Oral Health and Coronary Artery Disease, A Review Article

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ARTICLE INFO	ABSTRACT
	Atherosclerosis is the most common cause of myocardial infarction and ischemic stroke. Various risk factors have been identified for atherosclerosis. Recently, bacterial and viral organisms, which are involved in chronic inflammatory processes, have been also implicated in atherosclerosis development. Individuals with a prior history of periodontal diseases and/or tooth loss are considered to be at a higher risk for peripheral arterial disease, compared to those without periodontal diseases or tooth loss. Evidence suggests that periodontitis contributes to the overall burden of infection and inflammation and may lead to cardiovascular events and stroke in susceptible patients. In this article, we aimed to review the available data on the relationship between periodontal diseases and cardiovascular diseases, especially coronary artery disease. At least sixty papers were reviewed during 2014-15. Of these, 44 were included in our study.

Introduction

Periodontitis is a localized, chronic inflammatory disease, which is induced by bacteria and destroys both connective tissues and the supporting bone of the teeth. In the general population, the prevalence of severe periodontitis has been estimated at nearly 5% (1).

Initial epidemiological evidence suggests an association between periodontitis and coronary artery diseases (CADs). Systemic bacteremia, systemic inflammation, and immune-mediated reactions constitute a triad of mechanisms, supporting the link between periodontal and vascular damages (2,3). However, it is still unclear to what extent these periodontitis-mediated components contribute to vascular damage.

After more than 20 years since the initial epidemiological evidence on the association between periodontitis and CADs, substantial, though controversial, data have been reported in favor of such a relationship, considering the presence of various uncontrolled confounding factors and different assessment methods for periodontal diseases.

In this review article, studies assessing the association between oral health and CADs were evaluated. A number of studies have demonstrated such an association, while none have shown a cause-and-effect relationship between these conditions, so far.

Evidence Acquisition

According to above-mentioned key words, a comprehensive search was accomplished precisely through the following databases: ISI web of science (ISI), Medline, Pubmed, Scopus, Embase, Chemical abstracts, Current contents, Cinahl, BIOSIS, Google scholar. This task which was started on January 2014 was completed by three of our authors. The purpose of our research

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was to find out whether there is a relationship between poor oral hygiene and increased incidence of coronary artery disease. To this end, every topic or paper pertaining to our question was included in the review. Those encompassed publications from 1989 to 2012. Investigations not strictly related to our issue were excluded.

Results

Atherosclerosis is the most frequent cause of myocardial infarction (4). Various anatomical, physiological, and behavioral risk factors have been identified for atherosclerosis, including changes in serum lipid concentration, tobacco smoking, arterial hypertension, diabetes, obesity, sedentary lifestyle, family history of CAD, age, gender, stress, and symptoms of clinical depression. Recently, bacterial and viral organisms, involved in chronic inflammatory processes, have been also implicated in atherosclerosis development (5).

Individuals with a prior history of periodontal diseases and/or tooth loss are at a higher risk for peripheral arterial disease, compared to those without periodontal diseases or tooth loss (6). In this regard, Kinane and Bouchard in 2008 presented a report on the Sixth European Workshop on Periodontology and conducted a systematic literature review. They concluded that periodontitis contributes to the total burden of infection and inflammation and may lead to cardiovascular events and stroke in susceptible individuals. Based on their evaluation, the impact of periodontal therapy should be further investigated (7).

Moreover, Weidlich , in 2008 performed a review study concerning the association between periodontal and systemic diseases. Based on the findings, a causal relationship still needed to be confirmed, although the majority of studies revealed an association between periodontitis and systemic conditions (e.g., CADs). According to this study, further research, particularly well-designed interventional investigations with larger sample sizes, need to be conducted in Brazilian populations (8).

Persson in two recent meta-analyses in 2008 concluded that flow-mediated dilation of the brachial artery and carotid intima-media thickness are linked to periodontitis, as confirmed by some previous studies. However, further research is required to confirm the early improvements of such surrogate markers following periodontal therapy. (9)

While intensive periodontal therapy may enhance inflammatory responses and impaired vascular functions, further studies are required to assess the outcomes of periodontal therapies in subjects with confirmed cardiovascular diseases

(CVDs). Tooth eradication may also reduce the systemic inflammatory burden of patients with severe periodontitis; however, the role of confounding factors remains unclear (9).

