Annals of R.S.C.B., Vol. 24, Issue 1, 2020, pp. 97-107
Received 18April2020; accepted 23June2020

A Review On Periodontal Medicine And Cardiovascular Disease- The Two-Way Relationship

Dhwani K Dedhia, *VijayalakshmiRajaram, Jaideep Mahendra,

Burnice NalinaKumari C, Ambalavanan N

Faculty of Dentistry – Meenakshi Ammal Dental College,

Meenakshi Academy of Higher Education and Research, Chennai, India.

drvijaya.perio@madch.edu.in[2*]

Abstract

Periodontal Medicine is a fast growing field of Periodontology that focuses on new data and establishes a strong link between periodontal health and systemic health and disease.Periodontal Medicine deals with a two way relationship in which periodontal disease in an individual may be a powerful influence on an individual's systemic health/disease or the role of systemic disease on influencing an individual's periodontal health or disease.

Key words: Periodontal medicine, systemic diseases, periodontal disease

I. Introduction

In developed countries, cardiovascular illnesses are the leading cause of death. Around 7 million individuals die each year as a result of cardiovascular disorders. The causes of cardiovascular diseases are defined by a number of factors; however, a major fraction of these cannot be described using traditional risk factors. It was reported recently that chronic inflammation plays an important role in cardiovascular disease (CVD) etiology. Periodontitis is a chronic inflammatory disease affecting periodontal tissues. Several chronic inflammatory markers rise during periodontal disease. Since it was thought that CVD had an etiological cause, the possibility of a link between periodontal disease and CVD has been investigated for years. As a result, several investigations on the likelihood of periodontal disease causing CVD have been conducted, and a link between periodontal disease and CVD has been demonstrated.

II. Concept of oral sepsis

1st introduced by William Hunter in 1900.

III. Concept of focal infection

Introduced by Frank Billings in 1911.

IV. Era of focal infection(1900-1950)

In 1911 Frank Billings, Professor of Medicine & head of focal infectionresearch team at Chicago, replaced the term Oral Sepsis with 'FocalInfection.In 1915 he defined a 'focus of infection as a circumscribed area oftissue infected with pathogenic organism.

V. Massacre of teeth (1915-1950)

Focal infection was implicated as a causative factor for miscarriage, phlebitis, anaemia & toxaemia in pregnancy &was considered to be a predisposing factor for 'Gastric cancer'.What followed was the massacre of teeth. All teeth that were endodontically or periodontally involved were extracted to avoid a possible focus of infection.In 1951, Williams &Burket reviewed a series of papers on focal infection & found 'that there is no good scientific evidence that removal of infected teeth would relieve or cure arthritis, heart disease, kidney, eye, skin or other disorder.

VI. Fall out of focal infection

The focal infection idea has fallen out of favour, according to a 1952 editorial in the Journal of the American Medical Association, because many patients with disorders allegedly caused by foci of infection have not had their symptoms eased by excision of the foci. Furthermore, infection foci are as common in apparently healthy people as they are in people with disease, according to statistical analyses.Timeline overview from 1900 to 2020 showing the29 milestone studies in periodontal medicine[1] (Fig 1).

Annals of R.S.C.B., Vol. 24, Issue 1, 2020, pp. 97-107
Received 18April2020; accepted 23June2020

