Investigating Potential Correlations between Endodontic Pathology and Cardiovascular Diseases Using Epidemiological and Genetic Approaches

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Abstract

Introduction: Apical periodontitis (AP) and cardiovascular diseases (CVDs) are chronic conditions triggered by an inflammatory process and sharing similar pathogeneses and molecular players. Previous studies have suggested that AP may perpetuate a systemic inflammation state and, in turn, contribute to CVD. In this study, we investigated the potential association between endodontic pathology and CVD using epidemiological and genetic approaches. **Methods:** Epidemiologic analysis was performed by querying the medical and dental records of >2 million patients. We retrieved information on positive/negative history for endodontic pathologies and CVDs using diagnostic and treatment codes from a dental school–based and a hospital-based patient electronic health record system. A case-control genetic association study was also performed; 10 single nucleotide polymorphisms in genes identified as strongly associated with CVDs were genotyped in 195 cases with AP and 189 control individuals without AP. Data analyses were performed using the chi-square and Fisher exact tests. $P \leq .05$ indicates significant difference between groups. **Results:** Significant associations were found between the presence of endodontic pathology and a history of hypertension, myocardial infarction, cerebrovascular accident, pacemaker, congestive heart failure, heart block, deep vein thrombosis, and cardiac surgery ($0.0001 \leq P \leq .008$). A modest association was found for heart murmur and atrial fibrillation ($P = .04$). A trend toward positive association ($P = .05$) was also found between AP and a single nucleotide polymorphism in *KCNK3*, a gene known to be involved in increased susceptibility to hypertension. **Conclusions:** Significant associations were found between endodontic pathology and various CVDs and CVD-related risk factors, particularly hypertension. A trend toward a positive association was also found between AP and *KCNK3*, suggesting that common genetic variations may underlie different diseases. Additional studies with larger sample sizes have the potential to elucidate common mechanisms underlying AP and CVD. *(J Endod 2019;45:104–110)*

Key Words

Apical periodontitis, association, cardiovascular disease, endodontic pathology, gene

Significance

This is the first study assessing the association between endodontic pathologies and cardiovascular diseases combining a retrospective study using an integrated dental-medical health record repository and a prospective genetic association study.

Apical periodontitis (AP) is a process of inflammation and destruction of the apical periodontal structures that results from untreated bacterial invasion into the pulp (1). Cardiovascular diseases (CVDs) comprise the second most common cause of disease-related death worldwide (2). Intriguingly, previous studies have suggested a potential link between AP and CVD because they share similar pathogenesis mechanisms and maintain a local and systemic chronic inflammation state if left untreated (3–5). Both diseased tissues are of connective tissue origin which undergo a process of vasodilation, increased cellular metabolism, discharge of cellular mediators, cellular influx, and extravasation of fluids with tissue breakdown as a consequence of the inflammatory process (6). Furthermore, considerable overlap exists in the molecular players involved in the pathogenesis of both AP and CVD. The expression of proinflammatory cytokines, particularly interleukin (IL)-1 and tumor necrosis factor alpha, are markedly increased in areas of tissue destruction and bone resorption; tumor necrosis factor alpha, IL-1β, prostaglandin E2, IL-1β, IL-8, immunoglobulin A, and immunoglobulin G expression are also increased (6–10).

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Taken together, the underlying hypothesis for considering AP as a potential risk factor contributing to CVD is based on the notion that AP and its localized inflammatory response may contribute to a systemic immune-inflammatory response not restricted to the localized lesion (7). A recent systematic review of the literature addressing the association between AP and CVD concluded that although a deep connection between CVD and periodontal disease has been well-documented, the potential cardiovascular effects of AP remain broadly unidentified and controversial (11). Indeed, numerous studies have supported a positive association between AP and CVD, whereas others have yielded negative or inconclusive evidence (5).

