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Review

Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature

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ABSTRACT

Cardiovascular diseases (CVD) have a complex etiology determined by risk factors, which are in turn associated to a strong genetic component and to environmental factors. In the biological background for the development of CVD, low-grade chronic inflammation plays a role as a pathogenetic determinant of atherosclerosis.

Dental infections have been associated with CVD. Periodontal disease is a chronic infection of the supporting tissues of the tooth that can lead to teeth loss. In recent years, a number of reports have demonstrated the possible relationship between periodontal disease and CVD. Apical periodontitis, on the other hand, is the late consequence of an endodontic infection, which is caused by the persistence of coronal caries and involves the root canal system of the tooth. Most of the time, it is a chronic infection. Some studies have found a correlation between a “composite status” of oral health (eg. caries, tooth loss, periodontal disease) and CVD, but only a few of them have addressed the association between apical periodontitis and CVD.

This “state of the art” paper represents the first stage of an incoming study on the relationship between chronic endodontic infection and CVD.

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1. Introduction

Atherosclerosis is a multifactorial disease which represents the most common cause of coronary heart disease (CHD). A strong genetic component is implicated in the genesis of atherosclerosis in association with several anatomical, physiological, and behavioral risk factors, including changes in serum lipid profile, smoking, arterial hypertension, diabetes, obesity, sedentary lifestyle, age, and gender. Many cell types, including platelets, endothelial cells, activated monocytes, macrophages, and smooth muscle cells, are involved in the formation of atherosclerotic plaques [1]. CHD acute events are usually precipitated by thrombosis occurring at the site of atherosclerotic lesion disruption. Some CV risk markers, such as low-grade chronic inflammation, play a role in the pathogenesis of the disease [2,3]. Recently, bacterial and viral organisms involved in chronic inflammatory processes have also been examined [4].

The hypothesis that infection and inflammation may actively be involved in atherogenesis is supported by an increasing number of reports [5].

In recent years, two patterns of association have emerged: i. a connection between a chronic low-grade inflammation and/or infection and the slow progression of atherosclerosis and ii. a relationship between an acute systemic inflammatory response and a temporarily increased risk of severe CV events. A renewed interest in the role of infections is currently being developed, with regard to various infectious pathogens, such as *Helicobacter pylori* and *Chlamydia pneumoniae* [6–8].

Dental infections may represent a favorable background for atherosclerosis and CVD [9,10].

Two are the landmark dental infectious diseases: periodontal disease and apical periodontitis. Periodontal diseases are those diseases that affect one or more of the periodontal tissues supporting the tooth (alveolar bone, periodontal ligament, cementum, gingiva) [11]. Periodontal disease is divided into two main categories: 1. Periodontitis: an inflammatory disease of the supporting tissue of the teeth caused by groups of specific microorganisms, resulting in the progressive destruction of the periodontal ligament and the alveolar bone, with pocket formation, recession, or both; 2. Gingivitis: a dental plaque-induced gingival disease and non-plaque induced gingival disease. Periodontal infection is initiated by specific invasive oral pathogens (aerobic and anaerobic bacteria) that colonize dental plaque biofilms on the root surface of the tooth. Biofilms, in general, have an organized structure, composed of bacteria in a matrix of salivary glycoproteins and extracellular polysaccharides. Local and

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systemic factors can also modulate an individual's susceptibility to apical periodontitis.

In general, clinical signs of gingivitis are characterized by the presence of any of the following: redness and sponginess of the gingival tissue, bleeding on provocation, changes on contour and presence of calculus or plaque with no radiographic evidence of crestal bone loss.

Clinical signs that suggest the presence of periodontal pockets include a bluish red, thickened marginal gingiva; a bluish red, vertical zone from the gingival margin to the alveolar mucosa; gingival bleeding and suppuration; tooth mobility. The symptoms include localized pain or pain "deep in the bone". The only reliable method of locating periodontal pockets and determining their extent is careful probing of the gingival margin along each tooth surface.

