Association of Radiographically Diagnosed Apical Periodontitis and Cardiovascular Disease: A Hospital Records–based Study

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Abstract

Introduction: Numerous studies have demonstrated an association between oral health status and systemic diseases. However, reports examining apical periodontitis (AP) and cardiovascular disease (CVD) are few. This study investigates whether an association exists between AP and CVD. Methods: The present study was a pair-matched, cross-sectional design that used medical and dental chart review. The AP group (n = 182) was defined as subjects with radiographic AP, and the non-AP group (n = 182) was defined as subjects without any radiographic AP. Samples for both groups were pair-matched by age and gender. Diagnosis for CVD, hypercholesterolemia, hypertension, and diabetes were identified by using International Classification of Diseases, Ninth Revision, Clinical Modification and collected from electronic medical records. Documentation of alcohol use, smoking, race, and body mass index within the electronic medical records was also collected. Presence or absence of AP, missing teeth, teeth with root canal treatment, caries experience, and history of periodontal disease were collected from the electronic dental records. Analysis was performed by using Pearson χ², the paired t test, and conditional multivariate logistic regression. Results: AP was significantly associated with CVD, hypercholesterolemia, race, missing teeth, caries experience, and number of root canal treatments in our bivariate analysis. Our final adjusted conditional logistic regression model showed statistically significant positive associations between AP and CVD (odds ratio, 5.3; 95% confidence interval, 1.5–18.4). Conclusions: Subjects with AP were more likely to have CVD than subjects without AP by 5.3-fold. However, further research is needed to elucidate temporality and reinforce association between CVD and AP. (J Endod 2016;42:916–920)

Key Words

Apical periodontitis, cardiovascular disease, endodontics, root canal treatment, systemic disease

The link between oral and systemic health has been debated for more than a century. In the early 1900s the focal infection theory gained popularity and evoked fear among its subscribers. The theory suggested that many systemic illnesses were consequences of focal infections originating in the mouth (1, 2). Poor science and lack of evidence-based practice led to harmful consequences to patients. At the peak of its popularity, edentulous therapy became the primary preventive measure (3). The theory was discredited by the mid-1900s; however, interest in the oral and systemic connection persisted. By the beginning of the twenty-first century, publications on the topic had grown exponentially. The first peer-reviewed study investigating oral health and cardiovascular disease (CVD) was published in 1989 (4); by 2010, the rate of publication on the subject matter had increased to more than 160 peer-reviewed articles per year and more than 500 total articles since 1989 (5). Although the periodontal disease and CVD link has received the most attention, a growing number of studies have examined other associations between various oral health factors such as tooth loss, xerostomia, and caries and systemic factors including vascular disease, diabetes, aspiration pneumonia, and preterm birth. Few studies have examined the association between apical periodontitis (AP) and CVD.

AP is an inflammatory process of endodontic origin usually occurring at or near the apex of the tooth root. The biological explanatory model for the AP and CVD relationship resembles the well-established mechanistic evidence that exists for the periodontal disease and CVD relationship (6–9), and both AP and periodontal disease share similar bacterial flora, primarily gram-negative anaerobes, and similar destructive inflammatory reactions (10, 11). Bacteria and inflammation have also been implicated in platelet aggregation, atherosclerosis, and the progression of CVD (7, 9).

The World Health Organization defines CVD as a group of disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism (12). The goal of the current study was to investigate an association between CVD and AP. In addition, other known covariates were analyzed for their relationship with AP.

Materials and Methods

The present study used a pair-matched, cross-sectional study design with data ascertained through chart review and examination of dental radiographs. AP was defined radiographically by a periapical radiolucency exceeding twice the width of the normal periodontal ligament space (13–17), and patients with at least 1 tooth exhibiting radiographic evidence of apical pathology were designated as AP cases. All measurements were recorded by 1 observer. Radiographic AP appearance has been
validated and correlated to histologic findings of periapical inflammation (18). The non-AP group was composed of persons without radiographic evidence of apical pathology; these individuals were pair-matched (1:1) to AP cases on age (±10 years) and gender.

The study was conducted at New York University-Lutheran Medical Center (NYU-LMC), a tertiary care teaching hospital and its associated sites in Brooklyn, NY. Electronic medical and dental records spanning 56 months from July 7, 2008 to February 28, 2013 were reviewed. Patient data were gathered by using Veterans Health Information Systems and Technology Architecture electronic medical records (EMRs) and Dentrix (Henry Schein Practice Solutions, American Fork, UT) Enterprise RT 4.0 electronic dental records (EDRs). The hospital’s EMRs and EDRs were integrated and shared patient demographic information.

