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Potential Association Between Apical Periodontitis and Cardiovascular Disease: A Narrative Review of Evidence and Clinical Implications

ABSTRACT

Apical periodontitis (AP) affects 52% of adults globally, yet its systemic cardiovascular implications remain understudied compared to periodontal disease. This narrative review synthesizes current evidence on the potential bidirectional association between apical periodontitis and cardiovascular disease (CVD), examining proposed mechanistic pathways and clinical implications. A comprehensive literature search was conducted using PubMed, Web of Science, and Scopus databases, including clinical studies, animal models, and mechanistic investigations. Epidemiological evidence suggests that patients with apical periodontitis have a 1.38-5.3 times higher risk of cardiovascular disease compared to controls. Three major pathways are proposed to explain the potential link from apical periodontitis to cardiovascular disease: bacterial translocation through oral-gut axis disruption, systemic inflammation characterized by elevated interleukin-1β, interleukin-6, tumor necrosis factor-α, and C-reactive protein, and oxidative stress-induced endothelial dysfunction. Conversely, emerging evidence indicates that cardiovascular disease accelerates periapical lesion progression through RANKL/RANK/OPG pathway dysregulation, microcirculatory compromise, and enhanced macrophage M1 polarization. Root canal treatment significantly reduces systemic inflammatory markers with parallel improvements in flow-mediated dilation, suggesting a potential cardiovascular benefit. While substantial evidence supports bidirectional associations, definitive causal relationships require prospective validation through large-scale cohort studies and randomized controlled trials examining whether endodontic intervention reduces cardiovascular event rates.

Keywords: Apical periodontitis, cardiovascular disease, chronic inflammation, multidisciplinary treatment, oral-systemic health

REVIEW

INTRODUCTION

Apical periodontitis (AP) is one of the most common inflammatory oral diseases, affecting approximately 52% of adults globally.[1] Among people over 65 years old, the rate of periapical lesions in root canal-treated teeth is 52.3%.[1-3] According to its course, AP can be divided into acute and chronic types. Chronic AP is characterized by persistent inflammation of the periapical tissues resulting from prolonged exposure to pathogenic microorganisms within the root canal system. This condition manifests clinically as inflammatory lesions with progressive resorption of alveolar bone in the periapical region.[4] Essentially, AP is the result of interactions between the root canal system microbiome, microbial virulence factors, and host immune responses.[5] The symptoms in the chronic phase of AP are relatively inconspicuous, but long-term existence can lead to serious oral problems and potential systemic complications.[6]

Epidemiological data show that both AP and cardiovascular disease (CVD) display marked age-related patterns, with significantly increased risks in elderly populations.[3,7,8] Cardiovascular disease has become one of the main causes of death globally, accounting for 32% of global deaths.[9,10] Among these, atherosclerotic CVD is most common, with pathogenesis involving multiple factors including genetics,

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environment, and lifestyle habits. Notably, inflammatory responses play a central role in CVD development, leading to vascular endothelial cell damage, promoting lipid deposition and thrombus formation.[11] There is mounting evidence that chronic inflammatory conditions, including oral infections, may serve as modifiable risk factors, shifting research focus toward understanding the role of oral health in cardiovascular pathophysiology.

While the relationship between periodontal disease and cardiovascular health is well-established,[12-14] the specific association between AP and CVD represents a relatively understudied area despite compelling biological rationale. Due to its often asymptomatic chronic course, AP may allow prolonged systemic exposure to bacterial products and inflammatory mediators without clinical detection.[15] Especially in elderly populations, asymptomatic chronic AP is highly prevalent and often remains undiagnosed for prolonged periods.[3,16]This silent source of chronic inflammation is hypothesized to be capable of increasing the risk of systemic diseases, such as CVD.[17]

This paradigm shift in understanding—from viewing AP as a local infection to recognizing its potential systemic implications—is strongly emphasized in the review by Cintra et al[17] Given the similarities in pathological characteristics and pathogenesis between AP and periodontitis, in-depth research on the possible association between AP and CVD has important scientific value.[18]Additionally, microorganisms and their metabolic products in AP lesions can affect the cardiovascular system through blood circulation. For example, certain oral pathogens, such as Porphyromonas endodontalis, may promote the formation and development of atherosclerosis.[19, 20] Based on the specificity of the oral microbiome in patients with AP, systematically elucidating the potential association between AP and CVD has important clinical significance.

