Periodontitis and cardiovascular disease

SADJ March 2013, Vol 68 no 2 p60 - p63

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ABSTRACT

Periodontal medicine has been studied and reviewed extensively since its introduction to the dental fraternity. The association of periodontal disease with and its effects on the cardiovascular system are amongst the many topics explored. A summary of the research into these associations and the possible mechanisms of any relationship is presented. Although a link between these two chronic inflammatory diseases is evident, the very heterogeneity of the relevant studies has not provided evidence sufficient to support an actual causal relationship. More stringent epidemiologic and intervention studies are required.

INTRODUCTION

"Periodontal medicine", as defined by Williams and Offenbacher in 2000, has initiated a wealth of research which has explored the potential that periodontitis may induce effects on other systems distant from the oral cavity.[1] The term was coined to describe these systemic effects that were already being explored and had been reported on in the preceding decade or two. The question thus arose, as enunciated by Miller as early as 1891, "do oral infections have effects on distant body systems?"[2] Initial acceptance of the concept resulted in the widespread practice of untoward and unwarranted dental extractions.[3] To this day prophylactic antibiotics are still prescribed, by some, in susceptible cardiac patients, with the intention of the prevention of infective endocarditis. Such practice lends recognition to the "focus of infection" theory of old.

The literature abounds with research which has investigated the association between periodontitis and cardiovascular diseases. Several observational, cross sectional and intervention studies, as well as reviews, have been published. This paper considers the current evidence for the association.

Gingivitis and periodontitis are the two most common forms of periodontal diseases affecting the majority of the population, with a prevalence rate of up to approximately 90% collectively.[4] Gingivitis is the mildest form of the two, limited to the gingivae, whilst periodontitis involves the attachment apparatus inclusive of alveolar bone loss, the hallmark of periodontitis. This is accompanied by loss of gingival connective tissue attachment. Periodontitis is an irreversible and chronic inflammatory disease initiated by periodontopathic bacteria, but in addition the susceptibility of the host and the initiation of an immune response play an essential role in its pathogenesis. Clinically it is characterised by inflammatory changes of the gingivae, deep pocketing around teeth, loss of clinical attachment and radiographic evidence of alveolar bone loss. The result is gingival recession. Soft and hard deposits on teeth, supra- and sub-gingivally, are usually seen and contribute to the destructive process. Tooth mobility and/or migration is seen in persons with advanced periodontitis.[4]

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ACRONYMS

CRP:	C-Reactive Protein
HbA1c:	glycosolated haemoglobin molecule
HSP:	Heat Shock Proteins
ICAM-1:	Intercellular Adhesion Molecule-1
IL-6:	Interleukin-6
Pg :	*Porphyromonas gingivalis*

Cardiovascular disease similarly presents a spectrum of pathologies that affect the heart and circulatory system. Atherosclerosis is the common platform from which all other clinical cardiovascular modalities arise, including ischaemic heart disease, cerebrovascular disease and also disease of the peripheral circulation. Lack of early diagnosis and or failure in management can predispose potentially fatal acute events, including myocardial infarction, stroke and acute coronary syndromes.[2, 5, 6] Survivors of such episodes are often left with devastating effects on their quality of life.

Cardiovascular disease is the second most common cause of death worldwide. In South Africa, 14.7% of reported deaths are attributed to diseases of the circulatory system.[7] The global trend is somewhat higher, with approximately 30% of all deaths caused by atherosclerotic vascular disease.[8] The difference between the national and global trend is related to the impact of the HIV/AIDS epidemic in South Africa.

Uncontrolled cardiovascular disease imposes a significant burden on the sufferer, particularly affecting his/her quality of life. Prevention and management of acute events such as myocardial infarction and strokes have significant financial implications. These costly preventive measures are required

to improve the quality of life and to prolong life expectancy. The current global prevalence of periodontitis is not well defined but in its severe form is reported to range from 5-15%.[9] Most of the available data are from the developed world. The prevalence rates reported from diverse countries are difficult to compare as markedly variable study designs were employed. Furthermore no standardised means of disease measurement was employed.