Plausible biological mechanisms in support of an association between AP and CVD rely on characteristics that may predispose an individual to either 1 or both conditions (12). However, the effects of genetic predisposition supporting a potential correlation between AP and CVD has not yet been explored. It is possible that individual gene variants underlying and possibly linking these 2 conditions are yet to be discovered to justify previous epidemiological associations. In this study, we investigated the potential association between AP and CVD and CVD-related risk factors using epidemiological and genetic approaches.

Materials and Methods

Epidemiologic Association Study

This study was approved by the UTHealth Committee for the Protection of Human Subjects (HSC-DB-17-0661).

Data Mining Using Dental Records. Information on the presence of endodontic pathologies and CVDs from the dental records was obtained from the BigMouth Dental Data Repository. BigMouth is an oral health database created in 2012, which acquires information from electronic health records that dates back to 1996 and are contributed by dental schools who are part of the Consortium for Oral Health Research and Informatics. This database incorporates data from 7 dental schools and is hosted at the University of Texas Health Science Center at Houston School of Biomedical Informatics, Houston, TX. The current participants are Harvard School of Dental Medicine, Boston, MA; Tufts University School of Dental Medicine, Boston, MA; The University of California at San Francisco School of Dentistry, San Francisco, CA; The University of Pittsburgh School of Dental Medicine, Pittsburgh, PA; The University of Michigan School of Dentistry, Ann Arbor, MI; University of Colorado School of Dental Medicine, Aurora, CO; and the University of Texas Health Science Center at Houston School of Dentistry (UTSD), Houston, TX. BigMouth was developed on i2b2, an open source data warehousing tool. BigMouth contains over 2 million patients whose protected health information has been removed with the exception of dates and zip codes. It contains information on demographics, diagnoses, procedures, periodontal measurements, odontogram/tooth measurements, medical and dental histories, prescription medications, patient insurance, and provider (hygienist, dentist, dental student, and resident).

We limited our search to the records of 154,512 patients who received dental treatment at UTSD. All searches were limited to patients aged 18–65 years old. First, we assessed the number of patients with a self-reported history of CVDs who had received endodontic treatment from August 1996 to April 2016. Information on individual history for the following adverse cardiovascular events as indicators of CVDs were retrieved using diagnostic terms as implemented in the BigMouth repository: hypertension, rheumatic fever, heart murmur, mitral valve prolapse, myocardial infarction, cerebrovascular accident, cardiac surgery, chest pain, angina, irregular/rapid heartbeat, palpitations, pacemaker, heart valve disease, presence of blood clots, infective endocarditis, coronary artery disease, congestive heart failure, atrial fibrillation, heart block, cardiac arrhythmia, and deep vein thrombosis. These entries were found as a standardized format in a list of subsets of CVD in the full medical history or medical screening forms of each patient as entered in the electronic health record.

Next, we assessed information on the types of endodontic diagnoses and treatments suggesting the presence of endodontic pathology (to exclude information on the treatment of vital teeth because of restorative needs and/or trauma). Information on the following endodontic treatments was retrieved using standardized treatment codes: therapeutic pulpotomy, pulpal debridement, root canal treatment, incomplete endodontic treatment, root canal retreatment, apical surgery, root amputation, and intentional replantation. We also assessed the number of patients without a self-reported history of CVDs who had never received endodontic treatment to be considered as controls.

Finally, our search yielded patients in the following categories: patients with CVD+ Endo+ (positive history of CVD plus endodontic pathology/treatment), CVD+ Endo− (positive history of CVD and no endodontic pathology/treatment), CVD− Endo+ (no history of CVD plus endodontic pathology/treatment), and CVD− Endo− (no history of CVD and no endodontic pathology/treatment).

