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Review Article

Lesions of endodontic origin: An emerging risk factor for coronary heart diseases

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ABSTRACT

A high inflammatory state, such as atherosclerosis, is a major underlying cause of coronary heart diseases (CHDs). Inflammatory mediators are known to lead to endothelial dysfunction and play a key role in initiation, progression, and rupture of atherothrombotic plaque. Chronic inflammatory dental infections such as periodontitis and lesions of endodontic origin or chronic apical periodontitis (CAP) may provide an environment conducive for such events. Atherosclerosis has shown to share a common spectrum of inflammatory markers with apical periodontitis. The possible correlation between CHD and CAP is emerging at microbiological, clinical, inflammatory, and molecular levels. This less recognized fact should be discussed more among the dental and medical fraternity so that more awareness and positive approach toward oral health can be created among patients and health-care providers.

1. Introduction

Atherosclerosis, which is a condition characterized by a high inflammatory state, is a major underlying cause of coronary heart disease (CHD), as it may precipitate myocardial infarction, stroke, or peripheral vascular disease. The disease follows a somewhat silent clinical course, and the first clinical symptom often arises at a well-advanced stage.[1,2] Inflammatory mediators are known to lead to endothelial dysfunction and play a key role in initiation, progression, and rupture of atherothrombotic plaque. Long-standing chronic inflammatory state anywhere in the body is a known contributing factor for many degenerative diseases, and chronic inflammatory dental infections such as dental caries, periodontitis, and endodontic lesions may provide an environment conducive for such events. The microbe-induced inflammatory reaction of the oral connective tissue causes a symptomatic vasodilatation, resulting in an increased permeability of the endothelium that leads to the migration of leukocytes in the perivascular region and also the foray of bacteria.[3]

1.1. Inflammatory conditions of gingiva and teeth

1.1.1. Periodontitis

Periodontitis is defined as "an inflammatory disease of supporting tissues of teeth, i.e., the gingiva and the alveolar bone, caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession, or both."[4]

This inflammatory disease of the supporting tissues of teeth has long been linked to systemic diseases with high inflammatory quotient such as type 2 diabetes mellitus and CHD.[5,6] Many case-controlled, cross-sectional, and cohort studies have reported an association between periodontitis and increased cardiovascular, cerebrovascular, and peripheral artery disease, as determined by clinical disease, angiography, ultrasonography, and reduced flow-mediated dilation.[7,8]

1.2. Lesions of endodontic origin (chronic apical periodontitis)

Lesions of endodontic origin or apical periodontitis may be defined as "acute or chronic inflammatory lesion around the apex of a tooth caused by bacterial infection of the pulp canal system"[9] and usually presents in the presence or after restoration of deep caries

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lesions or fractured teeth.[10] Although the etiology for both conditions is different, this condition bears some similarities to chronic periodontal inflammatory disease, viz., similar pathogenic gram-negative microflora and a visible rise in systemic cytokine levels in both the clinical situations.[11,12] Thus, the systemic effects related to periodontitis may be applicable for lesions of endodontic origin too. An overabundant production of localized or systemic inflammatory mediators is seen in response to gram-negative bacteria in certain individuals, which may in turn lead to vascular or cardiovascular damage.[13,14] Detection of *Streptococcus mutans*, a major bacterial etiopathogen for dental caries in atherogenic plaque is also suggestive of a possible proatherogenic potential of dental caries.[15] Moreover, a recent multicentric study has shown that the prevalence of teeth with radiographic evidence of apical periodontitis is as high as 65% in Indian urban population. Thus, it is all the more important to recognize and address the effects of endodontic lesions or apical periodontitis on the systemic health, especially relating to the cardiovascular diseases.[16]

Although studies have shown that CHD and periodontitis are associated independently with the classical risk factors such as arterial hypertension, diabetes mellitus, smoking, and hypertriglyceridemia, only a few studies have explored the potential association between chronic apical periodontitis (CAP) and CHD[13,17] (See Table 1).

Thus, the aim of the present study is to present an overview of work done pertaining to the association of CAP and its treatment with atherosclerosis and CHD.

