Review Article

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Apical Periodontitis - Is It Accountable for Cardiovascular Diseases?

Dentistry Section

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ABSTRACT

The aim of this review was to assess the relationship between apical periodontitis and cardiovascular diseases and the predictive factors regarding this association. Cross sectional and observational studies have been included, which are mostly retrospective. A comprehensive search was performed in the Systematic Electronic Databases, PUBMED and MEDLINE from 1919 till September 2014. Articles were also hand searched. From 86 studies identified, all were read and 58 articles which were relevant were included in the text. Some articles were excluded because they were pertaining to periodontology and other systemic disorders. Some were solely animal studies and were thus excluded. Our results suggest an independent association between cardiovascular diseases and apical periodontitis. A causal relationship could not be established since weak parameters of risk have been assessed in the studies, population taken is difficult to compare and other confounding factors have not been ruled out. Only a more focused and better instituted scientific research can determine this association. Establishing a cause and effect relationship between apical periodontitis and cardiovascular diseases can affect the course of treatment of cardiovascular diseases. It is not only of interest from the scientific point of view but also from public health perspective.

Keywords: Bacteraemia, Inflammation, Interleukins, Root canal treatment

INTRODUCTION

Since decades, there have been speculations regarding the systemic and oral health inter-relationship. A logical association can be suggested between oral and systemic diseases; although no clear cause and-effect relationship has been established [1]. There are evidences that chronic infections are a risk factor for many systemic diseases like diabetes, atherosclerosis, osteoporosis, etc. This exploration has escalated the search for chronic infections that cause or aggravate systemic diseases.

Interest in the relationship of oral health to cardiovascular health is not new, but this association has been reinforced by the researchers only in the last decade [2]. Investigators currently regard inflammation to play a pivotal role in the development of atherosclerosis. The multifactorial etiology of cardiovascular disease shares many risk factors and associations with that of oral diseases [3]. In 1989, a case-control study found that dental health was significantly worse in patients with a history of acute myocardial infarction than in control subjects [4]. This study renewed the interest of physicians and dental surgeons to explore the relationship between oral and systemic health hazards. Studies have shown the presence of bacteria of oral origin in atherothrombotic plaques and vascular biopsies [5].

Historically, there was an advent of the focal infection theory, according to which enclosed lesions such as a necrotic pulp, could only drain into the circulation and was considered as the most dangerous foci of infection [6]. Better bacteriological culture techniques and study designs led to the demise of the focal infection theory [7]. However, in the recent years, the concept of focal infection theory has again gained importance. A research conducted on germ free chickens infected with an avian herpes virus had induced an arterial disease resembling human atherosclerosis. Infection induced indirect damage by releasing inflammatory mediators and initiating several immune related pathways [8].

Periodontitis and Cardiovascular Disease: Researchers have already established a relationship of cardiovascular diseases with periodontal diseases. A statistically significant increased risk of cardiovascular disease in patients with periodontitis is shown by observational studies and meta-analyses [9]. The chronic inflammatory burden of periodontitis and the host response provides the foundation for the model of the observed associations between periodontal disease and atherosclerosis, coronary heart disease and stroke [10]. Periodontal disease and atherosclerosis have shown to have similar etiologic pathways. Haematogenous spread of gram-positive and gram-negative bacteria; through a mechanism of molecular mimicry is a proposed mechanism. The presence of *Porphyromonas gingivalis, Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans* DNA has also been seen in atheromas of endarterectomy patients [10]. Periodontal disease is also associated with elevated levels of inflammatory markers, such as C-reactive protein which is a predictive pathogenic factor for vascular risk [11].

Both periodontal infections and endodontic infections have a similar and a complex microbiology and are associated with elevated cytokine levels. Absence of epithelial barrier between the necrotic pulp and periapical tissues makes the spread of bacteria and inflammatory mediators more pronounced in contrast to periodontal infections [12]. Researchers believe that there could also be an association between apical periodontitis and cardiovascular disease, however, no causal relationship has been found yet. This article aims to review all the probable endodontic factors that could lead to atherosclerosis and give an overview of the studies conducted till date to establish this association.