Data Mining Using Medical Records. In an attempt to validate the CVD history information obtained through the electronic dental records and BigMouth, we also assessed Allscripts, the electronic health record system for the University of Texas Health Science Center Physicians outpatient clinics, which contains data on >700,000 patients including laboratory data. Available data recorded in the BigMouth and Allscripts databases from January 1, 2000, to April 1, 2016, were extracted with the help of informaticians at the Office of Technology Services and Informatics at UTSD. Patients' dental and medical records were merged using the Master Patient Index tool developed at the University of Texas Health Science Center at Houston School of Biomedical Informatics (13). A cross-check was performed for patients with a record of endodontic diagnosis or treatment (symptomatic AP, asymptomatic AP, chronic apical abscess, acute apical abscess, therapeutic pulpotomy, pulpal debridement, root canal treatment, incomplete endodontic treatment, root canal retreatment, apical surgery, root amputation, and intentional replantation) and a record of adverse cardiovascular events as indicators of CVD (myocardial infarction, history of coronary revascularization, and stroke). Extracted data from the BigMouth and Allscripts databases were deidentified before being given to the investigator team. Edentulous patients, pregnant women, and patients with a history of cancer, HIV/AIDS, seizures/epilepsy, an organ transplant, or genetic diseases affecting bone metabolism were excluded from the record search.

Genetic Association Study

Sample Population. This study was approved by the University of Texas Health Science Center Committee for the Protection of Human Subjects (HSC-DB-12-0280). Patients from the UTSD endodontic clinic were invited to participate and a saliva sample, as well as dental/medical history, were collected. Patients with systemic conditions (ie, diabetes) or other hormonal alterations related to exacerbated or uncontrolled inflammatory responses and patients with medical conditions requiring the use of systemic modifiers of bone metabolism or other assisted drug therapy during the last 6 months before the study were excluded. Clinical and radiographic examinations, thermal and electric pulp sensibility tests, and palpation and percussion tests were performed to detect the presence of caries and/or pulpal/periapical pathologies and establish a diagnosis (14). An AP lesion (ie, periapical lesion) was characterized radiographically as a rarefaction lesion with the disappearance of the periodontal ligament space and discontinuity of the lamina dura (15). The presence of periapical lesions

was evaluated by 2 examiners according to the scoring system proposed by Orstavik et al (16). Individuals were grouped into "cases" or "controls" based on their clinical diagnosis, and the inclusion criteria were defined as follows: (1) cases (n = 195) were individuals presenting deep carious lesions (involving at least two thirds of the dentin depth) and an AP lesion (≥3 mm in diameter), and (2) controls (n = 189) were individuals presenting deep carious lesions (involving at least two thirds of the dentin depth) and normal apical tissues (no AP).

Selection of Single Nucleotide Polymorphisms and Genotyping. Because hypertension was the CVD-related factor yielding significant association with endodontic pathologies in the epidemiologic approach of this study, we selected to investigate the genetic association between hypertension genes and AP. Single nucleotide polymorphisms (SNPs) in genes significantly associated in previous genome-wide association studies of hypertension were genotyped in our case-control data set (6, 15). Details of the studied genes and polymorphisms are presented in Table 1.

Genotyping was performed using Taqman (Life Technologies, Foster City, CA) chemistry in a real-time polymerase chain reaction assay (17). Reactions were performed in a 5-μL final volume in a ViiA7 Sequence Detection System (Applied Biosystems, Foster City, CA). For quality control, a nontemplate control (water instead of DNA) was used as the negative control, and a DNA sample of a known genotype was used as the positive control in genotyping reactions. Genotype calls were performed automatically using EDS v.1.2.3 software (Applied Biosystems).

Data Analysis. Data analysis for the epidemiologic association study was performed using chi-square tests as implemented in an SPSS statistical software package (SPSS Inc, Chicago, IL). Analyses were performed pooled for all CVDs or stratified by the number of individuals in each of the categories (CVD+ Endo+, CVD+ Endo−, CVD− Endo+, and CVD− Endo−). P values ≤.05 were used to indicate statistical significance.