2. Material and methods

2.1. Search strategy

Related literature was searched using the MEDLINE/PubMed database, online Cochrane library, and Google scholar, with an emphasis on peer-reviewed dental journals till June 2017. The databases were searched by using keywords “coronary heart diseases” AND “chronic apical periodontitis” AND “atherosclerosis.” Only articles in English language were included, but no other restrictions were applied. In the search engine MEDLINE/PubMed, the MeSH term “coronary heart disease” revealed 295,084 results, and “atherosclerosis” revealed 12,689 results. On further filtering, “chronic apical periodontitis and coronary heart disease” revealed 12 items, and “chronic apical periodontitis and atherosclerosis” revealed 9 items.

3. Literature review

The present review attempts to analyze various published reviews, cross-sectional studies, and case-control studies relating to the association of CAP and CHD. The interrelationship of chronic infectious oral conditions of infectious diseases and systemic health is one of the much intriguing, yet less discussed, aspects of complete patient rehabilitation challenging the medical fraternity.[18,19] Several researchers have reported a positive correlation between chronic, inflammatory oral diseases such as chronic periodontitis and systemic conditions, viz., coronary artery disease (CAD), diabetes mellitus, stroke, pregnancy, and premature/low-birth-weight babies. The first Surgeon General's report on “Oral Health in America” published in 2000 recognized the importance of dental health in the overall general health and well-being of a patient, and oral diseases have been addressed as an “overlooked epidemic”.[20] Recognition and establishment of endodontic infection and consequent CAP as a potential risk factor or marker for CHD is still to be fully investigated, though researches have indicated a weak, but positive, association between the two conditions.[21–24] Barring a few case-controlled clinical trials, most of the studies obtained by the electronic search were retrospective cross-sectional studies, reviews, or cross-sectional surveys.

3.1. Studies on the microbial association of atherosclerosis and dental caries/endodontic lesions

Streptococcus mutans, the major caries-causing bacteria, is also a known pathogen for infective endocarditis and has been isolated in atherogenic plaques and extirpated heart valves, thus leading to the speculation of the role of oral streptococci in the development of cardiovascular disease. A molecular analysis of oral biofilm in atherosclerotic plaques and evaluation of decayed, missing, and filled teeth (DMFT) scores by Fernandes et al. revealed that *Streptococcus mutans* were found at a high frequency (100% specimens) in oral and vascular samples, even in edentulous patients, and its presence in atherosclerotic plaques suggests the possible role of this bacterium in the disease progression.[25] In a microbiological study using polymerase chain reaction (PCR) analysis, Nakano et al. (2006) studied specimens of atheromas, extirpated heart valves, and dental plaque from same subjects.[26] They found that although the composition of dental plaque was different from that of valvular plaque, a significant amount of *Streptococcus mutans* was present in both atheromas and valves. Their results suggested that *Streptococcus mutans* may be a causative agent for cardiovascular disease. Transient bacteremia after dental procedures such as scaling, extractions, root canal treatment, and even after chewing is a known phenomenon and may be the reason for the presence of oral streptococci in the cardiovascular region, but further studies are required to ascertain whether these strains were cariogenic or not.[27] It has been established that in less than a minute after an oral intervention, oral microorganisms can reach the heart, lungs, as well as the peripheral capillary system. Besides periodontal disease, chronic apical inflammations of endodontic origin could be considered as a possible source of bacteremia.

3.2. Studies on association of CAD and DMFT index/endodontic lesions

A possible clinical association between peripheral artery disease, periodontal disease, and dental caries was studied by Soto-Barreras et al., and it was seen that patients with attachment loss $\geq$4 mm had a six-fold increased risk of having peripheral artery disease and also a significantly high DMFT index and C-reactive protein (CRP) levels compared with the control group.[28] In a first of its kind cross-sectional retrospective study of computed tomography (CT) data of patients, Glodny et al. correlated patient's decayed, missing, and filled teeth or surface scores with the aortic calcification and concluded that patients with at least one tooth with caries or CAP had a higher atherosclerotic burden, whereas the number of restorations varied inversely with the atherosclerotic burden. They emphasized on the fact that initial caries, caries with or without pulpal involvement, and CAP are different stages of the same inflammatory condition, so caries without CAP may also be considered as an independent risk factor for atherosclerosis.[29] In another cross-sectional retrospective study of the whole-body CT scans of the patients, Peterson et al. (2014)[30] for the first time quantified aortic atherosclerotic burden by calcification scoring method and found that it related positively with some teeth with CAP but without any endodontic treatment. Conversely, endodontically treated teeth even with CAP did not contribute to the atherosclerotic burden. In this study, the factor CAP without endodontic treatment was more significant than gender, marginal periodontitis, and caries and about one-fourth as significant as age.[30] Caplan et al. (2009) evaluated the relationship between a