Periodontitis is one of the most common pathologies among human societies. Chronic colonization of bacteria, their toxins, enzymes, and metabolites, as well as the subsequent host immune responses, results in the progressive loss of periodontal attachment and premature loss of teeth. Regular brushing of the teeth and procedures performed by dentists on teeth and periodontium can produce transient bacteremia, which may initiate a secondary infection within a distant tissue or organ, including the arteries (10) .

Various studies have shown that *Porphyromonas gingivalis* (*P. gingivalis*) is a major periodontal pathogen, which is able to exacerbate atherosclerosis, following oral hematogenous spread due to bacteremia. *P. gingivalis* activates endothelial cells and upregulates various adhesion molecules, resulting in an increase in the likelihood of macrophage diapedesis, subsequent conversion to foam cells, and atheroma progression. These findings indicate the close relationship between periodontitis/periodontal pathogens and CVDs (11).

Mattila and colleagues were among the pioneering researchers, indicating a relationship between orofacial infections and atherosclerosis. In a paper published in 1989, they evaluated the number of teeth, caries foci, and gingival and bony pockets of 100 Finnish men and women with a prior history of myocardial infarction. They concluded that the dental health of these patients was significantly worse than that of 102 control subjects. Also, logistic regression analysis introduced periodontal disease as an independent predictor for the risk of myocardial infarction (12).

Additionally, in 1997, Grau et al. clinically assessed a group of 166 patients with acute ischemic stroke and 166 control subjects. They used the total dental index (TDI) to determine the status of caries, periapical lesions, periodontitis, and other dental lesions. Considering the low social status of participants and the risk factors for cerebrovascular ischemia (e.g., diabetes and tobacco smoking), poor dental status, as defined by TDI, was associated with an increased risk of cerebrovascular ischemic events. However, the authors noted that this relationship was less evident after taking other CVD risk factors into account (13).

DeStefano et al. in 1993 conducted the first prospective cohort study on this subject, based on a 14-year observation of 1000 subjects. The results indicated a 25% increase in the

prevalence of CAD in subjects with clinically diagnosed periodontal pockets. The association was even more pronounced in men below the age of 50 years. Also, risk of mortality was much higher in patients with periodontitis and CAD, compared to those with CAD only. However, the authors noted that this association might have been only random, resulting from the poor hygiene and lack of pro-health behaviors, which are common among patients with CVDs (14).

Moreover, Beck et al. in 1996 assessed the association between tooth loss and CVDs, using the data presented in the "Dental Longitudinal Study and Normative Aging Study", collected over 30 years. The results indicated that horizontal alveolar bone loss in pantomogram was positively correlated with the increased incidence of ischemic heart disease (IHD). It was also found that alveolar bone loss of over 40% was associated with a three-fold increase in IHD mortality. In addition, the results suggested that chronic periodontitis has a more pronounced impact on systemic health, compared to smoking, regardless of age, gender, diabetes, and other cardiovascular risk factors (15).

In this regard, Persson et al. in 2002 demonstrated an association between alveolar bone loss in pantomograms and increased calcium deposits on the walls of the internal carotid artery. The authors hypothesized that the degree of horizontal bone loss might be a good prognostic factor for myocardial infarction in subjects over the age of 60 years (16).

Beck et al. in a study, entitled "Atherosclerosis Risk in Communities Study" on 6,000 patients in 2001 showed an association between the severity of periodontitis and intimal-medial wall thickening of the internal carotid (17). Further analysis of the data presented in the "Dental Longitudinal Study and Normative Aging Study", collected over a period of 25-30 years, published in 1996, indicated that the cell surface of *Streptococcus sanguinis* is involved in a mechanism which promotes atherosclerosis development. This finding was first reported by Herzberg et al., who showed that a similar substance could be produced by *P. gingivalis* (18).

It should be mentioned that microorganisms, isolated from gingival pockets in periodontal disease, are aerobic bacteria (e.g., *Streptococcus* and *Actinomyces* species) and anaerobes including *Porphyromonas gingivalis*, *Prevotella intermedia*, *Peptostreptococcus* species, *Fusobacterium* species, *Treponema denticola*, *Eikenella corrodens*, and the microaerophile *Actinobacillus actinomycetemcomitans* (10, 19).

Kuramitsu et al. in 2001 demonstrated that *P. gingivalis* is capable of increasing NADH oxidase activity, which is implicated in the oxidation of low-density lipoproteins (LDLs) into oxidized LDL in atherogenesis (20). Srisatjabek et al. in 1999 by studying the in vitro interactions between *P. gingivalis* fimbriae and human endothelial cells demonstrated the capability of the bacteria to induce the expression of surface intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is a type of intercellular adhesion molecule, which facilitates macrophage migration under the endothelium, where it is subsequently transformed into foam cells (a characteristic of atheromatous process) (21).