Data analysis for the genetic association study was performed using the chi-square and Fisher exact tests as implemented in PLINK (18). The Hardy-Weinberg equilibrium in cases and controls was assessed, and differences in allele and genotype frequencies between cases and controls were compared. The Bonferroni method was applied to correct for multiple testing with an alpha of 0.005.

Results

Epidemiologic Association Study of CVDs and Endodontic Pathologies

Of the 154,512 patients seen at UTSD for dental treatment from 1996–2016, 23,301 individuals were identified as having an endodontic procedure for the treatment of an endodontic pathology. Overall, the pooled analysis for all CVDs combined revealed significant associations between the presence of endodontic pathologies in general with CVD history (P = .0001). When stratifying these patients based on their CVD history (CVD+ Endo+, CVD+ Endo−, CVD− Endo+, and CVD− Endo−), significant associations were also found between the presence of endodontic pathologies and hypertension (P = .0004), myocardial infarction (P = .0004), cerebrovascular accident (P = .0001), pacemaker (P = .005), congestive heart failure (P = .001), heart block (P = .008), deep vein thrombosis (P = .004), and history of cardiac surgery (P = .0001). Modest association was found for heart murmur and atrial fibrillation (P = .04). No associations were found for the remaining adverse cardiovascular events (rheumatic fever, mitral valve prolapse, chest pain, angina, irregular heartbeat, palpitations, heart valve disease, infective endocarditis, and cardiac arrhythmia) (Table 2 and Fig. 1).

Using the AllScripts medical record database merged to the dental records, we identified 10,869 patients who had a self-reported history of endodontic pathology, whereas 2292 patients had a medical diagnosis of CVD. Of these, only 98 patients were identified as having a simultaneous medical diagnosis of CVD and a history of endodontic pathology and/or treatment. Of the remaining patients, 2194 patients with CVD diagnoses did not have any information on dental history in their medical records, whereas 10,771 patients with a self-reported history of endodontic pathology did not have any information on individual or family history of CVD (data not shown).

Genetic Association Analysis

No evidence of deviation from Hardy-Weinberg equilibrium was detected for any of the tested polymorphisms (data not shown). Of the 10 hypertension-associated SNPs tested, we found a trend toward a positive association for an SNP in the *KCNK3* (potassium 2 pore domain channel subfamily K-member 3) gene (P_{trend} = 0.05). Individuals who have 1 or 2 copies of the allele C (ie, presenting with CC or CT genotypes) at the SNP rs1276988 may be at increased risk for hypertension (Table 3). The associated SNP rs1276988 is located at 2 kb upstream of the gene promoter and may have potential regulatory function on gene expression.

Discussion

In this study, we performed epidemiologic and genetic association studies to investigate the potential association between endodontic pathology and CVDs. First, we queried the dental and medical records of >2 million patients using a dental school–based and a

TABLE 1. Details of Single Nucleotide Polymorphisms (SNPs) Investigated

Gene	SNP Identification no.	Chromosome*	Base position*	Alleles*†	SNP location*	MAF CEU*‡
PDE3A	rs12579720	12	20020830	**C**/G	Intron	0.26 (C)
TWIST1	rs2107595	7	19009765	**G**/A	Upstream	0.16 (A)
SH3TC2	rs9687065	5	149011577	**A**/G	Intron	0.18 (G)
LRRC10B	rs751984	11	61510774	**C**/T	3′ untranslated region	0.14 (C)
KCNK3	rs1275988	2	26691496	T/**C**	Upstream	0.40 (C)
OSR1	rs1344653	2	19531084	**G**/A	Downstream	0.47 (G)
ITGA11	rs1563894	15	68343437	G/**A**	Intron	0.23 (G)
TBX2	rs2240736	17	61408032	T/C	Intron	0.25 (C)
VLDLR	rs872256	9	2496480	**A**/T	Intron	0.28 (T)
CRIP3	rs1563788	6	43340625	**C**/T	Intron	0.29 (T)

*According to the National Center for Biotechnology GRCh38.p7 assembly.