COMMON GROUND BETWEEN PERIODONTITIS AND CARDIOVASCULAR DISEASE

Both periodontitis and cardiovascular disease have a multifactorial aetiology. They share an array of risk factors.[2] Environmental and lifestyle risk factors may or may not be modifiable. These include increasing age, smoking, alcohol abuse, ethnicity, socio-economic status, male sex, diabetes mellitus (hyperglycaemia and insulin resistance), obesity and genetic predisposition.[2, 10, 11]

Various theories have been investigated to explain the association between periodontitis and cardiovascular disease. One theory proposed that the chronicity of moderate to severe forms of periodontitis elicits a systemic inflammatory response sufficient to affect the inflammatory pathogenesis of atherosclerosis.[2, 3, 11, 12, 13] A second theory is that the bacteraemia of periodontal pathogenic species arises via ulcerations of the junctional epithelium. This process is proposed to occur especially in persons of compromised immunity.[2, 3, 11, 12] A third, more complex mechanism is one of autoimmunity,[11] specifically the cross-reactivity of the host to periodontal pathogens such as *Porphyromonas gingivalis* (Pg). The antibodies directed at periodontal bacterial lipopolysaccharide cross-react with host endothelial components and thereby accelerate the atherogenic process. Endothelial damage has been reported due to the immune response to bacterial heat shock proteins (HSP).[2, 14]

ATHEROSCLEROSIS

The process of atherosclerosis is paramount in the pathogenesis of cardiovascular disease and thus a basic understanding is essential. Atherosclerosis itself comprises a major part of cardiovascular disease. The inflammatory events elicited by periodontal infections are purported to contribute continually toward atherogenesis.[11] Commonality for both diseases exists in the induction of inflammatory events, which incite increased vascular inflammation.

Atheromas form as a result of continual inflammation inflicted upon the vascular endothelium. Risk factors such as hypertension, high-saturated fat diet, obesity, hyperglycemia and insulin resistance perpetuate this sustained inflammatory state within the vascular endothelium. This enhances the expression of endothelial cell adhesion molecules, resulting in atheroma formation. When the atheroma becomes unstable or is physically disrupted, acute cardiovascular events ensue.[11]

THE ROLE OF PERIODONTOPATHIC BACTERIA

Periodontitis has a well-established bacterial aetiology.[15] Periodontopathic bacteria include amongst others: *P gingivalis* (*Pg*), *Tannerella forsythia* (*Tf*) and *Aggregatibacter actinomycetemcomitans (Aa)*.[4] Infection in a susceptible host by these putative pathogens elicits the release of an arsenal of weaponery such as leukotoxins, collagenases and proteases. Their presence precipitates an immune response that may be the means by which the atherogenic process is stimulated. These well-established periodontal pathogens have also been isolated from atheromatous plaques of the coronary circulation, aortic and heart valves.[5, 16, 17, 18] One such organism, Pg, has been found not only to invade both endothelial and epithelial cells, but also to contribute towards platelet aggregation,[11, 19, 20] the latter being a key feature in the development of atheromas (as described above). The immune response to the antigenic challenge presented by Pg also causes what has been described as molecular mimicry.[2] This process is known for the cross-reactivity of autoantibodies in response to Pg antigens, resulting in endothelial damage via host endothelial heat shock proteins.[14]

PERIODONTAL INTERVENTION AND SURROGATE MARKERS OF CARDIOVASCULAR DISEASE

Numerous workers have investigated the association of periodontitis and cardiovascular disease by examining the levels of known surrogate markers of cardiovascular disease in patients with periodontitis. These biomarkers include: intima medial thickness of carotid vasculature, flow mediated dilatation of the brachial artery, high density lipoprotein, low density lipoprotein, cholesterol fibrinogen, high sensitivity C-reactive protein (CRP), glycosolated haemoglobin molecule (HbA1c) and blood pressure.[5, 6] An elevation of the occurrence of these markers is known to occur in periodontitis.[21] Intervention studies investigating the effect of periodontal treatment on surrogate markers have been extensively reviewed.[22]

