden, reported a significantly increased risk of CVD if the patient had experienced untreated dental problems (OR 2.45, 95% CI 1.066–5.625).[30]

Various clinical biomarkers have been used to validate the hypothesis that periodontal disease could independently predict the development of clinical atherosclerosis. One of these biomarkers is the carotid-intima thickness, a strong indicator of cardiovascular risk significantly associated with the severity of the atherosclerotic process. In a study by Toregeani *et al.*, the treatment of periodontitis significantly decreased the carotid-intima thickness at 6 months after initiation. The reduction of carotid-intima thickness following periodontitis treatment could be considered a direct expression of the relation between this disease and atherosclerotic disease.[31]

The Baltimore Longitudinal Study of Ageing, carried out on 278 patients, proved that apical periodontitis is independently associated with the incidence of cardiovascular events.[32]

While the association between periodontal disease and atherosclerosis has been well established for many years, the role of periodontal disease as an independent risk factor for cardiovascular disease is not clearly supported by current evidence so far. There is accumulating evidence suggesting that the treatment of periodontitis could reduce atherosclerosis progression. However, larger longitudinal studies are needed in order to prove the power of this new risk factor in the complex family of CV risk factors.

PERIODONTAL DISEASE AND CORONARY ARTERY DISEASE

Groves *et al.*, in a study on 1,021 individuals out of which 473 diabetics, demonstrated that periodontal disease is significantly associated with the accumulation of calcium in the coronary artery wall in diabetic patients, proving that the presence of periodontal disease could be considered an

independent predictor of atherosclerosis development in a diabetic population.[33]

In a study on 82 patients undergoing coronary angiography, Ketabi *et al.* proved that parameters expressing periodontal disease, such as pocket depth, gingival recession, clinical attachment level, and bleeding on probing were significantly higher in patients with CAD as compared to patients with no coronary obstruction on angiography. Furthermore, they found a significant correlation between these parameters and the severity of CAD at angiography, proving that a direct link exists between periodontal disease and coronary atherosclerosis.[34]

At the same time, the treatment of periodontal disease seems to reduce the atherosclerotic burden along with the level of inflammation. A recent meta-analysis demonstrated that the treatment of established periodontitis led to an improved endothelial function and a significant reduction in the levels of CRP, Il-6, TNF-alpha and total cholesterol.[35,36]

However, it should be noted that according to the level of stability of coronary plaques, coronary artery disease has two different forms: (1) stable coronary artery disease, characterized by stable coronary plaques, which is associated with a chronic low-grade inflammation, and (2) acute coronary syndromes, triggered by the rupture of a vulnerable coronary plaque, process in which a suddenly exacerbated inflammation plays a major role.[37] While a large number of studies addressed the link between periodontal disease and chronic atherosclerosis, no study reported a clear correlation between this disease and acute coronary syndromes.

PERIODONTAL DISEASE AND CAROTID ARTERY DISEASE

The presence of DNA from bacteria causing periodontal disease has been identified in a large proportion of samples of carotid plaques obtained using endarterectomy.[38] Soder *et al.* proved a strong association between gingival inflammation and stroke and demonstrated, in a multiple regression analysis, an odds ratio of 2.2 (95% CI 1.02–4.74) for gingival inflammation for predicting stroke.[39]

A very large meta-analysis on 17,330 patients, designed to identify the association between carotid atherosclerosis and periodontal disease, proved that the presence of periodontal lesions is associated with a significant risk for carotid atheromatous plaque formation (OR: 1.08, p = 0.05).[40] Another study, conducted on 499 individuals, proved that patients with periodontitis had a significantly higher prevalence of carotid calcifications compared to patients with no periodontal disease.[41] All these data suggest that the mechanisms of endothelial plaque formation and progression, in relation to periodontal disease, are common both for carotid and coronary locations.

PERIODONTAL DISEASE AND PERIPHERAL ARTERY DISEASE

PCR analysis of the DNA and RNA of various oral bacterial species demonstrated the presence of *P. gingivalis*, *T. forsythia*, *F. nucleatum* and others in atherosclerotic plaques extracted from the peripheral arteries.[42–44] It has also been proved that the presence of *P. gingivalis* in atherosclerotic plaques accelerates the progression of abdominal aortic aneurysms,[42,43] and Kowalski *et al.* demonstrated that infection with oral pathogens is associated with a significantly greater lumen loss at 6 months after stent implantation, proving that periodontal disease and associated bacteria can also be involved in the complex mechanism of in-stent restenosis.[45] Armingohar *et al.* extracted DNA from vascular biopsies obtained from patients with peripheral vascular disease and found a significantly higher bacterial load in patients with vascular disease associating periodontal disease as compared to those without periodontal disease.[46,47]

