

## ASSOCIATION BETWEEN PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

Rehman MM<sup>1</sup> & Salama RI<sup>2</sup>

**SUMMARY:** Studies have supported the notion that subjects with periodontitis and patients with multiple tooth extractions as a result of chronic advanced periodontal disease (PDD) have a greater risk of developing Cardiovascular disease (CVD) than those who had little or no periodontal infection. Periodontitis may predispose affected patients to CVD by elevating systemic C-reactive protein level and pro-inflammatory activity in atherosclerotic lesions and accelerate development of cardiovascular diseases. Oral health variables including loss of teeth, positive plaque Benzoyl-D-L-Arginine- Naphthyl Amide test (BANA) scores, and compliant of xerostomia may be considered as risk indicators for CVD. Exact mechanism which links PDD and CVD has not been firmly established. The link between PDD and CVD may be attributed to bacteria entering blood stream and attaching to the fatty plaque in coronary artery and contributing to clot formation which can lead to heart attack. Inflammation caused by PDD increases the plaque build up.

The association between the two disease entities is cause for concern. However, dental and medical practitioners should be aware of these findings to move intelligently to interact with inquiring patients with periodontitis. They should be urged to maintain medical surveillance of their cardiovascular status, and work on controlling or reducing all known risk factors associated with CVD, including periodontal infection.

**KEYWORDS:** Periodontal disease, Cardiovascular disease, Risk factors

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### INTRODUCTION

Cardiovascular disease (CVD) remains a major cause of death in UK and western world. Smoking, serum cholesterol concentration, hypertension, diabetes and genetics are signifi-

cant risk factor for the development of cardiovascular disease. Other risk factors include viral and bacterial infection, which can precipitate a myocardial infarction (MI) in certain susceptible people. Evidence is now emerging that oral health, in particular periodontal diseases (PDD), may also be a significant risk factors for the development of CVD.<sup>1-5</sup>

Periodontal Disease comprises a group of inflammatory conditions of the supporting tissue of the teeth caused by bacteria and is classified into gingival diseases (clinical inflammation confined to the gingiva) and periodontal diseases (progressive destruction of periodontal ligament and alveolar bone with pocket formation). Periodontitis usually develops from pre-existing gingivitis; however, not every gingivitis develops into periodontitis. Change in composition and pathogenic potential of plaque microorganisms versus host resistance

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1. Dr. Mohammed Mustahsen ur Rehman  
BDS, Ph.D (Periodontology)  
Deputy Dean, Dental Faculty
  2. Dr. Reem Ismail Salama DDS  
Graduate,
  - 1-2. Ajman University of Science & Technology Network,  
P.O. Box 1052 Abu-Dhabi Campus

#### Correspondence:

Dr. Mohammed Mustahsen ur Rehman  
E-mail: drmustahsen@hotmail.com

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factors and tissue related mechanisms are determinants for transition from gingivitis to periodontitis and progression of periodontal destruction.<sup>6</sup>

PDD is a bacterial disease and there seems to be some indirect link to cardiac health. It's believed that PDD bacteria enter the bloodstream and travel to major organs like the heart. The evidence for this connection is so strong that in 1998 the National Institutes of Health (USA) awarded a \$1.3 million grant for research studies about the link between PDD and CVD. National Institutes of Dental and Craniofacial Research (August 4, 2003) has reported a link between tooth loss and subclinical atherosclerosis. It is believed that the bacteria or toxins from diseased gums travel through the blood stream, contributing to the formation of artery-clogging plaques. The oral bacteria attach to fatty plaques in the Coronary arteries and contribute to clot formation. PDD may contribute to infective endocarditis, a condition where the interior lining of the heart and valves becomes inflamed because of bacterial infections. The occurrence of strokes and death from strokes were shown to be higher in those patients with PDD. Individuals with more severe periodontitis had more heart valve abnormalities. A study in Pima Indians, have shown that the risk of MI was more than two time higher in individuals who had PDD than in those who had little or no periodontal infection.<sup>4</sup>

#### ***Possible mechanism that link periodontal disease with cardiovascular disease:***

Dental diseases have risk factor in common with coronary heart disease (CHD), smoking, diabetes, low socioeconomic status have been implicated to both PDD and CVD.<sup>1</sup> Patient with PDD have a higher plasma fibrinogen levels and white blood cells count compared to subject free of PDD. Such increase in fibrinogen and WBC may promote both atherosclerosis & thrombosis formation which may lead to CVD.<sup>7</sup>