†Ancestral allele in bold (reported on the forward strand).

‡Minor allele frequency in the European white population.

TABLE 2. The Number of Individuals with Cardiovascular Diseases (CVDs) and Endodontic Procedures from 1996 to 2016 (BigMouth Dental Data Repository)

CVD	Number of individuals				*P* value*
	CVD+ Endo+	CVD+ Endo−	CVD− Endo+	CVD− Endo−	
Hypertension	2805	10,544	7965	26,002	**.0004**
Rheumatic fever	64	240	10,201	34,897	.52
Heart murmur	358	1375	9988	33,990	**.04**
Mitral valve prolapse	222	684	10,073	34,513	.10
Myocardial infarction	223	986	10,098	34,360	**.0004**
Cerebrovascular accident	204	1036	10,169	34,814	**.0001**
Pacemaker	91	428	10,182	34,731	**.005**
Infective endocarditis	31	83	9448	31,647	.28
Coronary artery disease	268	1020	9252	30,852	.05
Congestive heart failure	108	625	9399	31,239	**.001**
Atrial fibrillation	133	541	9378	31,307	**.04**
Heart block	68	323	9435	31,507	**.008**
Cardiac arrhythmia	195	749	9336	31,117	.08
Deep vein thrombosis	50	259	9431	31,521	**.004**
Cardiac surgery	85	467	1669	5815	**.0001**
Chest pain	46	212	1703	6070	.11
Angina	33	141	1714	6135	.36
Irregular heartbeat	87	365	1663	5919	.18
Palpitations	55	185	1694	6091	.67
Heart valve disease	33	121	1716	6156	1
Blood clots	19	111	1729	6169	.05
All CVDs combined	5178	20,495	146,243	494,852	**.0001**

CVD+ Endo+, patients with a self-reported or documented diagnosis of CVD and a history of endodontic pathology and treatment; CVD+ Endo−, patients with a self-reported or documented diagnosis of CVD and no history of endodontic pathology or treatment; CVD− Endo+, patients with no history of CVD and a positive history of endodontic pathology and treatment; CVD− Endo−, patients with no CVD or endodontic pathology and treatment (universal controls).

*Chi-square test, $P \leq .05$ indicates significant differences between groups (shown in bold font).

hospital-based patient electronic health record system to obtain information on positive/negative history of endodontic pathologies and CVDs. Overall, our results confirm previous findings of positive association between endodontic pathology and CVDs or adverse cardiovascular events (3, 5, 12). Similar to other studies, we found significant associations between endodontic pathology with coronary artery disease and myocardial infarction (3, 12, 19, 20). Additionally, a significant association was found between the