The clinical feature that distinguishes periodontitis from gingivitis is the presence of clinically detectable tooth attachment loss (Fig. 1). Treatment of periodontal diseases are based on: extraction of hopeless teeth; oral hygiene, removal of calculus and root planning; surgical therapy and maintenance [12].

Apical periodontitis is caused by bacteria (in association with viruses and fungi) residing inside the root canal/s (endodontium) of the diseased teeth, and organized in a biofilm, as a consequence of pulpal infection, which is usually the ultimate result of a deep carious lesion.

The pathogenesis of apical periodontitis is due to a non specific inflammatory process and a specific immunologic reaction of the host in the periapical tissues: (cementum of the root, periodontal ligament and alveolar bone) in response to the infection coming from the endodontium. The establishment of this response is believed to be an attempt for the body to prevent the diffusion of the infection into the bone. With time, Apical Periodontitis causes the re-absorption of the periapical bone, its substitution with the inflammatory tissue, and the formation of a radiolucent lesion (periapical lesion). Clinical signs and symptoms associated with the different stages of apical periodontitis are represented by soft tissues swelling (periapical abscess), presence of sinus tract, pain to percussion of the tooth and to palpation of the periapical area. Yet apical periodontitis is usually a chronic infection and, in most cases, remains asymptomatic. Therefore, it is often diagnosed by the radiographic observation of a radiolucent area around the root of the affected tooth (Fig. 2). Over time, apical periodontitis may suffer an acute exacerbation and become symptomatic. Apical periodontitis can be treated by the instrumentation, disinfection and obturation of the radicular canal of the involved tooth (endodontic treatment). Unfortunately, the disease can persist or recur after treatment is completed. Then, periapical surgery or the extraction of the tooth should be considered as a final treatment [13].

Despite being different as to etiology and pathogenesis, periodontal disease and apical periodontitis show some similarities. They share a common microbiota (often Gram-negative anaerobic bacteria)

[14,15] and are both accompanied by elevated systemic cytokine levels [16,17].

Three possible metastatic pathways can be considered responsible for the consequences of oral infections on systemic diseases such as CVD:

1. metastatic spread of infection from the oral cavity, resulting from a transient bacteremia;
2. metastatic injury by circulating oral microbial toxins;
3. metastatic inflammation arising from an immune response to oral microorganisms [18].

In recent years, a number of reports have discussed the existence of a possible association between periodontal diseases and CVD, and have shown that these two diseases are associated in an independent way with the "classic" coronary risk factors [19]. Conversely, there are only few studies that have addressed the association between apical periodontitis and CVD.

The purpose of the present paper is to do a review of the literature on the "state of the art" of the relationship between CVD and both periodontal disease and apical periodontitis.

1.1. Search strategy

A MEDLINE search was conducted using the MeSH terms "cardiovascular disease (CVD)" or "atherosclerosis". A second search used the terms "infectious" and the final search combined the results of the first 2 searches and added the terms "periodontal disease" OR "apical periodontitis." Articles identified in this manner were retrieved and their reference lists searched for additional relevant articles. The search was limited to English-language publications, but no other restrictions were applied.

2. Periodontal disease and CVD

Periodontal disease is one of the most common oral infections, which often affects young people: in 1995 Bochniak et al. [20] reported that only 18.5% of the teenage population examined in their study had shown a healthy periodontal tissue. In the group aged between 35 and 44 years, the frequency of healthy periodontal tissue was reduced to 6.3%. Because of its high incidence, they concluded that periodontal disease could be counted among social diseases.

Aerobic and anaerobic bacteria are the microorganisms found within the gingival pockets in periodontal disease. *Streptococcus sp.* and *Actinomyces sp.* are included among the first, while *Porphyromonas gingivalis*, *Prevotella intermedia*, *Peptostreptococcus sp.*, *Fusobacterium sp.*, *Treponema denticola*, *Eikenella corrodens*, and *Actinobacillus actinomycetemcomitans* are included among the latter [21,22]. The chronic activity of bacteria, their toxins, enzymes and



Fig. 1. Panoramic radiograph showing a case of diffuse periodontal disease: some teeth are missing and the alveolar bone is reduced both vertically and horizontally in many sites.