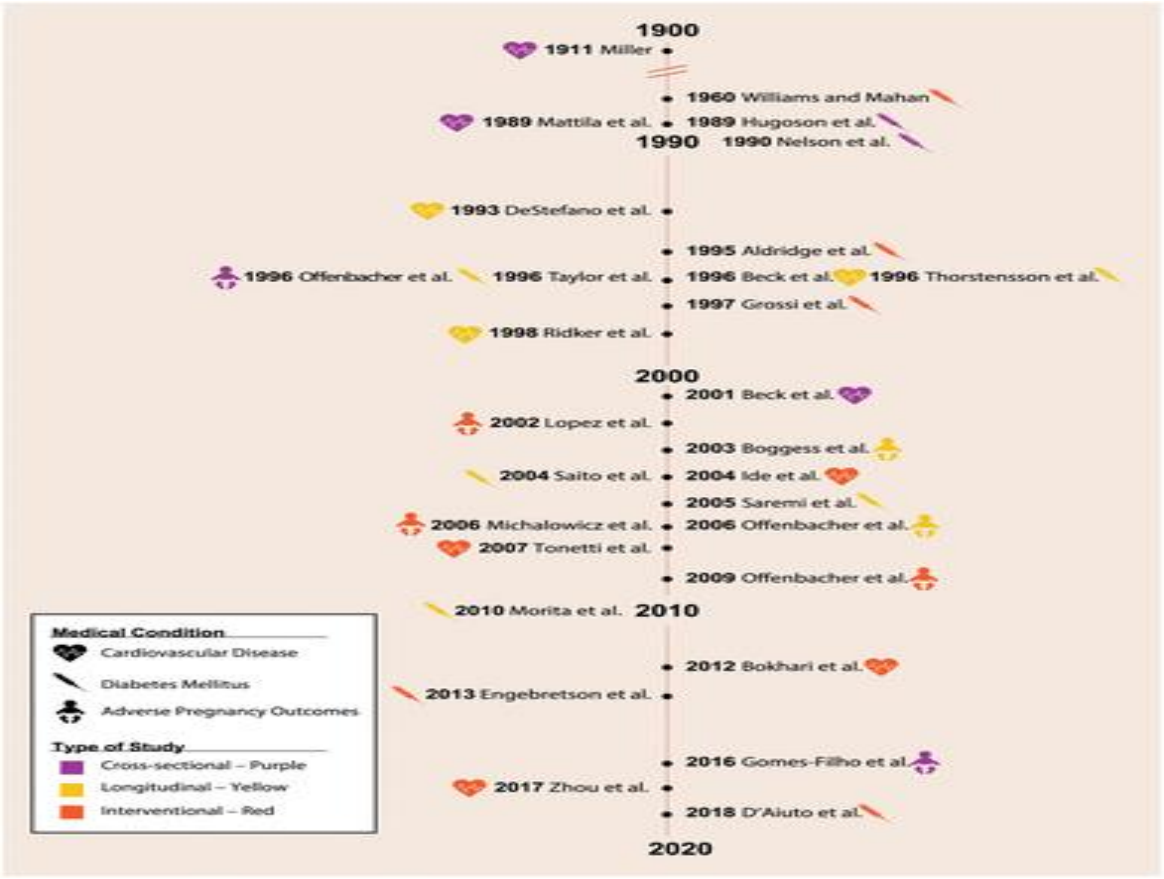

Figure 1: Timeline overview from 1900 to 2020 showing the 29 milestone studies in periodontal medicine[1]

VII. Criteria to assess whether evidence fromstudies support a causal relationship(Austin Bradford hill,1965)

Strength: A strong effect size for an association

Consistency: Similar findings across time and populations

Specificity: A single risk factor leads to a particular outcome

Temporality: The cause should always precede the effect

Biologic gradient: A dose-dependent relationship between exposure and outcome

Plausibility: A biological plausible mechanism for exposure and outcome

Coherence: Between the suggested causal factor and the biology of the disease

Experimental evidence: Evidence from an interventional study

Annals of R.S.C.B., Vol. 24, Issue 1, 2020, pp. 97-107
Received 18April2020; accepted 23June2020

Analogy: Evidence of similar association in other fields[2]

VIII. Systems affected by periodontaldisease

- Cardiovascular System
- Reproductive System
- Endocrine System
- Respiratory System
- Musculoskeletal System
- Renal System

IX. Periodontitis andcardiovasculardisease

Cardiovascular diseases can be congenital or acquired in nature. Acquired cardiovascular diseases can further be divided into ischemic heart disease and hypertension. The acute form ischemic heart disease results in thromboembolism, occlusion of coronary arteries which results in myocardial ischemia and finally myocardial infarction. The chronic form of ischemic heart disease results in artherosclerosis, narrowing of arteries leading to myocardial infarction.[3]

ATHEROSCLEROSIS is a condition that affects the large and medium-sized muscles as well as the large arteries. It is characterised by a localised thickening of the artery intima, the innermost layer lining the vessel lumen, and the media, a thick layer underneath the intima made up of smooth muscle, collagen, and elastic fibres.

The advanced lesion ATHEROMA is characterised by enhanced localised intimal plaques with a necrotic central core including lysed cells, cholesterol ester crystals, lipid-laden foam cells, and surface plasma proteins like fibrin and fibrinogen.