This comprehensive review synthesizes current evidence on the potential bidirectional associations between AP and CVD, examining the mechanisms underlying their mutual influence and the clinical implications for integrated patient care. Understanding these complex interactions may be essential for developing evidence-based strategies that optimize both oral and cardiovascular health outcomes (Figure 1).

HIGHLIGHTS

- Apical periodontitis (AP) is associated with a 1.38 to 5.3-fold increased risk of cardiovascular disease (CVD), highlighting its potential as an underrecognized systemic risk factor.
- The AP-to-CVD link is mediated by 3 major pathways: bacterial translocation via the oral-gut axis, systemic inflammation (elevated CRP, IL-1β, IL-6, TNF-α), and oxidative stress-induced endothelial dysfunction.
- Successful RCT significantly reduces systemic inflammatory biomarkers and improves endothelial function, suggesting a cardiovascular protective effect of managing oral infections.
- Cardiovascular disease may reciprocally aggravate periapical lesion progression through dysregulated bone metabolism (RANKL/RANK/OPG pathway), microcirculatory compromise, and immune modulation.
- Current evidence supports a bidirectional association, but definitive causality and the impact of endodontic treatment on hard cardiovascular outcomes require validation through large-scale prospective studies and randomized controlled trials.

METHODS

To ensure a comprehensive and balanced synthesis of the available literature, a systematic search strategy was employed, consistent with best practices for narrative reviews. Searches in 3 major electronic databases were conducted: PubMed, Web of Science, and Scopus. The search covered the period from January 2000 to December 2023 to capture contemporary evidence while including foundational studies.

The main search strategy combined keywords related to AP (e.g., "AP," "periapical periodontitis," "periapical disease," "endodontic disease") with terms related to CVD (e.g., "CVD," "coronary artery disease," "atherosclerosis," "hypertension," "stroke," "heart failure") using Boolean operators. The reference lists of relevant articles were also handsearched to identify additional studies.

Studies were included if they were: (1) original research articles (clinical studies, epidemiological investigations, animal models, or in vitro mechanistic studies) or systematic reviews; (2) published in English; and (3) directly investigated an association or mechanistic link between AP and CVD. Conference abstracts, editorials, opinion pieces, and case reports were excluded. The selection of studies for inclusion in this narrative review was based on their relevance to the predefined thematic areas: epidemiological evidence, biological mechanisms (in both directions), and clinical implications, with priority given to studies with robust methodologies. This structured approach was designed to provide a transparent and reproducible framework for the evidence synthesis.

The Potential Impact of Apical Periodontitis on Cardiovascular Disease and Proposed Mechanisms

It has been hypothesized that AP may have systemic effects on the cardiovascular system through multiple pathways.[21] This section will systematically review the relationship between AP and CVD from 2 aspects: clinical evidence and proposed action mechanisms.

Epidemiological and Clinical Evidence

Epidemiological studies provide preliminary evidence for the association between AP and CVD. An et al[22] found that the risk of CVD in the AP group was 5.3 times that of the control group. A cross-sectional study[23] demonstrated that the prevalence of CVD in the AP group (38%) was significantly higher compared to the non-AP group (17%); carotid ultrasound examinations[23] showed that AP patients not only had