The link between CVD and PDD is explained

by the fact that levels of Von Willebrand's factor antigen are higher in diabetics, patients with giant cell arteritis and gram-negative infection of relevance to thrombogenesis. Endotoxins from gram-negative bacteria will induce the release of von Willebrand's factor antigen from human endothelial cells.<sup>8</sup>

The interaction between products from bacterial plaque, lipopolysaccharide (LPS) and the host immune & inflammatory response is fundamental in interpreting the underlying mechanism that link PDD with CVD.<sup>9</sup>

The existence of monocyte phenotype that releases high levels of pro-inflammatory mediators such as PGE<sub>2</sub>, IL-1B and TNF-alpha when challenged with bacterial LPS. These mediators have a fundamental role in the pathogenesis of periodontal destruction. Patients with aggressive form of PDD possess a hyperinflammatory monocyte phenotype or an IL-1B. Such monocyte play a role in atheroma formation and provide a biological basis that link the PDD with the CHD. The interaction between monocyte and LPS may be related also to thrombogenesis, atheroma and CHD. Various cytokinase can initiate platelet adhesion and aggregation and promote the formation of lipid-laden foam cells and the deposition of cholesterol in the intima. Also cytokines released from monocyte, together with (PD) will increase smooth muscle proliferation leading to thickening of the vessel wall that predisposes to atheroma formation.<sup>10-13</sup>

#### ***Inflammation of the periodontium as a risk factor to cardiovascular disease:***

Inflammatory PDD increase the risk of (CVD).<sup>14,15</sup> Inflammation in the vessel wall plays an essential role in the development of atherosclerosis.<sup>16,17</sup> The relationship between CVD and PDD can be dependent on the risk factors both diseases have in common,<sup>18-20</sup> but there may be a more direct relationship resulting from the systemic effects of PDD.<sup>14</sup> Periodontal infections may cause vascular events via LPS and inflammatory cytokines, contributing to the pathogenesis of CVD.<sup>21</sup> Periodon-

tal pathogens themselves have been shown to increase platelet aggregation and thromboembolic events.<sup>22</sup> The pathogens associated with PDD were identified on atheromas, which supports the etiological role of these pathogens in CVD.<sup>23</sup> In a seven year prospective study, Mattila et al.<sup>24</sup> observed dental infections to be significant risk factors for CVD and also for further coronary events. Subjects with the severe probing depths and bone loss at baseline had higher risk for developing CVD than those with minimal periodontal diseases or gingivitis.<sup>14,15,25</sup>

The studies have also shown an association between dental health and AMI and atherosclerosis.<sup>26-28</sup> Periodontal infection contribute to elevated systemic C- reactive protein (CRP) level, which depend upon the severity of the disease after adjusting for age, smoking, body mass index, triglycerides and cholesterol.<sup>3</sup> Elevation of C- reactive protein has been found to be a predictor of increased risk for CVD.<sup>29</sup> The possible correlation between CRP and PDD might be possible underlying pathway in association between PDD and high risk for CVD.<sup>3</sup>

#### ***Risk factors common for both PDD and CVD : Smoking***

Smoking is significantly associated with PDD and AMI.<sup>26, 30,31</sup> Mattila<sup>27</sup> also found smoking to be more common among AMI patients than the control group.

Certain, herpesviruses, particularly cytomegalovirus and Epstein-Barr virus, may be recovered from both periodontitis lesions in the oral cavity and coronary artery disease<sup>32</sup>. Herpesviruses may independently give rise to both PDD and CVD.

#### ***Genetically determined hyper inflammatory response:***

It suggests that persons jointly affected by periodontitis and CHD exhibit a genetically-determined hyper inflammatory immune response to bacterial challenge. Abnormally

elevated secretion of tissue damaging & pro-inflammatory mediators like prostaglandin E2 & inter-leukin 1-B from peripheral blood monocytes in hyper inflammatory positive phenotype individuals are proposed to account for the increased risk for both periodontitis and CHD.<sup>6,33,34</sup>

#### ***Risk indicators for CVD: Xerostomia***

Xerostomia is a common complaint of older people<sup>35</sup> and it has been associated with poor oral hygiene, the inability to chew and involuntary weight loss among both institutionalized and independent older adults.<sup>36,37</sup> It was found that people with complaints of xerostomia avoid crunchy (carrots), dry (bread) and sticky (peanut butter) foods, but not crumbly (cake) or chewy (red meat) foods.<sup>38</sup> This choice of foods could lead to the selection of the high-calorie, high-fat foods that are associated with obesity and CVD.