Cardiovascular illnesses including atherosclerosis and myocardial infarction are caused by a combination of genetic and environmental factors. Age, obesity, diabetes, and hypertension are all genetic factors. Smoking, nutrition, socioeconomic status, and exercise are all environmental influences.Smoking, hypercholesterolemia and hypertension, classic risk factors, exist in one-third to two-thirds of cases. It is believed that genetic factors play a role in approximately half of the cases with periodontitis.

Research suggests that inflammation plays an important role in the pathogenesis of both diseases. Elevation of systemic markers is considered among the risk factors for CVD.[4]Periodontal disease's propensity to cause CVD in people is determined by the number of gram-negative bacteria, the detectability of proinflammatory levels, the composition of immunological or inflammatory infiltration, and the high correlation between peripheral fibrinogen and white blood cell count.There are various opinions on periodontal disease inducing cardiovascular disease

through the direct or indirect effects of oral bacteria. At first, bacteria such as *Streptococcus sanguinis (S. sanguis)* and *P. gingivalis* induce platelet aggregation and lead to thrombus formation. *S. sanguis* caused myocardial infarction when injected in rabbits.[5]

Antibodies against periodontal organisms are thought to be concentrated in the heart, where a cascade of processes triggered by produced T cells activate complement and precipitate a heart attack. One or more periodontal pathogens were discovered within atheromas in people with severe periodontitis.

The second mechanism is an overabundance of proinflammatory mediators such PGE2, TNF, and IL-1 in the host in response to lipopolysaccharide (LPS) or microbial alterations. These mediators are linked to individual variances in T cell receptors and monocyte secretory capabilities.[7]

Individuals with a hyperinflammatory monocyte phenotype secrete 3-10 times more peripheral blood monocytes than those with a normal monocyte phenotype. The inflammatory response can be directly triggered and regulated by genes that govern T cell monocyte response and host-microbe environment. Individuals with periodontal disease have a hyperinflammatory monocyte phenotype.[8]

The link between periodontitis bacterial and inflammatory agents and cardiovascular disease could be the third pathway. By travelling via the bloodstream, periodontal bacteria can produce bacteremia, or bacterial invasion might directly harm the endothelium, causing atherosclerosis.[9] LPS can lead to accumulation of inflammatory cells on major blood vessels and can also stimulate degeneration of vascular muscle, vascular lipid and intravascular coagulation and proliferation of blood thrombocyte function. These changes occur due to activation of biological mediators in smooth muscle, such as PGs, ILs and TNF-α. In addition, it was shown that the presence of LPS increases the sensitivity of endothelial cells against *P. gingivalis*.[10]

Ghorbani et al reported that an increase was observed in the contractility of coronary arteries accompanied by endothelial dysfunction with LPS originating from *P. gingivalis*. Increased fibrinogen and WBC counts in periodontitis patients could be a side effect of the aforesaid mechanisms or a characteristic of people who are at risk for both cardiovascular disease and periodontitis.[11]

X. Periodontitis and c reactive protein

CRP is an independent risk factor for cardiovascular disease because it generates complement-mediated inflammation, which contributes to atheroma development. CRP levels rise as a result of periodontal infections, putting the patient at risk for atherosclerosis.[12]

XI. C-reactive protein and fibrinogen – act as inflammatorymarkers

CRP causes monocyte/macrophages to produce tissue factor, which initiates the coagulation cascade and improves blood coagulability. CRP also activates the complement system, which exacerbates inflammation. These proteins in the acute phase act as a link between the CVS and PD pathways. Thus, periodontal diseases may have both direct effects on major blood vessels & indirect effects that stimulate changes in cardiovascular system.[13]

Annals of R.S.C.B., Vol. 24, Issue 1, 2020, pp. 97-107
Received 18April2020; accepted 23June2020