Patients from EDRs were selected on the basis of random encounter dates within the endodontic and general practice residency practices; dates were randomized by using the Random Calendar Date Generator (19). We included patients who were 30 years of age or older during the review period and had no less than 3 encounters recorded in both the EMRs and EDRs. For study inclusion, EDR charts were required to have a complete patient examination and treatment plan as well as a full mouth set of digital radiographs. Subjects with less than 10 teeth present were excluded. During the period reviewed, all radiographs within the hospital system were taken with Schick by Sirona CDR 2000 sensors. Sirona digital imaging software, CDR Dicom Version 3.5 was bridged to the Dentrix software.

An a priori power analysis indicated that a sample of 172 individuals in each group (AP and non-AP) would achieve a power of 80% to detect an odds ratio (OR) of 2.0 or more when the prevalence of exposure among the control group was 20%, assuming an alpha level of 0.05 and using logistic regression.

The independent variables collected from EDRs and EMRs for each patient were age of patient at date of observed radiograph(s), gender, race, alcohol use, smoking history, body mass index (BMI) (obesity measure), history of periodontal disease indicated by treatment or treatment plan, number of teeth with existing root canal treatment (RCT), number of missing teeth (calculated by subtracting number of present teeth from 32), and caries experience indicated by teeth with existing restorations or caries. Among the AP group, the number of teeth with AP was measured.

On the basis of patient-specific EMRs, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were reviewed to identify individuals with CVD-related systemic diseases (12). Table 1 illustrates the range of ICD-9-CM codes used: 414 (coronary artery disease), 427 (arrhythmias), 745-746 (congenital heart defects), 390-398 (rheumatic heart disease), 425 (cardiomyopathy), 413 (angina pectoris), 786.50 (unstable angina), 410 (myocardial defects), 390-398 (rheumatic heart disease), 425 (cardiomyopathy), of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease*</td>
<td>410-414, 420-429</td>
</tr>
<tr>
<td>Cerebrovascular disease*</td>
<td>430-438</td>
</tr>
<tr>
<td>Peripheral arterial disease*</td>
<td>440-448</td>
</tr>
<tr>
<td>Rheumatic heart disease*</td>
<td>390-398</td>
</tr>
<tr>
<td>Congenital heart disease*</td>
<td>745-746</td>
</tr>
<tr>
<td>Deep vein thrombosis/pulmonary embolism*</td>
<td>451-459</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>272</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401.9</td>
</tr>
<tr>
<td>Diabetes mellitus II</td>
<td>250</td>
</tr>
</tbody>
</table>

*ICD codes classified for CVD identified in italics.

![TABLE 1. ICD-9-CM Codes Abstracted from EMRs](image)

Results

Data from 364 patients were included in the analysis, 182 AP and an equal number of age-matched, gender-matched non-AP patients.

Characteristics of patients in the AP and non-AP groups are presented in Table 2. Because of the pair-matched design used, the AP and non-AP groups were similar on age (mean, 49 years) and gender (73% female) distribution. Bivariate analysis revealed statistically significant, positive relationships between the presence of AP and each of the following: CVD, hypercholesterolemia, race/ethnicity, missing teeth, number of RCTs, and caries experience.

A subgroup analysis of the AP group (N = 182) in Table 3 demonstrated no statistically significant association between CVD and number of teeth with AP. However, among the AP group, a statistically significant association between CVD and number of teeth with existing RCTs was found. When a multivariable model was used, neither findings were statistically significant.

![TABLE 2. Characteristics of Persons in AP and Non-AP Groups](image)
Clinical Research

Table 3. Subgroup Analysis of AP Group (n = 182)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>CVD (n = 58)</th>
<th>Non-CVD (n = 124)</th>
<th>P value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of teeth with AP</td>
<td>1.8 (1.2)</td>
<td>1.6 (0.8)</td>
<td>.225</td>
<td></td>
</tr>
<tr>
<td>No. of RCTs</td>
<td>2.4 (2.2)</td>
<td>1.5 (1.8)</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; RCT, root canal treatment; SD, standard deviation.

When adjusted for the potential effects of multiple covariates, our model estimated 5.3-fold higher odds of having at least 1 AP among persons with CVD, relative to those without CVD. Our findings reinforce previous findings of an AP-CVD association (24, 25, 29–31); however, they contradict statistically non-significant findings by Frisk et al (32), whose sample was relatively homogenous, consisting of only Swedish women (n = 1056). In another study of all male subjects, investigators found a significant association between AP and CVD among young men (29). Petersen et al (33) also reported that men with AP had a greater risk for CVD. Because age and gender are potential effect modifiers of the AP-CVD relationship, those variables may have played a role in the conflicting results across studies. We controlled for confounding by these variables through our pair-matched design and use of conditional logistic regression; however, matching on these variables precluded our ability to assess the influence of age and gender as effect modifiers.