Table 1
List of relevant studies.

Authors/year/place	Hypothesis/problem evaluated	Methodology	Results
Costa TH et al. (2014)[24]	To establish the relationship between chronic apical periodontitis and coronary artery disease	Cross-sectional study (103 patients who underwent coronary angiography)	The patients with chronic apical periodontitis had 2.79 times higher risk of developing coronary artery disease. Chronic apical periodontitis was independently associated with coronary artery disease.
Caplan DJ (2014)[37]	This study evaluated whether incident radiographically evident lesions of endodontic origin were related to development of coronary heart disease (CHD)	At baseline and every three years for up to 32 years, 708 male participants received complete medical and dental examinations, including full-mouth radiographs.	Among those aged ≤40 years, incident lesions of endodontic origin were significantly associated with time to CHD diagnosis ($p < 0.05$). Among those aged >40 years, no statistically significant association was observed.
Peterson et al. (2014)[30]	To estimate the effect of chronic apical periodontitis and its management on atherosclerotic burden	Retrospective, cross-sectional study; a total of 531 patients (11,901 teeth), with mean age of 50 years (range 8–89 years; 259 females/272 males), who had had a whole-body computed tomography (CT) scan were evaluated.	The volume of the aortic atherosclerotic burden for patients with at least one chronic apical periodontitis (CAP) lesion was 0.32 ± 0.92 mL higher than that for patients with no CAP (0.17 ± 0.51 mL; $p < 0.05$).
Segura-Egea et al. (2012)[18]	To investigate the prevalence of apical periodontitis and endodontic treatment in hypertensive patients and control subjects without hypertension.	In a cross-sectional study, records of 40 hypertensive patients and 51 control subjects were examined. Periapical status of all teeth was assessed by using the periapical index score.	Apical periodontitis in 1 or more teeth was found in 75% of hypertensive patients and in 61% of control subjects ($p = .15$; odds ratio, 1.94; 95% confidence interval [CI], 0.78–4.81). Among hypertensive patients, 65% of root-filled teeth had apical periodontitis, whereas in the control subjects, 43% of the root-filled teeth were associated with apical periodontitis ($p > .05$).
Willershausen et al. (2009)[33]	To study whether the association between dental chronic inflammatory diseases and the occurrence of acute myocardial infarction (AMI) could be established to study possible risk factors for CHD.	125 patients with AMI aged between 50 and 82 years; the control patients were a group of matched subjects (gender, age, ethnicity, and smoking habits) in good health.	Patients with AMI exhibited a significantly higher number of missing teeth ($p = .001$), less teeth with root canal fillings ($p = .0015$), a higher number of radiologic apical lesions ($p = .001$), and a higher PSI value ($p = .001$) than individuals without myocardial infarction. The medical data showed nonsignificant correlation between C-reactive protein (CRP) and the number of radiologic apical lesions.
Caplan et al. (2009)[31]	To evaluate the relationship between self-reported history of endodontic treatment (ET) and prevalent CHD among dentate participants with the risk of atherosclerosis	15,792 patients visited hospital between (1987-1989)	Among participants with 25 or more teeth, those reporting having had ET two or more times had 1.62 (95% CI, 1.04–2.53) times the odds of prevalent CHD compared with those reporting never having had ET.
Frisk and Hakeberg (2005)[22]	Endodontic status in Swedish populations and possible association between apical periodontitis (AP) and CHD	3499 women participants and random samples of dentate individuals ($n = 2066$) aged 20–70 years	No significant association between AP and CHD and socioeconomic risk factors and AP
Joshipura et al. (2006)[23]	Possible association between pulpal inflammation (endodontic treatment) and incidence of CHD	34,683 participants	Strong association between a positive self-reported history of endodontic treatment and incidence of CHD
Arroll et al. (2010)[34]	To explore the relationship between CRP as a marker of inflammation and presence and number of root canal treatments in primary care patients.	Cross-sectional survey of 134 patients; blood test for serum CRP in patients	The CRP level for those with ≥3 root-treated teeth was 1.68, whereas the level for those with <3 was 2.36, but the p value was not statistically significant ($p = 0.198$).
Berlin-Broner Y et al. (2017)[38]	To assess the association between apical periodontitis and cardiovascular disease	Systematic review; 13 of the 19 included studies found a significant positive association between apical periodontitis and cardiovascular disease, although in two of them, the significance was present only in univariate analysis. Five studies failed to reveal positive significance, and one study reported a negative association.	Although most of the published studies found a positive association between apical periodontitis and cardiovascular disease, the quality of the existing evidence is moderate to low, and a causal relationship cannot be established.