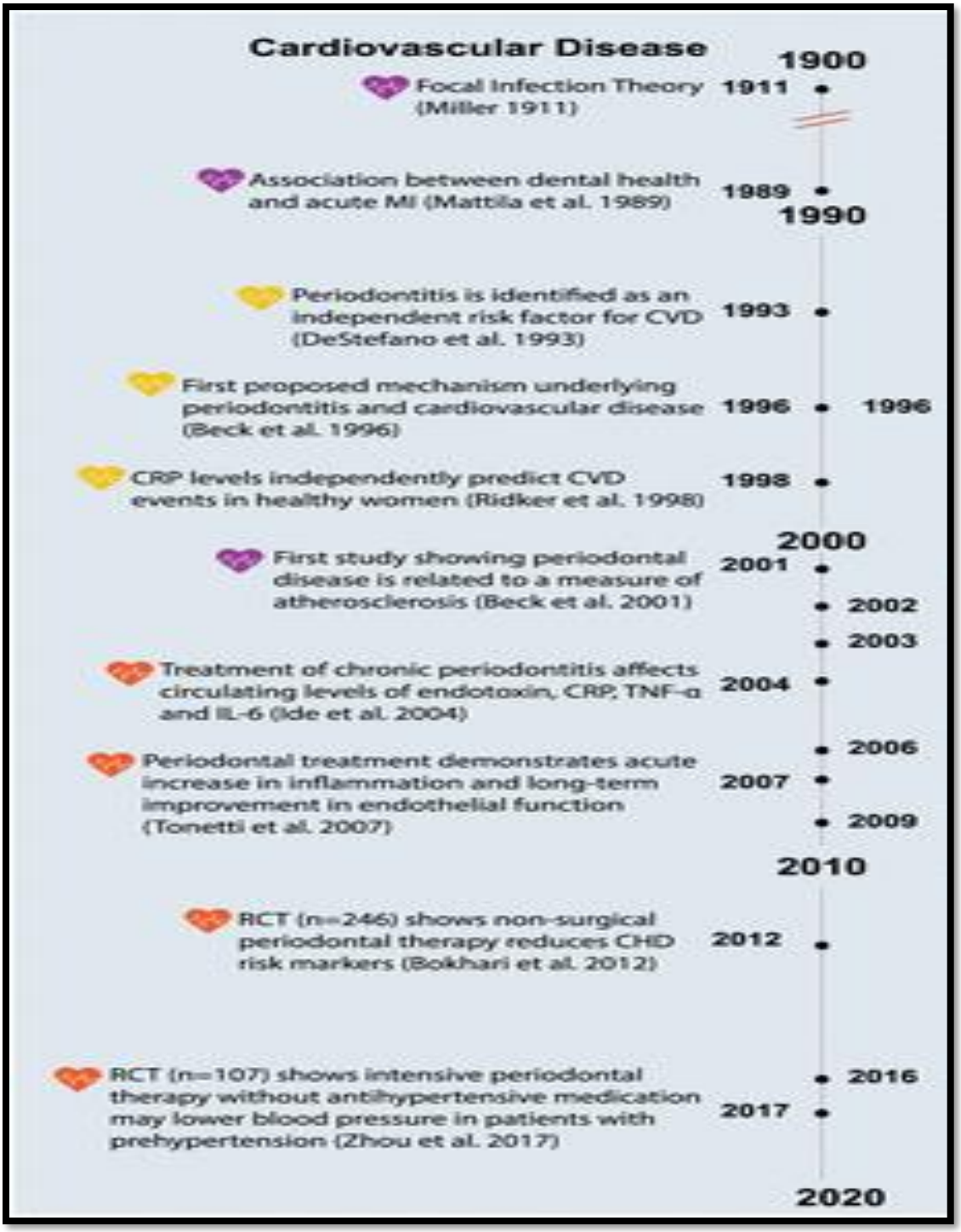

Figure 2: Timeline overview from 1900 to 2020 showing the milestone studies in Periodontitis & CVD association[1]

Annals of R.S.C.B., Vol. 24, Issue 1, 2020, pp. 97-107
Received 18April2020; accepted 23June2020

XII. The primary putative facts that support the biological connection between periodontitis and systemic diseases

- Usual implication of infection in the pathogenesis of both diseases
- Transient and low grade bacteremia and endotoxemia caused by periodontal diseases
- Systemic immune responses and inflammationtriggered by periodontal diseases
- Expression of virulence factors by periodontal pathogens
- Presence of periodontal pathogens in nonoral tissues like atheromatous plaques[14]

XIII. Clinical research activity in periodontal medicine: a systemic mapping of trial registers

Clinical trial registry in biomedical research from1990s (Fig 3)
To increase transparency in clinical research[15]