#### ***Missing teeth***

The number of missing teeth in elderly subjects was significantly associated with CVD in randomly selected study population.<sup>39,40</sup> It may be as edentulous people with and without dentures and partially dentate people change their eating habits after they lose their teeth.<sup>41,42</sup> They may avoid certain nutritious food because of difficulty in chewing, and select high calorie, high-fat foods whose consumption is recognized as a risk factor for CVD.<sup>43</sup> The dietary-induced elevation of serum low-density lipoprotein levels has been shown to increase monocytic responses to LPS.<sup>29,44</sup> In multivariate analysis, a high BANA test score was positively associated with CVD in subjects with missing teeth.<sup>45</sup>

#### ***Role of periodontal bacteria in CVD***

Microbial infection associated with periodontitis would contribute to CHD and act as an adjunctive etiological factor to other established risk factors after the metastatic spread

of the plaque organisms into the bloodstream via transient bacteremias. It has been proposed that transient bacteremias from inflamed gingival tissues introduce pathogenic microorganisms from subgingival dental plaque biofilms into the bloodstream, where they induce pathologic damage to blood vessels & promote clot formation.<sup>46</sup>

The BANA (benzoyl-D-L -arginine-naphthyl amide) test of more than 60 plaque bacterial species tested, only *Porphyromonas gingivalis* (*P.gingivalis*), *Treponema denticola* and *Bacteroides forsythus* (gram-negative periodontopathic species) always exhibit strong BANA activity, species, like the *Capnocytophaga*, occasionally exhibit weak BANA activity. The three strongly BANA, detects the presence of an enzyme(s) that hydrolyzes the synthetic trypsinlike substrate BANA, in plaque samples<sup>47</sup> removed from teeth with periodontal pathology.<sup>47-50</sup> Thus, a higher plaque BANA score would indirectly indicate that these gram-negative periodontopathic species are elevated on the tooth surfaces of subjects with CVD. Their elevation in the dental plaque would support the various hypotheses linking chronic bacterial infection to CVD via effects mediated by endotoxins or (LPS).<sup>51-53</sup> LPS has long been known to promote atherosclerosis and thrombus formation.<sup>54,55</sup> An additional factor in this process could be an exaggerated host response to LPS mediated by the presence of hyper responsive monocytic cells.<sup>56</sup> Certain patients with early-onset or refractory periodontitis have peripheral blood monocytes that secrete three fold to 10-fold greater amounts of PGE2, IL-1B and TNF when exposed to LPS in vitro.<sup>6</sup>

The major bacterial pathogen in adult periodontitis, *P. Gingivalis* possess platelet-aggregation capability unique among subgingival plaque microorganisms<sup>57,58</sup> and is a common inhabitant of atheromatous plaques removed from carotid and coronary arteries.<sup>59</sup> *P. gingivalis* has been shown to invade coronary and carotid endothelium in cell culture,<sup>60,61</sup> can induce platelet activation and aggregation through the expression of collagen-like plate-

let aggregation-associated proteins which play a role in thrombus formation,<sup>62,63</sup> can increase serum lipid levels,<sup>64</sup> enhanced atheroma formation as well as increased calcification of the atherosclerotic plaques and increased levels of proinflammatory mediators such as IL -6, vascular cell adhesion molecule-1, and matrix metalloproteinase-2 in an animal model.<sup>65,66</sup> Finally, *P. gingivalis* has been shown to produce a mammalian endothelin-converting enzyme, which activates endothelin, a powerful vasoconstrictor involved in hypertension.<sup>67</sup>

Preliminary data from a clinical study involving periodontal pathogens and MI indicated patients experiencing a non-fatal MI were significantly more likely to harbor *P. gingivalis* and *B. forsythus*.<sup>68</sup> Studies on human atheromas obtained during endarterectomy have found multiple periodontal pathogens in the atheromas, including *P.gingivalis*, *P. intermedia*, *B. forsythus* & *A. actinomycetemcomitans*.<sup>69,70</sup> *P. gingivalis* and other pathogenic bacteria are able to induce foam cell formation(an important characteristics of CVD)in murine macrophage cell line, which is mediated by LPS fraction of the cell. Since the rupture of the atherosclerotic plaque appear to be an important factor in acute coronary syndrome.<sup>71</sup> The relation between oral health and Cardiovascular Diseases (CVD) is obscure. More detailed knowledge of the infectious burden component of periodontal disease may result in a stronger association with cardiovascular disease.

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