The exact mechanism of etiology of atherosclerosis is not well understood. It has been proposed that it arises from an inflammatory reaction to the cardiovascular risk factors at the molecular level [13]. Bacteria and/or their virulence factors directly stimulate the leukocytes, fibroblasts, mast cells, endothelial cells, dendritic cells and lymphocytes, leading to increased serum levels of inflammatory markers such as cell adhesion molecules, interleukins and Tumor Necrosis Factors [TNF-α], proatherogenic enzymes, immunoglobulins, transforming growth factors and

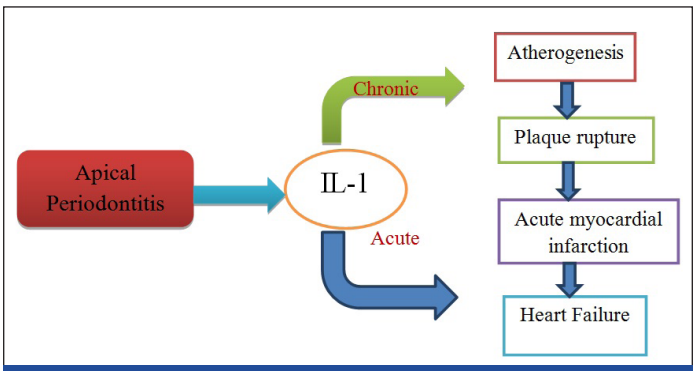
acute phase proteins such as serum amyloid A and C-Reactive Protein (CRP), which are predictors of cardiovascular disease risk [14]. In addition, degranulation of mast cells results in the secretion of histamine and leukotrienes which further amplify the inflammatory cascade [15]. These cytokines stimulate the Nuclear Factor-Kappa-Beta (NF-κβ) pathway, which leads to increased production of cellular adhesion molecules, chemokines, growth factors and other enzymes such as cyclo-oxygenases and nitric oxide synthase. Enhanced activity of the NF-κβ pathway appears to correlate with an increased risk of developing atherosclerotic plaques [16].

Inflammation in Apical Periodontitis and Cardiovascular Disease: Apical periodontitis occurs as a consequence to endodontic infection when the host defences give way to microbial factors [17]. Apical periodontitis contains the infection from the tooth to periapical tissues. Periapical pathology leads to cytokine production and ultimately, bone resorption [18].

Interleukin-1 (IL-1): After periapical lesion is established, a cellular damage as well as liberation of inflammatory mediators occurs. IL-1, 6, 8 and 17 are of importance in the development of apical periodontitis [10]. Patients with apical periodontitis have three to ten fold greater amounts of IL-1 [10]. IL-1β is the predominant form of interleukin found in human periapical lesions and their exudates [19]. Experimental studies have shown that upregulation of IL-1 activity favours the progression of atherosclerosis [20]. IL-1 is responsible for the formation, growth and complication of the atherosclerotic plaque. IL-1β contributes to the proliferative intimal response by mediating tissue response, to endothelial injury [21]. An increase in IL-1 activity causes a destabilization of the plaque due to upregulation of matrix metalloproteinases at the site of plaque formation, leading to thrombosis [22]. IL-1 also modulates cell adhesion and subsequent monocyte infiltration into the subendothelial space. Following adhesion, monocytes enter the intima and differentiate into macrophages and then into foam cells, that is one of the essential steps for atherogenesis [Table/Fig-1] [23].

Interleukin-2 (IL-2): IL-2 is significantly increased in patients with apical periodontitis compared with control group, confirming state of chronic inflammation [24]. Serum Asymmetrical Dimethylarginine (ADMA) level also increases in patients with apical periodontitis. ADMA is considered as a reliable indicator of potential endothelial compromise. Exposure of endothelial cells to exogenous ADMA increases reactive oxygen species generation and increased TNFα and IL-6 levels. It has been hypothesized that apical perodontitis, IL-2, and high circulating ADMA levels have a cause–effect relationship. Chronic inflammatory state produced in apical periodontitis might represent the primummovens(first cause) of other effects. Proinflammatory cytokines released into systemic circulation appear to be the cause of increased inflammatory response in distant sites [25].