According to the cytokine theory, inflammatory mediators, released by the cells of the immune system, contribute to the damage of vascular endothelial wall. Also, bacterial endotoxins, e.g., lipopolysaccharides, bind to CD14 receptors of monocytes, macrophages, and vascular endothelial cells; however, they are not capable of transferring the signal through the cell membrane.

Kinane and Hajishentniegahi et al. in 2002 independently revealed the key role of Toll–like receptors, present on the surface of immune system cells including macrophages, monocytes, and granulocytes. (22, 23) These receptors recognize bacterial endotoxin molecules, initiate intracellular signaling, and mediate the transcription of a factor responsible for the release of proinflammatory cytokines, such as prostaglandin-E2 (PGE-2), interleukin-1 (IL-1), interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α).

The aforementioned processes activate the arachidonic acid cascade and initiate further synthesis of prothrombotic agents, such as leukotrienes (LTB4 and LTC4 by erythrocytes and granulocytes), prostaglandins (PGE1 and PGE2 by leukocytes and myocytes of the vascular wall), and thromboxane A2 (by platelets). The compounds stimulate monocyte/macrophage chemotaxis and adhesion to endothelial cells, which in turn lead to intracellular lipid accumulation and formation of foam cells (22, 23).

Plasma of patients with chronic inflammatory processes contains elevated levels of fibrinogen and C-reactive proteins (CRPs). According to a study by D'Aiuto et al. in 2004 TNF-α activates IL-6 secretion, which stimulates the liver to produce CRP, and advances the synthesis of clotting factors, which may induce arterial microthrombosis and cardiovascular pathology (24). A report by the American Heart Association, in conjunction with the Centers for Disease Control and Prevention, in 2003 showed that serum CRP level of > 3 mg/L is associated with a high risk for cardiovascular complications, based on the epidemiological

study of 40,000 patients (25).

Based on a study by Moutsopoulos and Madianos in 2006, patients with periodontitis have elevated systemic inflammatory markers, such as CRP, IL-6, haptoglobin, and fibrinogen. The values of these markers were higher in periodontal patients with acute myocardial infarction, compared to those with only acute myocardial infarction. This finding supports the notion that periodontal disease is an independent contributor to systemic inflammation (26).

Moreover, the autoimmunization theory emphasizes the significance of heat shock protein-65 (HSP65), expressed on oral pathogens such as *P. gingivalis*, *Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans*. Schett et al. found anti-HSP65/60 antibodies in the saliva of subjects with chronic periodontitis, whereas no such finding was reported in subjects with a healthy periodontium (27). In 1999, the same antibodies were reported by Mayr et al., who investigated the potential role of *Chlamydia pneumoniae* and *Escherichia coli* infections in atherogenesis (28). The above-mentioned reports suggest that periodontal disease is a significant risk factor for peripheral arterial disease.

Jansson et al. in 2001 compared the causes of mortality among 1,393 patients who had previously undergone dental checkups. After making adjustments based on the effects of age, gender, and tobacco smoking on mortality, a statistically significant correlation was found between dental calculus deposits/oral health and coronary artery disease (CAD) mortality. The relationship was even more evident when tobacco smoking was taken into account (29).

Not all epidemiological studies have confirmed the effects of periodontal conditions on cardiovascular morbidity. Joshipura et al. in 1996, assessed a total of over 70,000 patients, aged 40-75 years and found no significant association between tooth loss and CHD. Moreover, monitoring was carried out among healthcare professionals, who submitted mailed questionnaires on their oral health status; this procedure markedly limited the reliability of the results. Nevertheless, tooth loss was associated with CHD, mainly in subjects with periodontal history (30).

Considering the findings reported in previous epidemiological studies, the involved mechanisms were assessed to determine the association between chronic periodontitis and the atherosclerotic and thrombotic components of CVDs. Overall, three hypotheses have been conceptualized, which seem to complement one another. The theory of bacterial invasion assumes the direct action of bacteria and their toxins in the endothelium.

Moreover, Haraszthy et al. by the use of polymerase chain reaction in 2000 demonstrated the presence of genetic components in gingival pocket bacteria in 44% of examined atheromatous plaques. The most frequently identified microorganisms were *Bacteroides forsythus* (30%) and *P. gingivalis* (26%) (31). Moreover, Stelzel et al. in 2002 reported similar findings, based on the examination of human aorta specimens (32).