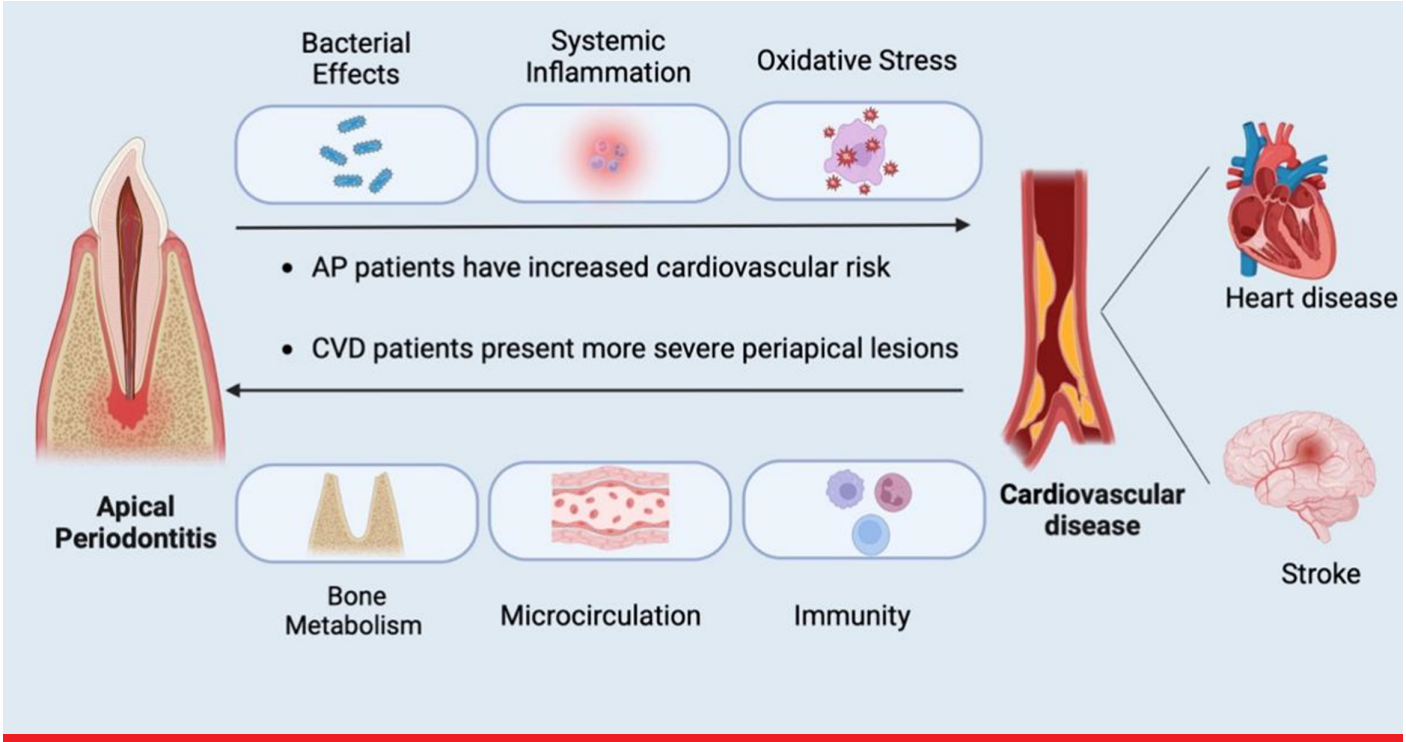

Figure 1. The bidirectional relationship between AP and CVD.

increased carotid intima thickness but also generally exhibited vascular endothelial dysfunction. Additionally, long-term follow-up studies by Petersen et al[24]reported that AP patients had a 1.38-5.3 times higher risk of developing CVD within 10 years compared to normal individuals.

Among various types of CVD, the association of AP with coronary heart disease is most significant. A case-control study conducted by Costa et al[25]showed that the risk of coronary artery disease in the AP group was 2.79 times that of the control group, and this correlation remained significant even after adjusting for traditional factors such as age, gender, and smoking. Through multivariate risk analysis, Malvicini et al[26] found that the presence of AP was associated with a 5-fold and 15-fold increased risk of carotid plaques and intima-media thickening, respectively, and the risk increased with the number of AP-affected teeth.

Regarding the relationship between AP and hypertension, experimental studies and clinical observations provide in-depth insights. Milojevic et al,[27] using a spontaneously hypertensive rat model, found that AP was associated with aggravated cardiac dysfunction and oxidative stress. Conversely, the coexistence of hypertension and AP also led to a significant increase in the area of periapical lesions. This finding suggests that there may be a synergistic mechanism between the 2 diseases. However, the results of epidemiological studies are not entirely consistent. A systematic review of 8 relevant studies[28] showed that there may be no direct correlation between the prevalence of hypertension and AP. But notably, hypertensive patients had significantly lower retention rates of teeth after root canal treatment (RCT), a finding that has important guiding significance for developing clinical treatment strategies.

In studies on stroke, Leão et al[29] showed that the number of AP-affected teeth ≥2 was significantly associated with carotid atherosclerotic burden (CAB) ≥50%. This finding suggests that AP may participate in the formation and progression of cerebral arterial atherosclerotic plaques and that multiple AP could be an important indicator for assessing the risk of cerebrovascular disease.