C-reactive protein (CRP), a product of the liver, is released in response to infection and trauma. It has been established as a marker for the development of recurrent ischaemic events in patients with unstable angina (cited by Ouyang *et al* in 2011).[22] CRP has proved to be the strongest and most independent predictor of incipient cardiovascular disease.[11] CRP is increased in other acute cardiac events such as myocardial infarction and in chronic coronary heart disease. It has been shown that patients with periodontitis have higher concentrations of CRP.[23] Furthermore, reviews and meta-analysis have reported a statistically significant improvement in CRP levels after periodontal treatment.[22, 23]

Marked improvements in lipid profiles were found in patients after periodontal treatment, with an additional beneficial effect when adjunctive antibiotics were used. A significant effect was seen only in patients with elevated lipid profiles at baseline, and not in patients with lipid profiles within normal parameters or already controlled by medication.[22]

Periodontal disease has been shown to be associated with elevated serum pro-inflammatory cytokines.[21] Some intervention studies have shown a post-treatment reduction in the levels of pro-inflammatory cytokines, which are involved in the pathogenesis of both periodontitis and cardiovascular disease. Interleukin-1, interleukin-6 (IL-6), interleukin-8, tumour necrosis factor–α, intercellular adhesion molecule-1 (ICAM-1), p-Selectin and E-selectin are included, but an even greater body of evidence exists reporting a reduction of serum IL-6 following periodontal intervention in persons with cardiovascular disease.[22, 24]

A key step in atherogenesis is endothelial dysfunction, which is seen in persons with periodontitis.[22] Studies have consistently shown that periodontal treatment reduces endothelial dysfunction in periodontitis patients who are systemically healthy. Endothelial dysfunction is measured by brachial flow mediated dilation, a surrogate marker of cardiovascular disease.[25]

Intimal medial thickness of coronary vasculature is a measure of cardiovascular health and of subclinical atherosclerosis.[26] Workers such as Cairo *et al* have found that severe periodontitis is associated with subclinical atherosclerosis in a young population.[26] Other studies have found that this surrogate marker shows recovery or is reduced in a subset of patients who received periodontal intervention (cited in Ouyang *et al* 2011).[22]

CONCLUSION

The periodontitis-cardiovascular link is complex and difficult to define. The literature has provided sufficient evidence for there being an association between these two chronic inflammatory diseases. There remains controversy on some levels as to a cause- and effect relationship. A recent editorial (SADJ February 2012) eloquently presents the dilemma and proposes that, whilst the evidence may not be precise in refuting the cause and effect relationship, nevertheless is able to support the association between the diseases.[27] The paradox, already noted, is that these chronic diseases share common risk factors. These confounding factors make it difficult to interpret with confidence the outcomes of studies of different design.[28] Observational studies, by the nature of their design, are especially prone to bias.[28] Intervention studies have looked at the effect of periodontal treatment on different parameters of cardiovascular disease. Given that the expression of some of the surrogate markers of cardiovascular disease were improved (CRP and IL-6) with periodontal intervention, nonetheless it is recognised that these parameters do not act in isolation as promoters of the pathogenesis of cardiovascular disease. The heterogeneity which characterises the available intervention studies (study design, duration, selection criteria, different end points or outcomes) is evident also in the disparities amongst the observed results.[22] Epidemiologic studies as well as more stringently controlled intervention studies are required to determine the long term effect of periodontal intervention on cardiovascular disease outcomes and quality of life.

Declaration: No conflict of interest declared.