As expected, our final model also showed a significant association between AP status and number of RCTs. A systematic review reported a significantly higher proportion of AP in teeth with RCTs than in teeth without RCTs, 36% and 2%, respectively (34). Our study found that for each existing RCT there was a 3.4-fold increase in having AP, a significant association between these 2 variables.

RCT has commonly been used as a surrogate for AP or pulpal inflammation in studies investigating the link between endodontic-related inflammation and CVD (24, 25). However, use of RCT as a proxy has limitations. RCT and AP have several obvious differences; RCTs could present with or without AP, and if AP is present, it likely indicates a process of healing rather than an indication of ongoing inflammation, depending on when the RCT was completed and the quality of RCT (35, 36).

The biological plausibility for the association between periodontal disease and CVD has been well-detailed in the literature (6–11). More recently, studies have emerged outlining the biological mechanisms and supporting the plausibility of an AP and CVD relationship (20, 21). Various studies have demonstrated an independent association between AP and known inflammatory markers implicated in CVD (20–22).

These inflammatory markers include inflammatory cytokines and enzymes, as well as C-reactive protein, matrix metalloproteinases, asymmetric dimethylarginine, and reactive oxygen species. Gotti et al (23) reported that compared with non-AP controls, AP subjects had greater levels of proinflammatory markers and endothelial cell activation, an indication of acute CVD events and atherosclerosis. Although contributions have been made to better understand the biological link between AP and CVD, studies of association have been far from conclusive.

Commonly, AP and CVD status are gathered from patient self-report and/or surveillance data (24, 25). Self-reported data present limitations; patients are subject to recall bias and may often be unaware of their current and past dental and medical status (26, 27). Consequently, inaccuracies may lead to misclassification. A more objective and reliable method of identifying medical disease is the use of diagnostic codes such as ICD-9-CM found in EMRs (28). To our knowledge, this is the first study to investigate an AP-CVD association by reviewing ICD diagnostic coding to establish medical diagnoses and minimize misclassification of CVD and other diagnoses.

Discussion

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infection and inflammation such as prophylaxis in trauma cases. Therefore, RCT and AP may have differing effects on CVD. Petersen et al (33) demonstrated that AP teeth without RCT were significantly associated with CVD, whereas AP teeth with RCT were not. Our study showed the number of completed RCTs was statistically significant in the final model. The correlation between RCT and AP would likely be higher in our sample compared with findings from other studies because all our subjects were patients with multiple visits with completed examinations; therefore, most patients would have already had AP identified and consequently treated with RCT. Although it is intuitively obvious that the number of RCTs would be a predictor of AP as found in our results, we also found that the number of RCTs was independently associated with both AP and CVD.

We explored the exposure-response relationship between both number of teeth with AP and CVD and number of teeth with existing RCTs and CVD. The subgroup analysis of subjects with AP (n = 182) demonstrated that those with CVD were statistically more likely to have a greater number of teeth with existing RCTs than those without CVD. Subjects with CVD also had greater number of teeth with AP than those without CVD, but the association was not statistically significant. The null finding may partially be explained by the underreporting of true AP in our sample. For instance, teeth with AP may have already been treated at time of record. Also, the method of radiographic detection of AP excludes inflamed teeth with AP not detectable by radiographs. Last, our sample size was reduced by half to conduct the subanalysis because all subjects without AP, the non-AP group, were excluded. A larger sample may yield more conclusive results. Therefore, the exposure-response relationship should be further explored.

Caries, the primary cause of endodontic infections, and missing teeth have been shown to be associated with AP (37, 38). In agreement, we also found caries and missing teeth to be significantly associated with AP in our unadjusted descriptive analysis. However, when both variables were included in our multivariable conditional logistic regression, neither variable was significantly associated with AP, possibly because of multicollinearity because missing teeth and carious teeth have statistically significant correlations with the number of RCTs.

Smoking has been found to have a strong association with AP (39). Surprisingly, we found no significant association in our sample. Possible explanations could stem from differences in reporting methodology, definition of smoking, and culture. In EMRs, smoking and alcohol were self-reported and, along with BMI, were the only medical variables not assigned ICD-9-CM codes. Smoking in EMRs was recorded as daily smoking, specifically smoking more than 5 cigarettes per day (yes/no). In contrast, some studies define smoking as having ever smoked. Variation in the definition of smoking, especially in the ill-defined “light” or “intermittent” smoking groups, may lead to miscategorization (40). Also, self-reporting of smoking varies according to cultural, psychological, and cognitive factors of individuals (41). The study by López-López et al (39) was conducted in Spain where arguably smoking is more socially accepted than in the United States. Social stigma around smoking may have contributed to underreporting of smoking in our study. Random misclassification and underreporting would have favored a null finding such as ours.