Based on these research findings, the role of timely and standardized RCT in potentially reducing patients' cardiovascular risk has also received attention. Results from a prospective intervention study[30] found that after proper RCT, patients' flow-mediated dilation significantly improved. This improvement was closely related to the decrease in inflammatory marker levels. Garrido et al[31] confirmed that in systemically healthy young patients with AP, high-sensitivity C-Reactive Protein (hs-CRP) levels significantly decreased after RCT. A recent systematic review and meta-analysis [32] further confirmed that RCT can significantly reduce the levels of circulatory inflammatory markers, with the most significant decreases in CRP and IL-1. Bergandi et al[33]found elevated levels of various factors in the serum of AP patients, including Endothelin-1 (ET-1), Interleukin-1β (IL-1β), and soluble CD14 (sCD14), all of which significantly improved after RCT. In summary, standardized RCT not only improves local infection but also reduces systemic inflammation levels, which may help lower CVD risk, while also providing an important theoretical basis for the oral-cardiovascular multidisciplinary diagnosis and treatment model. A prospective

interventional study in CVD patients with AP demonstrated significant reduction in serum inflammatory biomarkers following non-surgical RCT.[34] Taken together, these findings suggest that standardized RCT not only improves local infection but also reduces systemic inflammation levels, which could help lower CVD risk, while also providing an important theoretical basis for the oral-cardiovascular multidisciplinary diagnosis and treatment model.

Proposed Action Mechanisms

The mechanisms by which AP might affect the cardiovascular system are complex, involving pathophysiological processes at multiple levels. Current research suggests the following potential pathways:

Systemic Effects of Bacteria and Their Products

The main pathogens of AP are gram-negative anaerobic bacteria,[35] which form biofilms in the root canal system and can cause a series of pathological changes if they enter the bloodstream.[27, 35] When entering the bloodstream, these bacteria could directly invade vascular endothelium and smooth muscle cells, potentially causing vascular damage.[20] Their products, such as lipopolysaccharide, may stimulate monocyte-macrophage adhesion and aggregation, promoting lipid deposition and atherosclerotic plaque formation.[36] Research has demonstrated an association between endodontic lesions and coronary artery disease, suggesting a potential link between periapical infections and cardiovascular events.[37]

With the deepening of microbiome research, the role of the oral-gut axis in the process of AP potentially affecting cardiovascular health has gradually been revealed. Gan et al[38] through 16S rRNA sequencing analysis found that gut microbiota α diversity increased in AP model mice, and oral infection bacteria led to overgrowth of commensal species in oral and intestinal microbiota. Further research [39] suggested that AP can affect intestinal barrier function by altering gut microbiota composition, leading to more bacterial products entering the bloodstream, thereby aggravating systemic inflammation and atherosclerosis. These findings are consistent with observations by Koren et al[40] in human samples, suggesting a possible pathway from AP to the occurrence and development of CVD.

Systemic Inflammatory Response

Multiple studies have explored the relationship between AP and systemic inflammatory states. A recent systematic review[41] confirmed that patients with AP exhibit a marked increase in systemic pro-inflammatory mediators, specifically IL-1β, IL-6, TNF-α, and CRP. Changes in these markers not only reflect the activity of the disease but are also closely related to the risk of cardiovascular complications. A substantial proportion of AP patients demonstrate hs-CRP levels exceeding 3 mg/L, which is indicative of moderate-to-high cardiovascular risk.[31] Bergandi et al[33] observed significantly elevated levels of inflammatory factors such as ET-1, IL-1β, and sCD14 in the serum of AP patients.

Animal experimental studies further explore the mechanisms of this inflammatory response. Chen et al[42] found in a hyperlipidemic rat model that chronic AP was significantly associated with promoting the development of aortic inflammatory responses, mainly manifested as upregulation of pro-inflammatory factors such as IL-1, IL-2, and IL-6 in serum, accompanied by increased inflammatory cell infiltration in aortic tissue. Pro-inflammatory factors are believed to directly damage vascular endothelial cells, increase endothelial permeability, promote lipid and inflammatory cell infiltration into the vessel wall, while pro-inflammatory cytokines may also induce vascular smooth muscle cell phenotypic transformation and proliferation, aggravating endothelial dysfunction and matrix degradation, thereby potentially accelerating the formation and instability of atherosclerotic plaques, accompanied by increased macrophage infiltration. Studies[29] have also found that RCT can significantly reduce the levels of these inflammatory markers and improve vascular endothelial function.