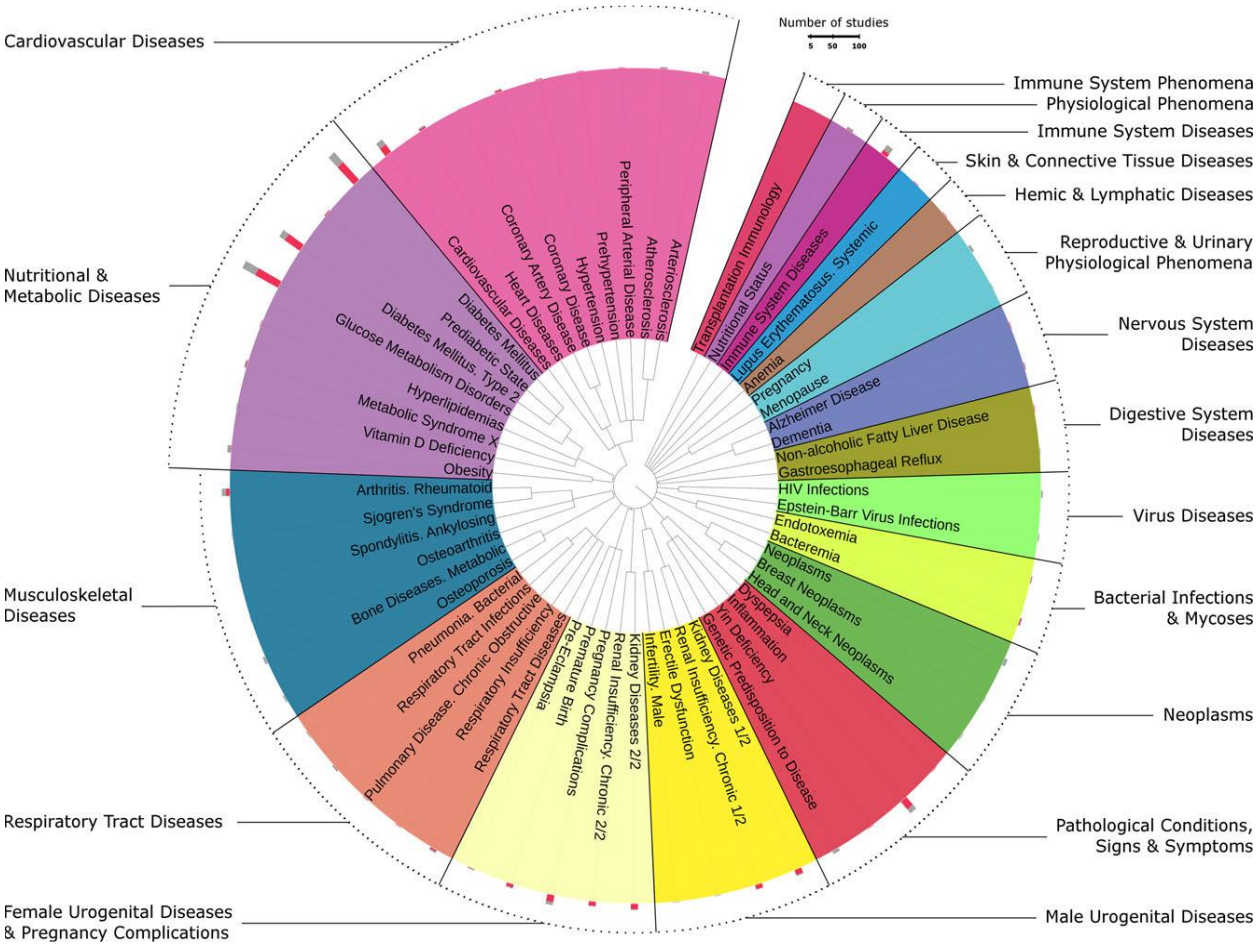

Figure 3: A systemic mapping of trial registers[15]

XIV. Limitations

- All registration records were considered as having the same level of methodological quality
- In multicenter trials, all centers data wasn't analyzed
- Only one quarter of RCTs published in oral heath journals are publicly registered
- Only registration records were taken into account, which have not been peer-reviewed
- Observational studies, laboratory research / animal research are not registered[16]

XV. Periodontal medicine in clinical practice

Periodontitis tends to be a "silent" disease until destruction results in acute oral symptoms.Most patients, as well as many medical professionals do not recognize the potential infection that may exist within the oral cavity.[17]

XVI. Patient education

- Must emphasize the inflammatory nature of periodontal infections,
- The increased risk for systemic disease associated with the infection
- The biologically plausible role periodontal infection may play in systemic disease.
- Enhanced community awareness may be derived from newspapers, magazines and other lay sources.
- However, many patients do not know the occult periodontal infections can have same effect as more clinically evident infections.[18]
- So proper diagnosing of periodontal infections, providing appropriate treatment and preventing disease recurrence or progression is necessary.[19]