self-reported history of endodontic treatment and prevalent CHD in Atherosclerosis Risk in Communities study. Final multivariable regression models indicated that among participants with 25 or more teeth, those reporting having had endodontic treatment two or more times had 1.62 times the odds of prevalent CHD compared with those reporting never having had endodontic treatment.[31] In a case-controlled clinical trial, Pasqualini et al. (2012) compared middle-aged adults with acute myocardial infarction (AMI) or unstable angina within 12 months, with healthy controls. Indicators of oral disease and compliance were evaluated. CD14 polymorphisms were analyzed by restriction fragment length polymorphism–PCR and CHD. No statistically significant association emerged between the CD14C (−260)T and the CD14C (−159)T polymorphism, endodontic or periodontal disease, and CHD, and they concluded that chronic oral infections might be an unconventional risk factor for CHD.[32] Willershausen et al. (2009) conducted a case-control study to assess an association between chronic dental inflammation and AMI and deduced that patients with a history of AMI exhibited an

increased number of periapical radiolucencies, had lesser root canal–filled teeth, and a higher number of missing teeth. Also, a nonsignificant increase in CRP levels could be seen in patients with a larger number of periapical radiolucencies.[33]

4. Conclusion/future directions

Atherosclerosis shares a common spectrum of inflammatory markers with apical periodontitis. Various immune inflammatory mediators against bacteria from an infected root canal via phagocytosis and activation of humoral and cellular responses, viz., inflammatory cytokines (interleukins 1β), tumor necrosis factor-α, reactive oxygen species, and matrix metalloproteinases, play a crucial role in the development of apical periodontitis and are also potentially responsible for endothelial dysfunction and atherosclerosis.[28,32,34] CRP levels are linked with different aspects of the cardiovascular risk spectrum and have been widely acknowledged as an important risk indicator for CHD and can forewarn future cardiovascular events. It has been seen that low-grade inflammation associated with a chronic infection, such as CAP, causes elevated levels of CRP. Thus, treatment and resolution of these conditions may be helpful in reduction inflammation and subsequently CRP levels.[33,34]

The possible correlation between CHD and CAP is emerging clearly at microbiological, clinical, inflammatory, as well as molecular levels.[35–37] More recently, Berlin-Broner Y et al. in a systematic review studied the association between apical periodontitis and cardiovascular disease and concluded that though there is positive association between apical periodontitis and cardiovascular disease, the quality of the existing evidence is moderate to low, and a causal relationship cannot be established.[38]

Though at present literature shows a weak, yet positive, association between CAP and CHD, let us not wait in inaction for the evidence to prove it. The oral health-care providers must expand their role and should emphasize on the fact that oral health can contribute to better overall health outcomes. Similarly, the medical health-care providers should encourage their patients to maintain oral health and should refer them to the oral health-care provider for regular checkups. Finally, the dental and medical fraternity should have an integrative approach toward the diagnosis and management of chronic diseases having a shared underlying etiopathogenesis and having an effect on the treatment outcomes.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ihj.2018.07.004.

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