Oxidative Stress State

Reactive oxygen species (ROS) are highly active byproducts of oxygen metabolism, playing a key role in the initiation and maintenance of the inflammatory response.[43] Oxidative stress occurs when there is an increase in the production of reactive oxygen species, a weakening of the antioxidant system function, or both. This enhanced oxidative stress has been confirmed to be closely related to various pathological processes.[44] Studies have found that AP can lead to local and systemic oxidative stress events: locally manifested as large amounts of ROS produced by pulp tissue, causing tissue damage and inflammation amplification; systemically manifested as decreased total antioxidant capacity in serum and increased levels of the lipid peroxidation product malondialdehyde.[45] Under pathological conditions, pulp tissue produces large amounts of ROS, aggravating local oxidative stress. These ROS are thought to not only directly damage vascular endothelium, reducing the bioavailability of endothelium-derived vasodilator nitric oxide and leading to endothelial dysfunction,[29] but also induce inflammatory responses and activate matrix metalloproteinases through various pathways, causing vascular structural remodeling, plaque instability, and potentially aggravating the atherosclerotic process.[45]

The above research reveals proposed mechanisms by which AP might affect the cardiovascular system through the systemic effects of bacteria, systemic inflammatory responses, oxidative stress, and other pathways. These mechanisms could interact with each other, forming a complex pathological network. Although current research has revealed multiple hypothetical potential mechanisms, there are still many aspects that need to be explored in depth regarding the possible association between AP and CVD. For example, whether there is a specific temporal relationship between autophagy and mitochondrial dysfunction, the specific regulatory network downstream of the HIF-1 signaling pathway, and the need to further explore the potential role of dental stem cells in promoting vascular and neural regeneration, as well as in-depth research on the specific mechanisms of bacterial exosomes in the initiation and progression of atherosclerosis.[46, 47] In addition, the reversibility of epigenetic

modifications and their clinical intervention value are also worth further research.[48] The in-depth elucidation of these mechanisms will not only help to better understand the potential interaction between the 2 diseases but will also provide an important basis for developing new therapeutic strategies and preventive measures. Future research directions should also focus on the development of individualized treatment plans, especially in considering the patient's general condition and comorbidities, and how to optimize RCT protocols to potentially reduce cardiovascular risk.

It is worth noting that in this hypothesized bidirectional relationship, CVD may also influence the occurrence, development, and prognosis of AP. Some progress has been made in mechanistic research in this area in recent years, but many questions remain.

The Potential Impact of CVD on AP and Proposed Mechanisms

With the deepening understanding of the relationship between oral and systemic health, the potential bidirectional relationship between AP and CVD has received increasing attention. While a large number of studies have suggested that AP may be associated with increased CVD risk, researchers have found that CVD might in turn affect the occurrence, development, and prognosis of AP. Current research hypothesizes that CVD may participate in the occurrence and development of AP by affecting local microcirculation, bone metabolism, and immune function, but these mechanisms still require additional research evidence for validation. This section will systematically review the potential impact of CVD on AP based on existing clinical observations and experimental research, analyzing its proposed mechanisms of action. This not only helps to deepen the understanding of the possible association between the 2 diseases but also provides new ideas for optimizing clinical treatment strategies.

Clinical and Experimental Evidence

Currently, research has observed the relationship between different types of CVD and AP from multiple aspects. The following will discuss coronary artery disease, hypertension, stroke, and other aspects separately (Table 1).

Coronary Atherosclerosis

Coronary atherosclerosis may affect the development of periapical lesions. Animal experiments[49] have shown that compared to the simple AP group, the experimental group with combined coronary atherosclerosis had larger periapical lesion areas and more severe inflammatory cell infiltration. Histological analysis also showed that the experimental group had significantly higher osteoclast activity, suggesting that coronary atherosclerosis may aggravate the progression of AP by affecting bone metabolism.

Clinical studies further support this finding, with Willershausen et al[50] finding that the detection rate of AP in acute myocardial infarction patients was significantly higher than in the control group. This finding was further confirmed by Liljestrand et al's large sample study,[37,50] especially in patients with acute coronary syndrome, where this association was more significant. A cross-sectional study,[51] by analyzing the association between CVD and AP, found that patients with CVD had significantly higher incidence and severity of AP. These research findings suggest that patients with coronary atherosclerosis may be more susceptible to severe periapical lesions, but the specific mechanisms remain to be further elucidated.