XVII. Conclusion

Periodontal medicine sheds new light on the oral cavity's role as a single, integrated system with the rest of the body. The function of periodontal infection in systemic illnesses is supported by biologically plausible pathways, however it should not be presented as the cause of such conditions. Before any causative role can be assigned, longitudinal investigations and intervention trials are required.[20]

REFERENCES

1. Beck JD, Papapanou PN, Philips KH, Offenbacher S. Periodontal Medicine:100 Years of Progress. J Dent Res2019;4:1053-1062.
2. Hill AB. The environment and disease: association or causation. Proc R Soc Med 1965;58:1217–1219.

3. Lalla E, Lamster IB, Drury S, et al. Hyperglycemia, glycoxidation and receptor for advanced glycationendproducts: potential mechanisms underlying diabetic complications, including diabetes-associated periodontitis. Periodontol2000;23:50-62.
4. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000;71:1554-1560.
5. Herzberg MC, Meyer MW. Effects of oral flora on platelets: possible consequences in cardiovascular disease. J Periodontol 1996;67:1138-1142.
6. Shapira L, Soskolne WA, Sela MN, Offenbacher S, Barak V. The secretion of PGE2, IL-1 beta, IL-6, and TNF alpha by adherent mononuclear cells from early onset periodontitis patients. JPeriodontol 1994;65:139-146.
7. Rylev M, Bek-Thomsen M, Reinholdt J, Ennibi OK, Kilian M. Microbiological and immunological characteristics of young Moroccan patients with aggressive periodontitis with and without detectable Aggregatibacteractinomycetemcomitans JP2 infection. Mol Oral Microbiol 2011;26:35-51.
8. Ghorbani B, Holmstrup P, Edvinsson L, Kristiansen KA, Sheykhzade M. LPS from Porphyromonasgingivalis increases the sensitivity of contractile response mediated by endothelin-B (ET(B)) receptors in cultured endothelium-intact rat coronary arteries. VasculPharmacol 2010;53:250-257.
9. Persson GR, Pettersson T, Ohlsson O, Renvert S. High-sensitivity serum C-reactive protein levels in subjects with or without myocardial infarction or periodontitis. J ClinPeriodontol2005;32:219-224.
10. Buhlin K, Gustafsson A, Pockley AG, Frostegård J, Klinge B. Risk factors for cardiovascular disease in patients with periodontitis. Eur Heart J 2003;24:2099-2107.
11. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol. 2000;71:1528-1534.
12. Craig RG, Yip JK, So MK, Boylan RJ, Socransky SS, Haffajee AD. Relationship of destructive periodontal disease to the acute-phase response. J Periodontol. 2003;74:1007-1016.
13. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004;109:IV6-I19.
14. D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. Am Heart J. 2006;151:977-984.
15. Monsarrat P, Blaizot A, Kémoun P, Ravaud P, Nabet C, Sixou M, Vergnes JN. Clinical research activity in periodontal medicine: a systematic mapping of trial registers. Journal of clinical periodontology. 2016;43(5):390-400.
16. Bennet AM, van Maarle MC, Hallqvist J, Morgenstern R, Frostegård J, Wiman B, Prince JA, de Faire U. Association of TNF-alpha serum levels and TNFA promoter

polymorphisms with risk of myocardial infarction. Atherosclerosis. 2006;187:408-414.

17. Abranches J, Zeng L, Bélanger M, Rodrigues PH, Simpson-Haidaris PJ, Akin D, Dunn WA, Progulske-Fox A, Burne RA. Invasion of human coronary artery endothelial cells by Streptococcus mutans OMZ175. Oral Microbiol Immunol. 2009;24:141-145.
18. Löe H, Anerud A, Boysen H, Morrison E. Natural history of periodontal disease in man. Rapid, moderate and no loss of attachment in Sri Lankan laborers 14 to 46 years of age. J ClinPeriodontol. 1986;13:431-445.
19. Beck JD, Eke P, Lin D, Madianos P, Couper D, Moss K, Elter J, Heiss G, Offenbacher S. Associations between IgG antibody to oral organisms and carotid intima-medial thickness in community-dwelling adults. Atherosclerosis. 2005;183:342-348.
20. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol. 2000;71:1528-1534.