Fig. 2. Two examples of periapical bone lesions of endodontic origin (arrowed).

metabolites, followed by a host immune response, lead to a progressive failure of periodontal attachment and premature loss of teeth.

Furthermore, clinical procedures performed by dentists on the teeth and periodontium, along with the daily brushing made by patients, produce a transient bacteriemia, which may cause a secondary infection in a distant tissue or organ, including arteries. A number of epidemiologic studies have considered the possible correlation between the presence of periodontal disease and the incidence of CVD.

In 1989, Mattila et al. published a paper indicating the relationship between periodontal infections and atherosclerosis [23]. They evaluated the panoramic radiographs of 100 Finnish men and women who had had a myocardial infarction and compared them with the presence and number of teeth, mouth caries, gingival and bony pockets. The conclusion was that the dental health of these patients was significantly worse than that of controls (102 subjects). The logistic regression analysis recognized periodontal disease as an independent predictor of myocardial infarction risk.

De Stefano et al. [19] realized the first prospective cohort study, based on a 14-year follow-up of 1000 subjects. The authors found a 25% increase in CHD in the patients who were clinically diagnosed with periodontal disease. This association was more pronounced in men under 50 years of age. In addition, the total mortality was higher in patients with periodontal disease and CHD than in those with CHD and healthy periodontium. That study also considered the possibility that this association could only be accidental, resulting from the combination of poor hygiene and lack of a health-conscious behavior often observed in patients with CVD.

Beck et al., by using data from the Normative Aging Study (NAS) and Dental Longitudinal Study (DLS), which lasted over 30 years, studied the co-presence of tooth loss and CVD [24]. They found a positive correlation between the horizontal alveolar bone loss in panoramic radiographs (indicative of periodontal disease) and the incidence of CHD. In that study, bone loss exceeding 40% was associated with a threefold increase in CHD mortality. The authors suggested that the effect of periodontal disease on systemic health is more relevant than that of smoking and other environmental CV risk factors.

The epidemiological investigation of Joshipura et al. [25] evaluated CHD incidence in relation to periodontal disease and to the number of teeth present in over 70,000 healthcare professionals. That study did not find any overall associations between periodontal disease and

CHD. Nevertheless, tooth loss was well correlated with increased coronary risk, especially among subjects with a positive periodontal disease history. As healthcare professionals were monitored by means of mailed questionnaires about their oral conditions, the results of that study could not be considered sufficiently reliable.

In 1997, Grau et al. [26] compared the clinical and radiographic dental status of 166 patients with acute ischemic stroke history with that of 166 healthy controls. That study used a total dental index (TDI) reflecting caries, periapical lesions, periodontal disease and other dental lesions, and considered the low social status along with traditional risk factors for cerebrovascular ischemia. The poor dental status, as defined by TDI, resulted associated with an increased risk of ischemic cerebrovascular events. On the other hand, this correlation became less significant after the adjustment for the other CVD risk factors.

Jansson et al. [27] investigated the relationship between periodontal health and fatal CVD in 1393 Swedish subjects who had already been investigated some 30 years earlier in the context of an epidemiological surveillance on dental health. Mortality rate and causes of death in the sample were registered according to death certificates. The interactional effect between dental plaque and oral health score (a sum of scores for number of missing teeth, apical lesions, caries lesions and marginal bone loss), adjusted for confounding variables, was significantly correlated to fatal coronary events. In this study, dental health proved to be a reliable risk marker for coronary death, especially in combination with smoking.

A second group of studies has focused on the possible mechanisms through which periodontal disease may contribute to trigger CVD pathogenesis. These atherogenic mechanisms are basically due to: 1. the induction of platelet aggregation caused by certain oral bacteria, 2. the release of large amounts of pro-inflammatory mediators, which is the consequence of a strong host response to oral bacterial stimulus and 3. the effect on the endothelium of bacterial and inflammatory products concentrated in the serum as a result of bacteremia.