Hypertension

In recent years, more and more studies have shown that hypertension may be an important risk factor associated with the severity of AP lesions. In vitro studies found that osteoclast differentiation in the hypertension group was nearly 2-fold higher compared to the normal blood pressure group, which could influence endodontic treatment outcomes and potentially accelerate alveolar bone resorption in the apical area.[52] Milojevic et al[26] further confirmed in a spontaneously hypertensive rat model that the coexistence of hypertension and AP was associated with not only aggravated cardiac dysfunction and oxidative stress but also a significant increase in the area of periapical lesions.

From an epidemiological perspective, a cross-sectional study showed that hypertension (especially secondary hypertension) is an important risk factor for periapical abscess, and the prevalence in patients with secondary hypertension is significantly higher than in patients with primary hypertension.[53] The study also found that the risk of periapical abscess was significantly reduced in patients taking angiotensin II receptor blockers. A prospective cohort study also found that hypertensive patients are more likely to develop severe AP lesions, and the severity of the lesions is negatively correlated with oral microbiota diversity.[54] These findings suggest a potential relationship between hypertension, oral microbiome composition, and AP development, though the specific mechanisms require further investigation.

In terms of treatment prognosis, a systematic review and meta-analysis[27] showed that although there may be no direct association between AP prevalence and hypertension, hypertensive patients have significantly lower tooth retention rates after RCT. Different cardiovascular drugs also appear to have different associations with AP: β-blockers and calcium antagonists may adversely affect the recovery of AP by affecting calcium-phosphorus metabolism, while statins show potential protective effects. Studies have found that statins may exert antibacterial, anti-inflammatory, and immunomodulatory effects by reducing CD-68 positive macrophages and downregulating the expression of Cyr61 in osteoblasts, thereby slowing the progression of AP.[55] A systematic review further suggested that statins may also promote the healing of AP by regulating bone metabolism.[56] These findings provide new ideas for the treatment of AP in hypertensive patients, suggesting that the potential impact on oral health needs to be considered when choosing cardiovascular drugs.

Other CVDs

In addition to coronary heart disease and hypertension, the relationship between other types of CVD and AP has also gradually received research attention. Studies have shown

Table 1. Summary of Research Evidence on the Effects of Cardiovascular Diseases on Apical Periodontitis

CVD Types	Authors (Year)	Methods	Study Object	Main Findings
Coronary atherosclerosis	Conti et al[49]	Experimental study	Rat model (n = 40)	Coronary atherosclerosis significantly aggravated periapical lesion size and inflammation
	Willershausen et al[50] Liljestrand et al[37]	Case-control study Cross-sectional study	AMI patients (n = 125) ACS patients (n = 508)	AMI patients showed 2.21-fold increased risk of AP AP significantly associated with ACS risk (OR = 2.72)
Hypertension	Martins et al[52]	Experimental study	ACS patients (n = 508)	Hypertensive conditions significantly enhanced osteoclast differentiation
	Milojevic et al[27]	Experimental study	In vitro cell experiment	Hypertension led to 43% increase in periapical lesion area
	Katz et al[53]	Cross-sectional study	Hypertensive patients (n = 913)	Secondary hypertension significantly increased periapical abscess risk
	Minty et al[54]	Prospective cohort study	AP+hypertension patients (n = 427)	Hypertension significantly reduced periapical microbiome diversit
	Cabanillas-Balsera[28]	Systematic review and meta-analysis	8 studies: investigating hypertension and AP relationship (prevalence and tooth retention)	No significant association between AP prevalence and hypertension. Significantly lower retention rate of root-filled teeth in hypertensive patients
Cardiomyopathy	Şehirli et al[57]	Experimental study	Cardiomyopathy model (n = 36)	Cardiomyopathy aggravated periapical tissue destruction with protective effects of NAC
Valvular heart	Wilson et al[58] Lockhart et al[59]	Clinical guideline Systematic review	Systematic review Clinical study synthesis	Strict antibiotic prophylaxis protocol required for RCT in valvular disease patients Established standardized antibiotic prophylaxis protocol for RCT

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AP, apical periodontitis; CVD, cardiovascular disease; NAC, N-acetyl-L-cysteine; OPG, osteoprotegerin; OR, odds ratio; RANKL, receptor activator of nuclear factor kappa-B ligand; RCT, root canal treatment; TLR, toll-like receptor.

that stroke, cardiomyopathy, and heart valve replacement may affect the occurrence, development, and prognosis of AP through different mechanisms.