CONCLUSIONS

The link between periodontal disease, inflammation and CVD has been well established. However, the relation of causality between these three entities has not been demonstrated so far. Further research is still needed in order to elucidate whether periodontal disease causes atherosclerotic plaque formation or they are rather common manifestations of the same inflammatory disease.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Slocum C, Kramer C, Genco A. Immune dysregulation mediated by the oral microbiome: potential link to chronic inflammation and atherosclerosis. *J Int Med*. 2016;280:114-128.
2. Chukkapalli SS, Easwaran M, Rivera-Kweh MF, et al. Sequential Colonization of Periodontal Pathogens in Induction of Periodontal Disease and Atherosclerosis in LDLRnull Mice. *Pathog Dis*. 2017; pii: ftx003.
3. Lu Q, Jin L. Human gingiva is another site of C-reactive protein formation. *J Clin Periodontol*. 2010;37:789-796.
4. Ross R. Atherosclerosis – an inflammatory disease. *New Engl J Med*. 1999;340:115-126.
5. Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis, and cardiovascular disease. *Critical reviews in oral biology and medicine*. 2004;15:403413.
6. Li J, Liu Y, Ren X, Chang L, Yue Z, Shi X. Effect of oral intervention on matrix metalloproteinase-2, 9 expression in carotid arteries and serum

interleukin-6 in rats with chronic periodontitis. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2014;49:554-559.

7. Ramirez JH, Parra B, Gutierrez S, et al. Biomarkers of cardiovascular disease are increased in untreated chronic periodontitis: a case control study. *Aust Dent J*. 2014;59:29-36.

8. Aarabi G, Eberhard J, Reissmann DR, Heydecke G, Seedorf U. Interaction between periodontal disease and atherosclerotic vascular disease — Fact or fiction? *Atherosclerosis*. 2015;241:555-560.

9. Chistiakov DA, Orekhov AN, Bobryshev YV. Links between atherosclerotic and periodontal disease. *Exp Mol Pathol*. 2016;100:220-35.

10. Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis, and cardiovascular disease. *Critical reviews in oral biology and medicine*. 2004;15:403413.

11. Carrion J, Scisci E, Miles B, et al. Microbial carriage state of peripheral blood dendritic cells (DCs) in chronic periodontitis influences DC differentiation, atherogenic potential. *J Immunol*. 2012;189:3178-3187.

12. Boillot A, Demmer RT, Mallat Z, et al. Periodontal microbiota and phospholipases: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Atherosclerosis*. 2015;242:418-423.

13. Mahendra J, Mahendra L, Nagarajan A, Mathew K. Prevalence of eight putative periodontal pathogens in atherosclerotic plaque of coronary artery disease patients and comparing them with noncardiac subjects: A case-control study. *Indian J Dent Res*. 2015;26:189-195.

14. Shor A, Kuo CC, Patton DL. Detection of Chlamydia pneumonia in coronary arterial fatty streaks and atheromatous plaques. *S Afr Med J*. 1992;82:158-161.

15. Kuo CC, Gown AM, Benditt EP, Grayston JT. Detection of Chlamydia pneumoniae in aortic lesions of atherosclerosis by immunocytochemical stain. *Arterioscler Thromb*. 1993;13:1501-1504.

16. Farsak B, Yildirir A, Aky€on Y et al. Detection of Chlamydia pneumoniae and Helicobacter pylori DNA in human atherosclerotic plaques by PCR. *J Clin Microbiol*. 2000;38:4408-4411.

17. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol*. 2000;71:1554-1560.

18. Ameriso SF, Fridman EA, Leiguarda RC, Sevlever GE. Detection of Helicobacter pylori in human carotid atherosclerotic plaques. *Stroke*. 2001;32:385-391.

19. Latsios G, Saetta A, Michalopoulos NV, Agapitos E, Patsouris E. Detection of cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae DNA in carotid atherosclerotic plaques by the polymerase chain reaction. *Acta Cardiol*. 2004;59:650-657.

20. Kozarov EV, Dorn BR, Shelburne CE, Dunn WA, Progulske-Fox A. Human atherosclerotic plaque contains viable invasive Actinobacillus actinomycetem comitans and Porphyromonas gingivalis. *Arterioscler Thromb Vasc Biol*. 2005;25:e17-18.

21. Kaplan M, Yavuz SS, Cinar B et al. Detection of Chlamydia pneumoniae and Helicobacter pylori in atherosclerotic plaques of carotid artery by polymerase chain reaction. *Int J Infect Dis*. 2006;10:116-123.

22. 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;2015:825397.

23. Liu F, Wang Y, Xu J, Liu F, Hu R, Deng H. Effects of Porphyromonas gingivalis lipopolysaccharide on the expression of key genes involved in cholesterol metabolism in macrophages. *Arch Med Sci*. 2016;12:959-967.

24. Filardo S, Di Pietro M, Schiavoni G, et al. Chlamydia pneumonie clinical isolate from gingival cervicular fluid: a potential atherogenic strain. *Frontiers in cellular and infection microbiology*. 2015;5:86.

25. Chukkapalli SS, Velsko IM, Rivera-Kweh MF, Zheng D, Lucas AR, Kesavalu L. Polymicrobial Oral Infection with Four Periodontal Bacteria Orchestrates a Distinct Inflammatory Response and Atherosclerosis in ApoEnull Mice. *Plos One*. 2015;10:e0143291.