Herzberg et al. [28] evaluated the effects of oral flora on CV function in rabbits by injecting platelet-aggregating doses of 4 to 40×10^9 cells of *S. sanguis*. They found that this infusion causes dose-dependent changes in blood pressure, heart rate, electrocardiogram and cardiac contractility. These changes were found consistent with the occurrence of myocardial infarction. A thrombogenic activity by *S. sanguis* could, therefore, justify the additional contribution of periodontal disease to CVD.

Deshpande et al. [29], by using an antibiotic protection assay and the transmission and scanning electron microscopy, observed the invasion of bovine and human aortic endothelial cells by *Porphyromonas gingivalis*. They hypothesized that this invasion could be a strategy developed by pathogens to avoid host immune response.

Haraszthy et al. [30] examined 50 human specimens obtained during carotid endarterectomy for the presence of *Chlamydia pneumoniae*, human *Cytomegalovirus* (HCMV), and bacterial 16S rRNA using PCR assays. Thirty-eight percent were positive for HCMV and 18% for *Chlamydia pneumoniae*. PCR assays for bacterial 16S rRNA also indicated the presence of bacteria in 72% of the surgical samples. Subsequent hybridization of the bacterial 16S rRNA positive specimens with species-specific oligonucleotide probes revealed that 44% of the 50 atheromas were positive for at least one of the target periodontal pathogens (*B. forsythus*, 30%; *P. gingivalis*, 26%; *A. actinomycetemcomitans*, 18%; *P. intermedia*, 14%). Fifty-nine percent of periodontal pathogen-positive surgical specimens were positive for 2 or more of the target species. The authors concluded that periodontal pathogens, present in atherosclerotic plaques, may influence the development and progression of atherosclerosis.

Kuramitsu et al. [31] demonstrated that *P. gingivalis* shows several properties that could play a role in CVD as mediators of LDL oxidation, foam cell formation, and atherosclerotic plaque rupture. In the Atherosclerosis Risk in Communities Study (ARIC), which involved 6000 patients, Beck et al. [32] reported an association between periodontal disease severity and the intima-media thickness of carotid artery. Subsequent analysis of data collected over a period of 25–30 years in NAS and DLS studies indicated that periodontal disease was a significant risk predictor for peripheral arterial disease. The study by Persson et al. [33] demonstrated an association between alveolar bone loss and increase in calcium deposit within the wall of the internal carotid artery.

Samples of aorta were taken from patients undergoing open-heart surgery to investigate the presence of periodontal pathogens by PCR and subsequent hybridization [34]. Bacterial DNA was found in 23 of 26 (88.5%) samples, in most cases only in concentrations around the detection limit. Four samples were clearly positive for *Porphyromonas gingivalis*. The authors emphasized the possible connection between periodontal pathogens entering the CV system and CVD.

D'Aiuto et al. [35] examined the outcomes of periodontal therapy in terms of changes in C-reactive protein (CRP)-associated CV risk. Serum inflammatory responses [interleukin-6 (IL-6) and CRP] were monitored 2 and 6 months after non-surgical periodontal treatment in 94 healthy subjects suffering from severe periodontitis. At 6-month control, patients who had a better oral response to periodontal therapy were more likely to have decreased their inflammatory risk category after correcting for age, gender, ethnicity and cigarette smoking. Moreover, a significant decrease in number of subjects with a medium and high CRP-associated risk was observed. The authors concluded that “periodontitis may add to the systemic inflammatory burden of the individual and may result in increased levels of CV risk based on serum CRP concentrations”. In 2005, Cavrini et al. [36] reported two cases of patients affected by hypertension and atherosclerotic lesions. *Porphyromonas gingivalis* and *Treponema denticola* were identified by PCR and FISH in atheromatous plaques in both patients. Obviously, those 2 cases alone do not allow a definitive conclusion on the correlation between periodontal disease and atherosclerosis.

3. Conclusions on the correlation between periodontal disease and CVD

A series of epidemiological studies [19,20,23–27] has suggested that periodontal disease may contribute to the genesis of CVD; observational studies [28–36], for their part, have addressed the mechanisms by which periodontal disease might influence the development of CVD.