Interleukin-6 (IL-6): Interleukin-6 (IL-6) is also raised in apical periodontitis, which may induce the formation of new osteoclasts from hematopoietic progenitor cells, in addition to activating pre-existing osteoclasts [26]. Level of IL-6 correlate with unstable angina, left ventricle dysfunction, propensity to diabetes and its complication, hypertension and obesity [27]. C-Reactive Protein (CRP), the major acute-phase reactant in humans, is mainly produced by hepatocytes in response to IL-6 and is then secreted into systemic circulation [28]. Levels of CRP are consistently associated with Cardiovascular Disease (CVD) and predict myocardial infarctions and stroke. A systematic review and meta-analysis, recently proposed that apical periodontitis is associated with increased levels of CRP [29]. The disease is clinically manifested by inflammatory mechanisms, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques. CRP directly influences complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation and thrombosis. It also causes enhancement of the procoagulant activity and the reduction of fibrinolysis [30,31].



[Table/Fig-1]: Interleukin-1 released in apical periodontitis and atherosclerosis.

Interleukin-8 (IL-8): IL-8 is a family of chemotactic cytokines produced by monocyte/macrophages and a variety of tissue cells including fibroblasts under the influence of IL-1β and TNFα, which has been detected in pulps diagnosed with irreversible pulpitis. The predominant anaerobic gram-negative flora of the infected root canals, i.e., *Porphyromonas endodontalis, P. gingivalis* and *P. intermedia* are able to induce the production of IL-8 by pulp fibroblasts, osteoblasts, neutrophils and macrophages [32,33]. IL-8 has been found in approximately 95% of periapical exudates collected from root canals. IL-8 also has a direct effect on osteoclast recruitment and activity, which may account for the significant osteolysis associated with apical abscess [34]. Scientific literature has evidential support that there is involvement of IL-8 in the establishment and preservation of the inflammatory microenvironment of the insulted vascular wall [35]. IL-8 has shown to mediate angiogenesis and contribute to plaque formation.

Tumour Necrosis Factor–α (TNF-α): The proinflammatory cytokine TNF-α has also been found in periapical exudate from teeth with periapical pathology [36]. Production of TNF-α leads to osteoclast activation and stimulation of proteolytic enzymes causing bone resorption. Activation of Plasminogen Activator (PA), and Matrix Metalloproteinases (MMP) also occurs, which are in charge of destroying extracellular matrix of the bone tissue. TNF-α, an early mediator of the acute-phase response, is involved in the production of chemokines, IL-6, and CRP as well as the recruitment of leucocytes during inflammatory reactions [34]. TNF-α is also known to induce smooth muscle proliferation and to increase adherence of leucocytes to endothelial cells by inducing the expression of cell adhesion molecules. TNF-α has an important role in lipid metabolism proposing an association with atherosclerosis [37]. It is known to increase serum concentrations of triglycerides by decreasing adipose tissue lipoprotein lipase activity, resulting in increased levels of free fatty acids and by stimulating the production of triglycerides in the liver [38].

Interleukin-17(IL-17): IL-17 has been recently detected in apical periodontitis lesions in humans. It may play a role in exacerbating inflammation in apical periodontitis lesions [39]. The regulation of matrix metalloproteinases of IL-17 may contribute to periradicular tissue destruction [40]. The levels of IL-17 are known to increase in symptomatic lesions with increased accumulation of PMNs [39]. IL-17 has shown to activate many signalling pathways, including NF-kβ, resulting in the expression of genes encoding proinflammatory cytokines TNF-α, IL-1, IL-6, Granulocyte Colony-Stimulating Factor (G-CSF), and Granulocyte–Macrophage Colony-Stimulating Factor (GM-CSF)], Chemokines (CXCL1, CXCL5, IL-8, CCL2, and CCL7), Matrix Metalloproteinases (MMP1, MMP3, MMP9 and MMP13), and antimicrobial peptides (defensins and S100 proteins). G-CSF-mediated granulopoiesis and recruitment of neutrophils to the

inflammatory sites is promoted by IL-17 [41]. A study has recently shown that the production of von Willebrand factor is promoted by IL-17 which induces endothelial cell apoptosis by activating caspase-3 and caspase-9. It also up-regulates the ratio of Bax/Bcl-2, indicating a role of IL-17 in vascular endothelial damage [42]. These effects indicate that IL-17 might play a role in atherosclerotic plaque formation and complication [43].