An association between diabetes and AP has been shown in previous studies (42, 43); however, our study did not find a significant association. The statistically non-significant finding may be explained by our method of classifying diabetes; we used diagnostic codes rather than directly measuring glycemic control through hemoglobin A1c or blood glucose levels. All subjects in our study were repeat patients who had a greater number of teeth with existing RCTs than those without CVD. Subjects with CVD also had a greater number of teeth with AP than those without CVD, but the association was not statistically significant. The null finding may partially be explained by the underreporting of true AP in our sample. For instance, teeth with AP may have already been treated at time of record. Also, the method of radiographic detection of AP excludes inflamed teeth with AP not detectable by radiographs. Last, our sample size was reduced by half to conduct the subanalysis because all subjects without AP, the non-AP group, were excluded. A larger sample may yield more conclusive results. Therefore, the exposure-response relationship should be further explored.

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Additional variables that did not show associations with AP were BMI, periodontal disease, and alcohol use. In agreement with a previous study (46) we also did not find any significant association with AP and hypertension in our final model.

There are several limitations to this study that warrant discussion. The World Health Organization’s definition of CVD and its ICD diagnostic coding was used to identify CVD. The broad definition of CVD includes conditions beyond those that are infectious and inflammatory in nature. Future studies should investigate the association of AP with specific CVD conditions with infectious or inflammatory mechanisms.

Certain characteristics of patients seen at NYU-LMC may have differed considerably from the population at large. For instance, there could be differences in culture, socioeconomic status, behavioral characteristics, health perceptions and literacy, as well as overall health status. More than 70% of our subjects were Hispanic, and in our sample, we found that Hispanic patients and patients of “other” race were less likely than whites to have AP. Also, most NYU-LMC patients were of low socioeconomic status, and nearly all were on Medicaid or subsidized free care. Many spoke little to no English and often used interpretive services. Furthermore, patients like those in our sample seeking hospital care were likely to have more illness with greater morbidity. Therefore, generalizability of our findings to larger diverse populations or other races may be limited. Further investigation into the influences of these variables including race and ethnicity is warranted.

Another limitation was the use of two-dimensional (2D) digital radiographs for AP identification. Interpretation of 2D radiographs can lead to underdiagnosis (47). Unlike chronic AP, most acute AP is radiographically undetectable and unrecorded. Also, AP must reach a sufficient threshold of bone destruction to be detectable; a classic study by Bender (48) demonstrated that at least 30% mineral loss must occur before radiographic detection. Furthermore, the size of radioluencies on a periapical film is smaller than the actual size of bone destruction, resulting in greater difficulty in identifying smaller AP (49). The lack of detection of acute AP cases and cases with radioluencies near or below the detectable threshold leads to underestimation of the true AP prevalence. Underdiagnosis may lead to an underestimation of the effect; therefore, the true association of AP and CVD may actually be greater. A review by Patel et al (50) showed that cone-beam computed tomography (CBCT) was far superior in detecting true AP than 2D digital radiographs. However, CBCT should be used with caution for AP identification. Pope et al (51) demonstrated that the use of CBCT showed a wide variation of periodontal ligament space size in normal healthy pulps. CBCT has strong sensitivity, the ability to correctly diagnose AP, but relatively weak specificity, the ability to correctly diagnose normal periapical tissues. Therefore, there may be greater potential for misclassification of healthy pulps.

The social and economic burden of CVD is high. According to the American Heart Association, the prevalence of CVD in the United States is more than 30%, with total annual direct costs of more than $200 billion (52). A review of multiple community-based studies showed a wide range of AP prevalence from 14% to 70% of participants (53). As tooth retention increases, it is possible that the burden of AP will increase, and consequently, CVD will increase. A systematic review of AP prevalence showed approximately 5% of all teeth had AP, or broadly 1 AP per patient (54). In view of the growing epidemic of CVD and the high rates of AP, further studies should investigate possible causal relations through prospective interventions.
Conclusion

Within the limits of this investigation, we found that patients presenting with AP were 5.3 times more likely to have CVD than patients without AP. Future studies should explore possible relationships between AP and specific CVD conditions, especially those with infectious or inflammatory mechanisms. Also, methods should be used to minimize misclassification of AP, CVD, and their risk factors. There is a need for well-powered randomized studies to clarify temporality and replicate a definitive association between specific CVD conditions and AP.

Acknowledgments

The authors deny any conflicts of interest related to this study.

References

1. Miller W. The human mouth as a focus of infection. Dental Cosmos 1891;33:689–713.