This association has been hypothesized to be attributable to a common inflammatory response trait, which exposes individuals to the development of both periodontal disease and atherosclerosis. Furthermore, periodontal disease is believed to provide a “biological burden” of inflammatory cytokines, which promote atherosclerosis and thrombotic events.

However, it should be noted that epidemiologic research cannot identify the cause: periodontal disease may occur together with some forms of CVD or represent an oral manifestation of the same disease. Future research should be aimed at determining whether periodontal disease can directly damage the CV system.

4. Apical periodontitis and CVD

Apical periodontitis is a sequel to endodontic infection and develops as the host response to microbial infection that comes from the root canal system of the affected tooth [37].

Endodontic infection that leads to apical periodontitis is caused by a mixture of oral bacterial species also found in dental plaque, dominated by obligate anaerobes (most frequently *Peptostreptococcus*, *Eubacterium*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Streptococcus*) [38].

Only a few studies have investigated the possible correlation between pulpal inflammation and/or apical periodontitis and CVD. An association has been noted between apical periodontitis and stroke, as well as between a “composite status of oral health” (caries, periapical lesions, number of endodontically treated teeth) and CVD [39,40].

This section can be further divided into two parts 1. the consequences of dental procedures performed to treat endodontic infections on systemic diseases, and 2. the association of apical periodontitis and CVD.

4.1. Consequences of dental procedures performed to treat endodontic infections on systemic diseases

In 1994, Debelian [41] observed that human periodontal and endodontic infections were associated with complex microfloras: approximately 350 bacterial species were identified in marginal periodontitis and other 150 were found in apical periodontitis. Both groups of bacteria mainly included anaerobic pathogens, among which gram-negative rods were the most frequently isolated. The proximity to the bloodstream of microflora present in the root canal and periapical tissues can cause a transient bacteremia during clinical dental procedures (e.g., tooth extraction, periodontal and endodontic treatments). Normally, microorganisms penetrated into the bloodstream are eliminated by the host within minutes. However, it is known that in patients with valvular heart disease or vascular diseases, a transient bacteremia may lead to infective endocarditis and myocardial or cerebral infarction. Other forms of systemic disease, such as brain abscesses, hematological and implant infections, have also been correlated with oral microorganisms [42].

It is thus evident that both endodontic surgical procedures and non-surgical instrumentation of root canals during endodontic treatments can produce a transient bacteremia. One study on bacteremia in conjunction with endodontic therapy was conducted on blood samples taken from the patients during and 10 minutes after root canal instrumentation [43]. Bacteremia occurred in 54% of patients when teeth were deliberately instrumented 2 mm beyond the apical foramen and in 31% of patients when instrumentation ended inside the root canal 1 mm short of the apical foramen. Biochemical tests and antibiograms showed that microorganisms isolated from both the tooth root canal and the bloodstream had the same profiles in each patient. In a subsequent report, bacteremia with predominance of anaerobes was detected in 30% of patients following endodontic treatment [44]. We must bear in mind that a tooth extraction causes bacteremia in 100% of times [45] and that the

risk to acquire bacterial endocarditis from a dental treatment ranges from 1 / 100,000 in patients with previous endocarditis to 1/a million in those with mitral valve prolapse and regurgitation [46].

4.2. Apical periodontitis (endodontic infection) and CHD

In 2003, Frisk et al. [47] published the first cross-sectional study that examined the possible association between various components of endodontic disease and CHD. A connection between dental infections, probable cause of vascular abnormalities, and the genesis of atherosclerosis was hypothesized. The study was conducted in Göteborg in 1992–93, on a representative sample of women (n = 1056) aged between 38 and 84 years. The dependent variable was CHD [i.e. angina pectoris and/or a history of myocardial infarction (n = 106)]. The independent variables were: number of root-filled teeth, number of teeth with periapical lesions (as radiolucencies seen in the radiographs), tooth loss, age, marital status, smoking, alcohol habits, waist/hip ratio, serum cholesterol and triglyceride concentrations, hypertension and diabetes. By using the multivariate logistic regression analysis, researchers could not prove that endodontic variables were predictive of CHD. Only age and tooth loss were significantly associated with CHD [OR = 1.07 (CI = 1.03–1.12) and OR = 2.70 (CI = 1.49–4.87), respectively]. The bivariate logistic regression analysis showed a significant association between endodontically treated teeth and CHD; conversely, the same analysis did not support any associations between periapical lesions and CHD.