In stroke patients, there are relatively few studies on the characteristics and influencing factors of AP. Leão et al[28] conducted a cross-sectional study of 240 hospitalized patients with ischemic stroke or transient ischemic attack, and the results showed that the number of AP-affected teeth ≥2 and the number of root canal-treated teeth ≥2 were significantly associated with carotid atherosclerotic burden (CAB) ≥50%. The study also suggested that the combined effect of periodontitis and AP may aggravate the progression of atherosclerosis. These findings suggest that cerebrovascular disease may aggravate the development of AP by affecting local blood supply and inflammatory states.

In terms of cardiomyopathy, Şehirli et al[57] through an adriamycin-induced cardiomyopathy rat model study systematically studied the characteristic manifestations of AP under cardiomyopathy for the first time. The study found that the cardiomyopathy combined with AP group showed more severe tissue destruction and inflammatory response, manifested as enhanced oxidative stress response, aggravated inflammatory response, and decreased tissue repair capacity. The study also found that the combined use of antioxidants such as N-acetyl-L-cysteine was associated with improved alveolar bone healing and vascular endothelial function after RCT.

In patients with heart valve disease, the treatment of AP needs to be particularly cautious. The latest guidelines issued by the American Heart Association[58]emphasize the importance of oral health management in these patients, especially in preventing infective endocarditis. The guidelines recommend a comprehensive oral examination before valve replacement surgery and timely treatment of potential infection foci, including AP. Lockhart et al's research[59] also confirmed that these patients need to follow strict antibiotic prevention protocols when undergoing RCT, emphasizing the importance of preventive treatment.

These findings from studies on stroke, cardiomyopathy, and valvular heart disease demonstrate that different types of CVD may influence AP development and treatment outcomes through various mechanisms, highlighting the importance of considering cardiovascular comorbidities in endodontic treatment planning.

Proposed Action Mechanisms

Bone Metabolism Changes

Cardiovascular disease may influence the development of AP through bone metabolism changes, with the RANKL/RANK/OPG signaling pathway serving as a critical proposed mediator in this process. The RANKL/RANK/OPG signaling pathway has been extensively studied in cardiovascular contexts, where research demonstrates that angiotensin II, a key mediator in hypertension and CVD, induces RANKL expression through the receptor activator of NF-κB ligand in

osteoblasts, leading to osteoclast activation.[52] Shimizu et al[60] further showed that angiotensin II can activate this signaling pathway by binding to its receptor, promoting osteoclast differentiation and activation. These findings establish a direct molecular link between cardiovascular pathophysiology and bone metabolism regulation, where osteoclasts are associated with bone destruction in various conditions including bone fractures, osteoporosis, and endodontic pathology.

In AP, this same RANKL/RANK/OPG signaling pathway plays a fundamental role in bone remodeling processes, directly affecting disease progression by regulating osteoclast formation and activity.[4] Given that both CVD and AP involve the same RANKL/RANK/OPG regulatory pathway, it is hypothesized that patients with CVD may experience accelerated bone resorption in periapical regions when AP develops. The systemic activation of this pathway by cardiovascular mediators like angiotensin II could amplify the local bone destructive processes characteristic of AP, potentially explaining clinical observations showing more severe periapical lesions in patients with cardiovascular comorbidities.[53]

In addition, hypertension may also interfere with calcium homeostasis in bone tissue by affecting calcium ion channels and calmodulin-dependent protein kinase activity. Especially in elderly hypertensive patients, the resistance of periapical tissues to inflammatory stimulation is further reduced due to generally decreased bone density.[53] It is worth noting that commonly used cardiovascular drugs also may participate in this process: β-receptor blockers and calcium ion channel blockers may aggravate osteoporosis by affecting calcium-phosphorus metabolism, while angiotensin-converting enzyme inhibitors may have a protective effect by inhibiting RANKL expression.[52]

Microcirculation Disorders

Cardiovascular disease, especially coronary atherosclerosis, may lead to microvascular dysfunction, affecting the blood supply to the pulp and periapical tissues. Studies have shown that coronary atherosclerosis may be associated with reduced blood supply to the pulp and periapical tissues through vascular disease affecting microcirculation.[22] Microvascular endothelial cell dysfunction reduces the bioavailability of nitric oxide, leading to impaired endothelium-dependent vasodilation. This dysfunction may be accompanied by potentially increased release of vasoconstrictors such as ET-1, collectively potentially causing microvascular spasm and thereby reducing the blood supply to periapical tissues.[29]