Heat Shock Proteins (HSP) released by some bacterial species and immune response induced by bacterial infection is hypothesised to be responsible for the initiation of early atherosclerotic lesions. Kosugi M et al., observed an association between immune responses to HSP produced by oral bacteria, chronic marginal and periapical periodontitis, CMV infection, dental metal allergy, and their combinations [44].

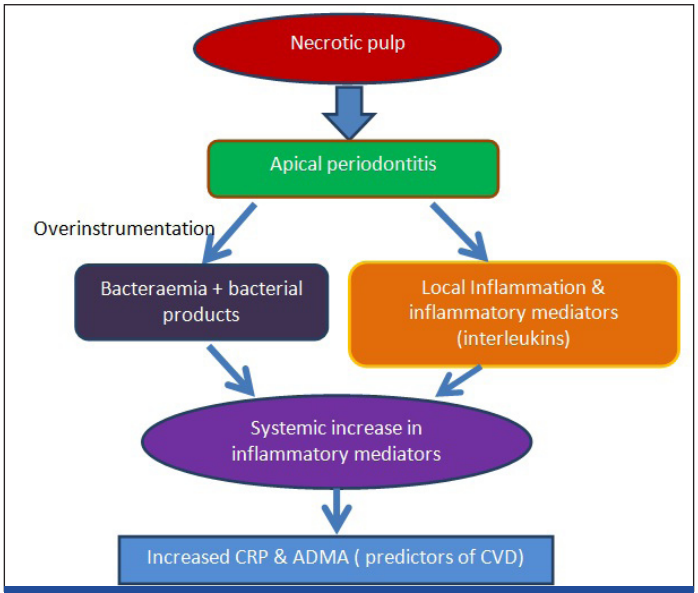
Endothelium, which is a functional barrier between the wall of the vessel and the bloodstream, plays a crucial role in the onset of atherosclerosis through its vascular regulatory functions, including control of vasomotor tone, local hemostasis, and proliferative processes [44]. The exposure of endothelial cells to cytokines induces a series of chemical-physical changes, including procoagulant activity, up-regulation of chemotactic and adhesion molecules, colony stimulating factor secretion and monocyte differentiation. Endothelial activation i.e., alterations in endothelial cell function, has been implicated in promoting the acute events in atherosclerotic vascular disease. Endothelial dysfunction induces thrombosis, vasospasm and vessel occlusion and has been implicated in the pathogenesis of acute myocardial infarction, stroke and other CVDs [45].

Bacteraemia and Implications on Cardiovascular System: Thus, from the above discussion, it could be hypothesized that endodontic microflora may predispose a patient to atherosclerosis through increased inflammatory mediators. However, it may also occur due to direct spread of endodontic bacteria into the bloodstream. Endodontic surgical and non-surgical instrumentation of root canals can produce a transient bacteremia [24]. Normally, micro-organisms that enter the bloodstream are eliminated within minutes. However, in patients with valvular heart disease, a transient bacteraemia may lead to infective endocarditis and myocardial infarction. The severity of tissue trauma due to instrumentation is an important causal factor for bacteremia. One important determinant of the onset of bacteremia appears to be the degree of the incidence of bacteremia was reportedly higher when the instrumentation reached beyond the confines of the root canal than in atraumatic endodontic procedures [46]. Researchers have been speculating this connection since decades. Many of the early reports linking endodontic treatment and bacteraemia were anecdotal, and failed due to the inability to use aseptic techniques during treatment and unavailability of modern culture techniques and molecular methods. A study was conducted on blood samples to assess bacteremia in conjunction with endodontic therapy during and 10 minutes after root canal instrumentation. It was reported that bacteremia occurred in 54% of cases in which deliberate instrumentation was done 2mm beyond the apical foramen and in 31% of cases when instrumentation ended with 1mm short of the apical foramen inside the root canal. It was confirmed through biochemical tests and antibiograms that microorganisms isolated from the root canals and bloodstream had the same profiles in each patient [47]. Another study showed detectable bacteraemia with conventional culturing in 30% of cases to detect bacteraemia in non-surgical root canal treatment [48] [Table/Fig-2].