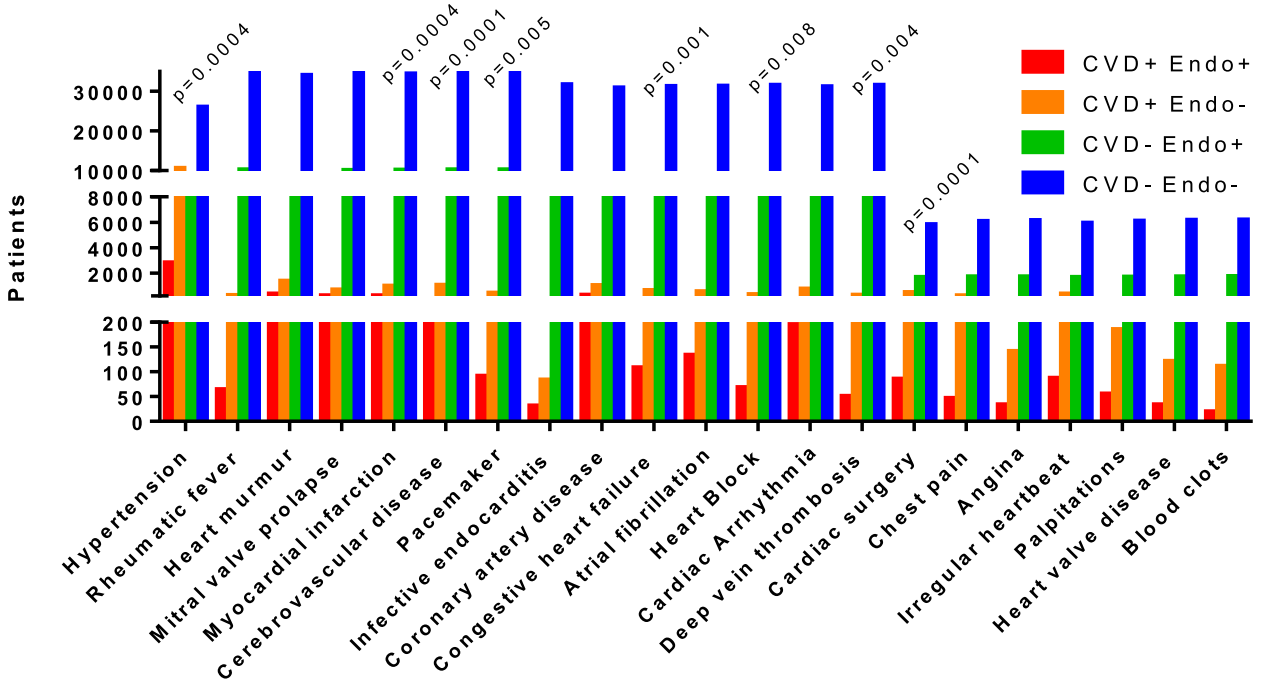

Figure 1. The number of patients stratified by a history of CVD and endodontic treatment (BigMouth Dental Data Repository). CVD+ Endo+ indicates patients with self-reported or documented diagnosis of CVD and a history of endodontic pathology and treatment, CVD+ Endo− indicates patients with self-reported or documented diagnosis of CVD and no history of endodontic pathology or treatment, CVD− Endo+ indicates patients with no history of CVD and a positive history of endodontic pathology and treatment; and CVD− Endo− indicates patients with no CVD or endodontic pathology and treatment (universal controls).

TABLE 3. Allelic and Genotypic Association Results for the Tested Polymorphisms

Gene	SNP Identification no.*	MAF (case)	MAF (control)	Alleles	Frequency cases	Frequency controls	*P* value†
PDE3A	rs12579720	0.35 (C)	0.40 (C)	CC/CG/GG	27/72/73	22/81/71	.59
				C/G	126/218	125/223	.85
				CC + CG vs GG	99/73	103/71	.76
				CC vs CG + GG	27/145	22/152	.41
TWIST1	rs2107595	0.20 (A)	0.21 (A)	AA/AG/GG	8/53/101	5/58/111	.62
				A/G	69/255	68/280	.57
				AA + AG vs GG	61/101	63/111	.78
				AA vs AG + GG	8/154	5/169	.33
SH3TC2	rs9687065	0.20 (G)	0.19 (G)	GG/GA/AA	8/41/104	8/36/98	.95
				G/A	57/249	52/232	.92
				GG + GA vs AA	49/104	44/98	.85
				GG vs GA + AA	8/145	8/134	.88
LRRC10 B	rs751984	0.23 (C)	0.20 (C)	CC/CT/TT	9/68/106	9/61/113	.74
				C/T	86/280	79/287	.54
				CC + CT vs TT	77/106	70/113	.45
				CC vs CT + TT	9/174	9/174	1
KCNK3	rs1275988	0.41 (C)	0.47 (C)	CC/CT/TT	46/68/79	48/80/59	.15
				C/T	160/226	176/198	.12
				CC + CT vs TT	114/79	128/59	**.05**
				CC vs CT + TT	46/147	48/139	.68
OSR1	rs1344653	0.40 (G)	0.35 (G)	GG/GA/AA	30/93/64	25/63/64	.27
				G/A	153/221	113/191	.32
				GG + GA vs AA	123/64	88/64	.14
				GG vs GA + AA	30/157	25/127	.92
ITGA11	rs1563894	0.22 (G)	0.19 (G)	GG/GA/AA	9/57/103	10/39/94	.43
				G/A	75/263	59/227	.64
				GG + GA vs AA	66/103	49/94	.38
				GG vs GA + AA	9/160	10/133	.54
TBX2	rs2240736	0.46 (C)	0.47 (C)	CC/CT/TT	47/76/58	37/74/60	.62
				C/T	170/192	148/194	.33
				CC + CT vs TT	123/58	111/60	.54
				CC vs CT + TT	47/134	37/134	.34
VLDLR	rs872256	0.43 (T)	0.46 (T)	TT/TA/AA	38/88/66	34/85/67	.91
				T/A	164/220	153/219	.66
				TT + TA vs AA	126/66	119/67	.74
				TT vs TA + AA	38/154	34/152	.71
CRIP3	rs1563788	0.40 (T)	0.48 (T)	TT/TC/CC	34/89/71	40/83/65	.65
				T/C	157/231	163/213	.42
				TT + TC vs CC	123/71	123/65	.68
				TT vs TC + CC	34/160	40/148	.35