26. Kimak A, Strycharz-Dudziak M, Bachanek T, Kimak E. Lipids and lipoproteins and inflammatory markers in patients with chronic apical periodontitis. *Lipids in health and disease*. 2015;14:162.

27. Paquette DWQ. The periodontal-cardiovascular link. *Compend Cont Educ Dent*. 2004;25:681-692.

28. Fåk F, Tremaroli V, Bergström G, Bäckhed F. Oral microbiota in patients with atherosclerosis. *Atherosclerosis*. 2015;243:573578.

29. Koren O, Spor A, Felin J, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci USA*. 2011;108 Suppl 1:4592-8.

30. Buhlin K, Gustafsson A, Hakansson J, Klinge B. Oral health and cardiovascular disease in Sweden. *J Clin Periodontol*. 2002;29:254-259.

31. Toregeani JF, Nassar CA, Nassar PO, et al. Evaluation of periodontitis treatment effects on carotid intima-media thickness and expression of laboratory markers related to atherosclerosis. *Gen Dent*. 2016;64:55-62.

32. Gomes MS, Hugo FN, Hilgert JB, et al. Apical periodontitis and incident cardiovascular events in the Baltimore Longitudinal Study of Ageing. *Int Endod J*. 2016;49:334-342.

33. Groves D, Krantz MJ, Hokanson JE, et al. Comparison of frequency and duration of periodontal disease with progression of coronary artery calcium in patients with type 1 diabetes mellitus versus non-diabetics. *Am J Cardiol*. 2015;116:833-837.

34. Ketabi M, Meybodi FR, Asgari MR. The association between periodontal disease parameters and severity of atherosclerosis. *Dent Res J (Isfahan)*. 2016;13:250-255.

35. Saffi Lumertz MA, Vargas Furtato M, Polanczyk CA, et al. Relationship between vascular endothelium and periodontal disae in atherosclerotic lesions. Review article. *World J Cardiol*. 2015;7:26-30.

36. Teeuw WJ, Slot DE, Susanto H, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and metaanalysis. *J Clin Periodontol*. 2014; 41: 70-79.

37. Cotti E, Dessi C, Piras A, Mercuro G. Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature. *Int J Cardiol*. 2011;148:4-10.

38. Figuero E, Sanchez-Beltran M, Cuesta-Frechoso S, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. *J Periodontol*. 2011;82:1469-1477.

39. Söder B, Meurman JH, Söder PÖ. Gingival Inflammation Associates with Stroke--A Role for Oral Health Personnel in Prevention: A Database Study. *PLoS One*. 2015;10:e0137142.

40. Zeng XT, Leng WD, Lam YY, et al. Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants. *Int J Cardiol*. 2016;203:1044-1051.

41. Bengtsson VW, Persson GR, Berglund J, Renvert S. A cross-sectional study of the associations between periodontitis and carotid arterial calcifications in an elderly population. *Acta Odontol Scand*. 2016;74:115-120.

42. Budzynski J, Wisniewska J, Ciecierski M, Kedzia A. Association between bacterial infection and peripheral vascular disease: A review. *Int J Angiol*. 2016;25:3-13.

43. Sessa R, Pietro MD, Filardo S, Turriziani O. Infectious burden and atherosclerosis: a clinical issue. *World J Clin Cases*. 2014;2:240-249.

44. Suzuki J, Aoyama N, AokiM, et al. High incidence of periodontitis in Japanese patients with abdominal aortic aneurysm. *Int Heart J*. 2014;55:268-270.

45. Kowalski M, Konturek PC, Pieniążek P, et al. Prevalence of Helicobacter pylori infection in coronary artery disease and effect of its eradication on coronary lumen reduction after percutaneous coronary angioplasty. *Dig Liver Dis*. 2001;33:222-229.

46. Armingohar Z, Jorgensen JJ, Kristoffersen AK, Abesha-Belay E, Olsen I. Bacteria and bacterial DNA in atherosclerotic plaque and aneurysmal wall biopsies from patients with and without periodontitis. *J Oral Microbiol*. 2014;6.

47. Papapanou P. Systemic effects of periodontitis: Lessons learned from research on atherosclerotic vascular disease and adverse pregnancy outcomes. *Int Dent J*. 2015;65:283-291.

48. Rathnayake N, Gustafsson A, Norhammar A, et al. Salivary Matrix Metalloproteinase-8 and -9 and Myeloperoxidase in Relation to Coronary Heart and Periodontal Diseases: a subgroup report from the PAROKRANK Study (Periodontitis and Its Relation to Coronary Artery Disease). *PLoS One*. 2015;10:e0126370.

49. Gupta M, Chaturvedi R, Jain A. Role of cardiovascular disease markers in periodontal infection: understanding the risk. *Indian J Dent Res*. 2015;26:231-236.

50. Etemadifar R, Konarizadeh S, Zarei A, Farshidi H, Sobhani A. Relationship between periodontal status and C-reactive protein and interleukin-6 levels among atherosclerotic patients in Bandar Abbas, Iran in 2014. *Electron Physician*. 2015;7(1):1010-1016.