In 2006, Caplan et al. [40] reported the results of the VA Dental Longitudinal Study, in which 708 participants (all males, mean age 47.4 years) were recruited. In accordance with the evidence that periodontal disease is more manifest in young male patients [20], the authors hypothesized that also young men with a greater number of endodontic lesions might be more prone to develop CHD. Patients underwent comprehensive medical and dental examinations (including panoramic radiographs) at baseline and every three years for up to 32 years (median 24 years). Cox regression models estimated the relationship between incident lesions of endodontic origin and time to CHD diagnosis. Thirty-five percent of all participants had at least 1 periapical lesion and 23.4% of them were subsequently diagnosed with CHD. Twenty-seven percent of participants aged ≤45 years and 41% of those aged >45 years had one or more periapical lesions. Among the subjects who were subsequently diagnosed with CHD, the youngest showed a greater number of apical lesions compared to older people. Among participants aged 40 years or younger, incident lesions of endodontic origin were significantly associated with time to CHD diagnosis, after adjustment for covariates of interest, with hazard ratios decreasing as age increased. Among participants aged >40 years, no statistically significant associations were observed.

Following these results, the authors [48] asserted that the “mechanisms linking endodontic disease to CHD risk might be similar to those hypothesized for the associations between periodontal disease and CHD, where a localized inflammatory response to bacterial infection leads to the release of cytokines into systemic circulation, with subsequent deleterious vascular effects” [39,48]. In accordance with the above assertion, the interdependence between CVD and endodontic infection could be demonstrated by the observation that also endodontic disease is produced by gram-negative anaerobes [49,50] and characterized by the release of cytokines [51,52] and high levels of inflammatory mediators [53,54]. Caplan et al. also explained that this association proves to be more effective among young people since, with time, older subjects may develop other characteristics more strongly associated with CHD pathogenesis. Alternatively, the explanation may lie in the “healthy survivor” phenomenon, meaning that older people tend to be healthier than other members of the same cohort who die before.

Using data from the Health Professionals Follow-Up Study (HPFS), with its large cohort of 34,683 participants, Joshipura et al. [55] evaluated the connection between pulpal inflammation and incidence of CHD. The hypothesis to be tested was that pulpal inflammation may lead to increased CHD risk. As an indicator of pulpal inflammation, the presence of one or more root canal therapy (RCT) was used. Participants were all male health professionals aged 40 to 75 years who had drawn every two years a mailed questionnaire concerning their health conditions. Individuals with prior CVD or diabetes were excluded. A significant correlation between RCT and CHD incidence was limited to the subgroup of dentists. Since the measure of pulpal inflammation was based on self-reported RCT, it is not known whether RCT were performed in response to a pulpal inflammation/infection. Moreover, the proportion of RCT related apical periodontitis is not known. One hypothesis for this outcome may be that dentists are less likely to submit themselves to root canal treatment if there is no diagnostic evidence of pulpal inflammation/infection. In accordance with some previous studies [26,27], the application of multivariate analysis to data from HPFS showed that dental caries were not associated with CHD and suggest a possible modest association between the latter and pulpal inflammation. These results could be explained as an actual lack of biologic interdependence, or as a failure of the questionnaire to distinguish from active caries and restorations, or by the fact that only deep caries may influence the patient's health status.

In a summary thesis from 2007 [58], Frisk mixed data from the above mentioned 2003 study [47] with the results of 2 epidemiological studies on apical periodontitis in the Swedish population [56,57]. The objectives of this thesis were to further clarify clinical and socio-economic risk factors for apical periodontitis and to reconsider, in a larger population, the possible association between apical periodontitis and CHD. In the Population Study of Women in Göteborg, participants aged 38–84 years were recruited for cross-sectional and longitudinal analysis of endodontic status over 24 years. A cross-sectional sample was used for exploring associations between apical periodontitis or socio-economic risk factors and CHD in multivariate logistic regression models. In the Population Study on Oral Health in Jönköping, random samples of women aged 20–70 years were used. Apical periodontitis was radiographically recorded and the root filling quality was assessed with respect to length and seal. Inadequate root filling quality was predictive of apical periodontitis with a 4.5 OR. On the other hand, the results did not reveal any significant associations between apical periodontitis and CHD nor between socio-economic risk factors and apical periodontitis.