MAF, minor allele frequency.

*According to the National Center for Biotechnology GRCh38.p7 assembly.

†Fisher exact test, significant if $P \leq .05$ (bold).

presence of endodontic pathologies with hypertension. To assess if common underlying mechanisms (eg, the presence of genetic variations of the host) could contribute to the potential association between AP and hypertension, we also performed a case-control association study to assess if polymorphisms in hypertension-associated genes were associated with AP, with the underlying hypothesis that common genetic variants could contribute to AP and predispose to CVD. These analyses revealed a trend toward an association between the *KCNK3* gene, a 2-pore domain leak potassium channel strongly implicated in increased susceptibility to hypertension (21–23).

AP represents a manifestation of the host defense in response to an endodontic infection (11). It is a process of inflammation and destruction of the apical periodontal structures that results from active confrontation between microbial pathogens in the dental pulp and the host immune response at the junction between the infected radicular pulp and the periodontal ligament (20, 24). In recent years, a number of observational studies have assessed the association between CVDs and endodontic disease, and both positive and negative results have been reported (4, 7, 17). The majority of the studies reporting positive associations showed that AP lesions are more frequent and more severe in patients with CVD than patients without CVD (16, 25). Regarding the types of CVDs most frequently found in association with endodontic pathologies and AP, coronary heart disease has been extensively studied with significant associations reported in a US population, whereas no associations were found in a Swedish population (19, 26). In a large population-based study from Finland, the presence of a widened periapical space (apical rarefactions/lesions) was strongly associated with stable coronary artery disease and acute coronary syndrome, concomitantly with higher subgingival levels of *Porphyromonas endodontalis* and serum immunoglobulin G (25). Furthermore, in patients who had suffered a myocardial infarction, a more detrimental oral health state that included a higher number of periapical lesions was also noted (20). In addition to these and other individual studies, recent systematic reviews and meta-analyses have supported a plausible relationship between CVD and AP although the quality of the existing evidence has been considerate low to moderate (3, 5, 7, 27). Discrepancies between studies are likely caused by heterogeneity among the studies including differences in sample sizes and populations studied, study design, and outcome parameters analyzed, which in turn might affect the results.