In 1998, Deshpande et al. published a paper on the invasion of *P. gingivalis* to bovine aortic and cardiac endothelium (33). Additionally, Konopka in 2003 mentioned the initiation of platelet aggregation by platelet aggregation-associated proteins, expressed on the cell surface of *Streptococcus sanguinis* as a mechanism, which promotes atherosclerosis development (34).

Azarpazhooh A. and Tenenbaum H.C. by reviewing six meta-analyses, published during 2003-2009, showed a poor but statistically significant association between CVDs and periodontal diseases (35-41). Although the risk approximation could be assumed modest (relative risk and/or odds ratio less than two), the high prevalence of both types of diseases indicates the high number of affected patients. Therefore, these meta-analyses suggest that periodontitis can increase the risk of either having or developing CVDs (35).

A pathophysiological association may exist between periodontitis and CVDs, although it might be difficult to confirm such a relationship. A meta-analysis of studies, published during 1966 and 2005, concluded that periodontal therapy has no effects on serum levels of CRP at two months after the treatment (42). The same conclusion was made through the analysis of pooled data from single cohort studies (mean overall difference in CRP: 0.2 mg/L, 95% CI: 0.15-0.55 mg/L; P>0.05). Consequently, according to these reports, CVD would not be reversed by periodontal treatment. However, other studies have indicated that CVD may indeed be reversed by periodontal treatment, further supporting the link between periodontitis and CVDs (43).

Blaizot A. et al. after analyzing 215 articles, published in 1998-2007 (47 observational articles), selected 29 studies, which could be combined in a meta-analysis. The pooled odds ratio, calculated based on 22 case-control and cross-sectional studies, was estimated at 2.35 (95% CI: 1.87-2.96; P<0.0001). The risk of developing CVDs was found to be significantly higher in subjects with periodontal diseases (34%), compared to those without periodontal diseases; the pooled relative risk of seven cohort studies was 1.34 (95% CI: 1.27-1.42; P<0.0001).

Based on the observational studies, subjects with periodontal diseases were exposed to a higher risk of developing CVDs. However, the decline in the risk of cardiovascular events, associated with the treatment of periodontitis, requires further investigations (44).

Conclusion

Based on the conducted observational studies, subjects with periodontal diseases are at a higher risk of CVD development. All studies on the relationship between periodontal diseases and CVDs are inconclusive, and a substantial amount of available data is based on epidemiological studies. The decline in the risk of cardiovascular events, associated with the treatment of periodontitis, requires further precise investigations via case-control and interventional studies. Overall, the mechanisms through which periodontal diseases could affect cardiovascular health include direct contamination by bacteria, immune-mediated injuries, and inflammation.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Thomopoulos C,Tsioufis C, Soldatos N, Kasiakogias A, Stefanadis C. Periodontitis and coronary artery disease: a questioned association between periodontal and vascular plaques. Am J Cardiovasc Dis. 2011; 1:76–83.
2. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol. 1996; 67:1103–13.
3. Garcia RI, Nunn ME, VokonasPS. Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease. Ann Periodontol. 2001; 6:71–7.
4. Marzec-KoronczewskaZ, Płońska E, Kaczmarek A. Chronic tooth infections as a risk factor for cardiovascular disease. Czas Stomat. 2001; 4:249–54.
5. Naoum JJ, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Lymphotoxin-alpha and cardiovascular disease: clinical association and pathogenic mechanisms. Med Sci Monit. 2006; 12:RA121–4.
6. Bokhari SA, Khan AA. The relationship of periodontal disease to cardiovascular diseases--review of literature. J Pak Med Assoc. 2006; 56:177-81.
7. Kinane D, Bouchard P. Group E of European Workshop on Periodontology. Periodontal diseases and health: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol. 2008; 35:333-7.
8. Weidlich P, Cimões R, Pannuti CM, Oppermann RV. Association between periodontal diseases and systemic diseases. Braz Oral Res. 2008; 22:32-43.
9. Persson GR, Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol. 2008; 35:362-79.
10. Bochniak M, Sadlak-NowickaJ. Periodontitisand cardiovascular disease--review of publications. Przegl Lek. 2004; 61:519–22.
11. Amano A, Inaba H. Cardiovascular diseases and periodontal diseases. Clin Calcium. 2012; 22:43-8.
12. Mattilla KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjälä SL, et al. Association between dental health and acute myocardial infarction. BMJ. 1989; 298:779–81.
13. Grau AJ, Buggle F, Siegler C, Schwarz W, Meuser J, Tasman AJ, et al. Association between acute cerebrovascular ischemia and chronic and recurrent infection. Stroke. 1997; 28:1724-9.
14. De Stefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. BMJ. 1993; 306:688–91.
15. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol. 1996; 67:1123–37.
16. Persson RE, Hollender LG, Powell VL, MacEntee M, Wyatt CC, Kiyak HA, et al. Assessment of periodontal conditions and systemic disease in older subjects. II. Focus on cardiovascular diseases. J Clin Periodontol. 2002; 29:803–10.
17. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2001; 21:1816–22.
18. Herzberg MC, Meyer MW. Effects of oral flora on platelets: possible consequences in cardiovascular disease. J Periodontol. 1996; 67:1138-42.
19. Meyer DH, Fives-Taylor PM. Oral pathogens: from dental plaque to cardiac disease. Curr Opin Microbiol. 1998; 1:88–95.
20. Kuramitsu HK, Qi M, Kang IC, Chen W. Role of periodontal bacteria in cardiovascular diseases. Ann Periodontol. 2001; 6:41–7.
21. Srisatjaluk R, Doyle RJ, Justus DE. Outer membrane vesicles of Porphyromonas gingivalis inhibit IFN-g mediated MHC class II expression by human vascular endothelial cells. Microb Pathog. 1999; 27:81–91.
22. Kinane D, Lappin DF. Immune processes in periodontal disease: a review. Ann Periodontol. 2002; 7:62-71.
23. Hajishengahis G, Sharma A, Russell MW, Genco RJ. Interactions of oral pathogens with toll-like receptors: possible role in atherosclerosis. Ann Periodontol. 2002; 7:72-8.
24. D'AiutoF, Ready D, Tonetti MS. Periodontal disease and C-reactive protein-associated cardiovascular risk. J Periodontal Res. 2004; 39:236–41.
25. PearsonTA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for health-care professionals from the Centers for disease control and prevention and the American heart association. Circulation. 2003; 107:499–511.