Endodontic Disease and Cardiovascular Disease: Endodontic diseases could act as a confounding variable taking into account high prevalence of apical periodontitis [25]. Hypertension and inflammatory markers have been closely associated in apparently healthy patients. It was found that patients with acute myocardial infarction had a higher number of missing teeth, higher number of radiographic apical lesions and higher periodontal screening index value as compared to individuals without myocardial infarction [49]. Periapical disease and endodontic treatment could be associated with hypertension. Relationship between high blood pressure and periapical status may be due to inflammatory response based on published data suggesting chronic inflammation as independent risk factor for hypertension [50].

Grau conducted a case control study and found a multivariate Odds Ratio (OR) of 2.60 (95% CI: 1.2-5.7) between a composite dental disease index and stroke [51]. When composite index was broken up into individual components stroke patients were more likely to have periapical lesions. Another study by Janson found significant association between number of periapical lesions and number of carious surfaces with cardiovascular death [52].

There are very limited studies conducted to evaluate the association between endodontic pathosis and cardiovascular disease. Their level of evidence and conclusions have been summarised in [Table/Fig-3].



[Table/Fig-2]: Association of endodontic disease and cardiovascular disease.

Author	Level of Evidence	Conclusion
Frisk F, Hakeberg M, Ahlqwist M, Bengtsson C [53].	Cross-sectional study	No significant association was found between endodontically treated teeth and cardiovascular disease or with periapical disease.
Caplan DJ, Chasen JB, Krall EA, Cai J, Kang S, Garcia RI, et al., [54].	Longitudnal study	The study suggests a significant association between lesions of endodontic origin and cardiovascular disease among younger patients.
Joshipura KJ, Pitiphat W, Hung HC, Willett WC, Colditz GA, Douglass CW [55].	Longitudnal study	The results suggest a possible modest association between pulpal inflammation and cardiovascular disease.
Willershausen B, Kasaj A, Willershausen I, Zahorka D, Briseño B, Blettner M, Genth-Zotz S, Münzel T [56].	Longitudnal study	An association between chronic oral infections and myocardial infarction has been suggested.
Caplan DJ, Pankow JS, Cai J, Offenbacher S, Beck JD [57].	Longitudnal study	The study suggested that those with a history of endodontic treatment were more likely to have cardiovascular disease than were those reporting no history of endodontic treatment.
Costa TH, de FigueiredoNeto JA, de Oliveira AE, Lopes e Maia Mde F, de Almeida AL [58].	Cross-sectional study	The patients with chronic apical periodontitis had a 2.79 times higher risk of developing coronary artery disease.

[Table/Fig-3]: Level of evidence and conclusions of the studies establishing the relationship between apical periodontitis & cardiovascular disease.

Epidemiological research (cross-sectional and longitudinal) can identify relationship but not causation [59]. A criteria was given by Slots in 1998 to establish a causal relationship between periodontal disease and systemic disease [60]. Prevalence and incidence of the systemic disease in question should be significantly higher in periodontitis patients than in periodontally healthy individuals (retrospective data); onset of the systemic disease should follow the onset of periodontitis (prospective data); Elimination of periodontitis should decrease the incidence of the medical disease (intervention research); the microorganism(s) of the systemic disease should be of the same species, biotype, serotype, and genotype as the oral microorganism(s) (research on specific etiologic agents). Human populations with periodontitis in controlled studies should develop the systemic disease more frequently than periodontally healthy populations. The postulated association between periodontal disease and medical disease should be biologically feasible. According to him, if the above criteria could be satisfied, then a causal relationship between periodontal disease and the systemic disease was probable. Even though, these postulates are regarding periodontitis, but the same criteria could be applied to establish a relationship between apical periodontitis and cardiovascular disease, as the etiology and the inflammatory mediators are same in both the cases.

CONCLUSION

A more precise research should be undertaken in assessing the relationship between apical periodontitis and cardiovascular disease. It is not only of interest from the scientific point of view but also from public health perspective. Only a more focused and better instituted scientific research can determine this association.

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