In the present study, the most significant association observed was between hypertension and endodontic pathology. In a previous study, no correlations between periapical status and hypertension were found albeit the sample size was limited to 40 individuals with hypertension and 51 control individuals (28). Later on, these same authors conducted a similar study using the records of 100 hypertensive patients (50 smokers and 50 nonsmokers) and found a higher prevalence of AP and root canal treatment in smokers when compared with nonsmokers (29). Although AP and hypertension are common conditions in the general population, the co-occurrence of both conditions in the same individuals warrants additional investigations and highlights that additional risk factors, genetic and environmental, may play a role in the mechanisms underlying AP and hypertension. We also identified additional positive associations between the presence of endodontic pathologies and myocardial infarction, cerebrovascular accident, pacemaker, congestive heart failure, heart block, cardiac arrhythmia, deep vein thrombosis, and cardiac surgery ($P < .008$). Nonetheless, for some CVDs (or conditions such as rheumatic fever, use of pacemaker, infective endocarditis, heart block, cardiac arrhythmia, deep vein thrombosis, cardiac surgery, chest pain, angina, irregular heartbeat, palpitations, heart valve disease, and a history of blood clot), our sample size may have been too small to detect associations.

Hypertension is a common condition and the biggest single contributor to disease and mortality worldwide. It is a complex trait resulting from the interaction between genetic and environmental factors (30). Hypertension is also a known major risk factor for CVD as well as cerebrovascular and renal disease (21). Genome-wide association studies have identified polymorphisms in a variety of disease-relevant genes as significantly associated with hypertension (21). In our genetic association analyses of AP with known hypertension-associated polymorphisms, a trend toward association was found between AP and a polymorphism in the *KCNK3* gene. *KCNK3* is a protein-coding gene encoding a member of the superfamily of potassium channel proteins that contain 2 pore-forming P domains (31). The encoded protein is highly permeable to outward flow of ions and therefore sensitive to changes in extracellular pH (32). *KCNK3* is widely expressed in human tissues; loss-of-function mutations in this gene cause both heritable and idiopathic pulmonary arterial hypertension, a rare disorder characterized by high blood pressure in the pulmonary arteries that can lead to elevated pulmonary arterial pressure, right ventricular failure, and death (22). The investigated *KCNK3* SNP rs1275988, located in the gene promoter with potential effects on gene transcription, was reported to be significantly associated with increased arterial pressure and body mass index, particularly at a later stage of life concomitant with a decline in compensatory mechanisms (23). Although the population used for the genetic association study had a limited sample size of 384 individuals, thus precluding extrapolation of the results to the general population, the close to nominal significance warrants additional investigations. Recently, studies have highlighted the possibility of genetic variation and genetic interaction effects underlying common disease risks such as coronary artery disease, stroke, and type 2 diabetes (33). Similarly, studies of chronic periodontitis genes in humans and mouse models have suggested the involvement of numerous genes whose roles in other systemic diseases are more established (34). Future genetic studies of oral diseases and conditions may also uncover important molecular factors and interactions that may elucidate potential associations between oral and overall health conditions.

Importantly, while the associations found between AP and CVDs using the epidemiologic approach are significant and reflect a large sample size (hence increasing study power and confidence in our findings), these associations cannot be directly related to causation because multiple factors underlie both conditions. The limitations of this study include the retrospective design and the use of self-reported information in the dental electronic records, the scarce availability of dental history information on the medical records, and an independent cohort of limited sample size for the genetic association study. Like many other studies of retrospective nature, one cannot discard the possibility of potential confounders in the analyses. On the other hand, the integration of dental and medical electronic health records holds a promising approach for the identification of dental patients at risk for adverse systemic conditions. Adding genetic data to clinical data contained in health records will be of significant value in further determining if endodontic pathologies may predispose individuals to CVDs and/or other diseases.

Conclusions

The results of this study support previous findings of a positive association between CVDs and CVD-related factors (eg, hypertension) with endodontic pathologies while highlighting the need for improvements toward the integration of medical and dental electronic health record databases for optimal patient care. Genetic studies represent valuable tools to help elucidate if potential etiologic overlap exists between endodontic pathologies and CVDs or other systemic conditions. Of note, the associations reported herein do not reflect a cause-effect relationship; however, individuals with endodontic pathologies may accumulate additional risk factors that later predispose to hypertension and/or other CVDs.

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