References

1. Williams RC and Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. Periodontology 2000 2000; 23:9-12.
2. Lockhart PB, Bolger A, Panos N *et al*. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: A scientific statement from the American Heart Association. Circulation 2012; 125: 2520-44.
3. Dentino A, Lee S, Mailhot J, Hefti A. Principles of periodontology. Periodontology 2000 2013; 61: 16-53.
4. Pihlstrom B, Michalowicz B, Johnson N. Periodontal diseases. The Lancet 2005; 19:1809 –19.
5. Persson GR and Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol 2008; 35 (Suppl.8) :362-79.
6. Taylor B, Tofler G, Morel-Kopp M *et al*. The effect of initial treatment of periodontitis on systemic markers of inflammation and cardiovascular risk: a randomised controlled trial. Eur J Oral Sci 2010; 118:350-6.
7. www.statssa.gov.za/publications/P03093/P03093, 2008.pdf
8. Roger VL, Go AS, Lloyd-Jones DM *et al*. On behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics: 2012 Update: a report from the American Heart Association. Circulation 2012; 125: e2-e220.
9. Dye BA, Choudhary K, Shea S,Papapanou PN. Serum antibodies to periodontal pathogens and markers of systemic inflammation. J Clin Periodontol 2005; 32: 1189-99.
10. Hujoel P, Drangsholt M, Spiekerman C, De Rouen TA. Periodontal Disease and Coronary Heart Disease Risk. JAMA 2000; 284: 1406-10.
11. Paquette DW, Brodala N, Nichols T. Cardiovascular disease, inflammation and periodontal infection. Periodontology 2000 2007; 44:113-26.
12. Friedewald VE, Kornman KS, Beck JD *et al*. The American Journal of Cardiology and Journal of Periodontology editors' consensus: periodontitis and atherosclerotic cardiovascular disease. J Periodontol 2009; 80: 1021-32.
13. Offenbacher S, Beck J, Moss K *et al*. Results from the periodontitis and vascular events (PAVE) study: a pilot multicentered, randomised trial to study the effects of periodontal therapy in a secondary prevention model of cardiovascular disease. J Periodontol 2009; 80: 190-201.
14. Ford P, Gemmel E, Chan A *et al*. Inflammation, heat shock proteins and periodontal pathogens in atherosclerosis: an immunohistologic study. Oral Microbiol Immunol 2006; 21: 206-11.
15. Socransky and Haffejee. Periodontal microbial ecology. Periodontology 2000 2005; 38: 135-7.
16. Haraszthy VI, Zambon JJ, Trevisan M *et al*. Identification of periodontal pathogens in atheromatous plaques. J Periodontal 2000; 71:1554-60.
17. Kozarov EV, Dorn BR, Shelburne CE. Human atherosclerotic plaque contains viable invasive Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis. Arterioscler Throm Vasc Biol 2005; 25: 17-8.
18. Hyvärinen K, Mäntylä, Buhlin, K *et al*. A common periodontal pathogen has an adverse association with both acute and stable coronary artery disease. Atherosclerosis 2012; 223; 478-84.
19. Ghizoni JS, Taveira LA, Garlet GP *et al*. Increased levels of Porphyromonas gingivalis are associated with ischemic and hemorrhagic cerebrovascular disease in humans: an *in vivo* study. J Appl Oral Sci 2011; 104-12.
20. Deshpande RG, Khan, MB, Genco CA. Invasion of aortic and heart endothelial cells by Porphyromonas gingivalis. Infect Immun 1998; 66: 5337-47.
21. Buhlin K, Hultin M, Norderyd O *et al*. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol 2000 2009; 36: 541-9.
22. Ouyang XY, Xiao WM, Chu Y, Zhou. Influence of periodontal intervention therapy on risk of cardiovascular disease. Periodontology 2000 2011; 56: 227-57.
23. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008; 35:277-90.
24. Higashi Y, Goto C, Hidaka T, *et al*. Oral infection inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. Atherosclerosis 2009; 206: 604-10.
25. Higashi Y, Goto C, Kitsuiki D *et al*. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension 2008; 51:446-53.
26. Cairo F, Castellani S, Gori AM. Severe periodontitis in young adults is associated with sub-clinical atherosclerosis. J Clin Periodontol 2008; 35:465-72.
27. Niederman R , Weyant R. Periodontal disease, cardiovascular disease, the American Heart Association, the American Academy of Periodontology, and the Rooster Syndrome. Evidence-Based Dentistry 2012; 13: 34-6.
28. Merchant A. Will periodontal treatment prevent heart disease and stroke? J Evid Base Dent Pract 2012; 12: 212-15.

EOWS070213CMD