26. Moutsopoulos NM, Madianos PN. Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. Ann N Y Acad Sci. 2006; 1088:251-64.

27. Schett G, Metzler B, Kleindienst R, Moschèn I, Hattmannsdorfer R, Wolf H, et al. Salivary anti-hsp65 antibodies as a diagnostic marker for gingivitis and a possible link to atherosclerosis. Int Arch Allergy Immunol. 1997; 114:246–50.

28. Mayr M, Metzler B, Kiechl S, Willeit J, Schett G, Xu Q, et al. Endothelial cytotoxicity mediated by serum antibodies to heat shock proteins of Escherichia coli and Chlamydia pneumoniae: immune reactions to heat shock proteins as a possible link between infection and atherosclerosis. Circulation. 1999; 99:1560–6.

29. Jansson L, Lavstedt S, Frithiof L, Theobald H. Relationship between oral health and mortality in cardiovascular diseases. J Clin Periodontol. 2001; 28:762–8.

30. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. J Dent Res. 1996; 75:1631–6.

31. Haraszthy VI, Zambon JJ, TrevisanM, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol. 2000; 71:1554–60.

32. Stelzel M, Caurads G, Pankuweit S, Maisch B, Vogt S, Moosdorf R, et al. Detection of Porphyromonas gingivalis DNA in aortic tissue by PCR. J Periodontol. 2002; 73:868-70.

33. Deshpande RG, Khan MB, GencoCA. Invasion of aortic and heart endothelial cells by Porphyromonas gingivalis. Infect Immun. 1998; 66:5337-43.

34. Konopka T. Periodontal medicine: a new research field in modern periodontology. Periodontol. 2003; 8:38–44.

35. Azarpazhooh A, Tenenbaum HC. Separating fact from fiction: use of high-level evidence from research syntheses to identify diseases and disorders associated with periodontal disease. J Can Dent Assoc. 2012; 78:c25.

36. Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003; 95:559-69.

37. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. J Periodontol. 2004; 75:1046-53.

38. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J. 2007; 154:830-7.

39. Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. J Periodontol. 2007; 78:2289-302.

40. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med. 2008; 23:2079-86.

41. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J. 2009; 59:197-209.

42. Ioannidou E, Malekzadeh T, Dongari-Bagtzoglou A. Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. J Periodontol. 2006; 77:1635-42.

43. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parker M, et al. Treatment of peridontitis and endothelial function. N Engl J Med. 2007; 356:911-20.

44. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J. 2009; 59:197-209.