In a recent study, Caplan et al. [59] evaluated the correlation between self-reported history of endodontic therapy (ET) and CHD prevalence. To that end, they used data derived from oral health questionnaires, medical evaluations and clinical dental examinations of 6,651 dentate participants in the Atherosclerosis Risk in Communities Study. Final multivariable regression models indicated that, among participants with 25 or more teeth, those who reported having undergone two or more ET showed a significantly higher prevalence of CHD than those reporting no history of ET. Among participants with 24 or fewer teeth, no significant differences in CHD prevalence were observed among groups, regardless of their ET history.

5. Conclusions on the correlation between apical periodontitis and CVD

While the deep connections between periodontal disease and CVD have been well documented by several studies, the potential CV consequences of apical periodontitis/endodontic disease remain largely unknown and controversial. The issue has been addressed only recently and has produced mixed results, with studies in favor of a positive correlation between apical periodontitis and coronary risk [40,59], and other negative [47,58] or inconclusive [55]. Unfortunately, the necessary

Table 1
List of the epidemiologic studies which investigated the association between Apical Periodontitis (AP) and Coronary Heart Disease (CHD).

Authors, year	Participants	Aim	Conclusions
Frisk et al. [47]	1056 women participants	Possible association between endodontic treatment or AP and CHD	By multivariate logistic regression: no association between endodontic variables and CHD. By bivariate logistic regression: association between endodontically treated teeth and CHD; no association between teeth with AP and CHD
Caplan et al. [40]	708 male participants in the VADLS ^a	Possible link between number of lesions of AP and CHD	Higher relationship between AP and development of CHD (especially in young age group)
Joshiyura et al. [55]	34,683 participants from HPFS ^b	Possible association between pulpal inflammation (endodontic treatment) and incidence of CHD	Strong association between a positive self-reported history of Endodontic Treatment incidence of CHD
Frisk [58]	3499 women participants from the PSWG ^c and random samples of dentate individuals (n 2066) aged 20–70 years from the PSOHJ ^d	Endodontic status in Swedish populations and possible association between AP and CHD	No significant association between AP and CHD and socio-economic risk factors and AP respectively.
Caplan [59]	6651 participants from the ARIC ^e	Possible association between endodontic disease (Endodontic Treatment) and CHD	Association of self-reported history of ET among participants with 25 or more teeth, with CHD

^a Veterans Affairs Dental Longitudinal Study.^b Health Professionals Follow-Up Study.^c Prospective Study of Women in Göteborg, Sweden.^d Population Study on Oral health in Jönköping, Sweden.^e Atherosclerosis Risk in Communities.

scientific rigorousness was not always applied for a better understanding of the relationship between the presence of periapical lesions and CV risk. In trials that have followed each other over time, weak surrogate parameters of risk have been used, several populations of different ages, difficult to compare, were studied and control groups have not been provided at any time.

Apical periodontitis is widely present in endodontically treated teeth and is often associated with a poor quality endodontic treatment [48]. Therefore, it is always more difficult to evaluate the “cumulative endodontic infectious burden” for average patients [40].

On the basis of the still equivocal suggestions of literature (Table 1) we should feel encouraged to better investigate this issue. A more precise understanding of the connection between endodontic infection and inflammation and CV risk would be of great interest not only from a scientific point of view but also from a public health perspective [42,59]. It is therefore extremely urgent to know whether apical periodontitis represents only the oral component of a systemic disease, or shares with it a common etiology. Only a more focused and rigorous scientific research can determine a definitive opinion on the relationship between endodontic disease and CVD. Therefore it would be important to use dental infection as an independent variable in future CVD research.

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