More importantly, local ischemia and hypoxia caused by microcirculation disorders may stimulate the expression of hypoxia-inducible factor-1α (HIF-1α), a key transcriptional regulator in both cardiovascular pathophysiology and periapical tissue responses.[61] Under hypoxic conditions, HIF-1α, on one hand, may trigger a selective autophagy process by upregulating the expression of mitochondrial protein BNIP3, clearing damaged mitochondria, reducing oxidative stress damage to tissues, which is an important protective mechanism for cells to cope with hypoxia.[62] Simultaneously, by transcriptionally activating the expression of vascular endothelial growth factor (VEGF), HIF-1α may promote angiogenesis to compensatorily increase local blood supply.[63] This activation of autophagy may help to clear damaged cellular components accumulated in the inflammatory microenvironment, playing a protective role in tissue repair.

Although HIF-1α may improve local blood supply by promoting angiogenesis through VEGF, the effect of this compensatory angiogenesis in the inflammatory environment of AP still needs further research confirmation. For patients with AP combined with CVD, this issue may be more worthy of attention.

Immune Function Changes

Current research suggests that immune system alterations may contribute to the relationship between CVD and AP, though direct mechanistic evidence remains limited. Toll-like receptor 4 (TLR4) has emerged as a potential connecting pathway, given its established roles in both cardiovascular pathology and periapical inflammation.

Periapical lesion pathogenesis studies demonstrate that TLRs play crucial roles in the development of periapical lesions caused by polymicrobial infections, with TLR4 signaling serving as the most important sensing pathway for both Gram-positive and Gram-negative bacteria and their subsequent inflammatory responses in polymicrobial pulpal infections. Experimental studies further confirm that elevated CD14 (cluster of differentiation 14) and TLR4 signaling are associated with deteriorated periapical inflammation, with TLR4 overactivation leading to more severe periapical tissue destruction, particularly under conditions of TLR2 deficiency.[64, 65]

In CVD, angiotensin II upregulates TLR4 expression and enhances inflammatory responses.[66] CVD research also demonstrates that TLR signaling can alter Treg/Th17 cell balance through regulation of dendritic cell function, leading to decreased secretion of anti-inflammatory factors (such as IL-10 and TGF-β) and affecting the resolution process of inflammation.[67]These findings suggest that CVD-related TLR4 activation might theoretically influence periapical inflammatory processes. However, direct evidence for this specific interaction is lacking, representing an important area for future investigation.

TNF-α, as a key inflammatory mediator, plays important roles in the pathogenesis of both CVD and AP. Research has demonstrated that the absence of TNFR1 can significantly inhibit osteoclast activity in experimentally induced AP, with TNFR1-deficient mice showing reduced periapical bone resorption.[68] This finding suggests an important role of the TNF-α–TNFR1 signaling pathway in bone resorption processes relevant to periapical lesions. In CVD, TNF-α plays a central role in promoting inflammatory responses and vascular damage, with elevated levels contributing to cardiac inflammation and remodeling.[69]

The hypothesized connection to AP emerges through TNF-α's effects on bone metabolism via the renin-angiotensin

system. Research has shown that TNF-α priming of osteoblasts enhances their responsiveness to angiotensin II, leading to increased RANKL expression and subsequent osteoclastogenesis.[70] Conversely, angiotensin II receptor blockers such as olmesartan can prevent this angiotensin II-enhanced osteoclast formation.[71] These findings suggest that cardiovascular pathophysiology may influence AP development through TNF-α-mediated pathways in the renin-angiotensin system, suggesting a potential mechanistic link between systemic cardiovascular inflammation and periapical bone destruction.

Additionally, future research needs to further explore other potential mechanisms by which CVD might influence AP. For instance, macrophage polarization imbalance may represent an important connecting link. Research has confirmed that in periapical lesions, macrophages are more prone to polarize toward the pro-inflammatory M1 phenotype, aggravating tissue damage through secretion of pro-inflammatory factors.[72]Similar mechanisms have been validated in periodontitis, demonstrating that macrophage M1 polarization can promote vascular endothelial dysfunction and accelerate atherosclerosis development.[73] Based on these established mechanisms, it is hypothesized that CVD patients may influence macrophage polarization processes in periapical lesions through systemic inflammatory states, though this hypothesis requires experimental validation.

Genetic Susceptibility and Environmental Factors

Genome-wide association studies have revealed that polymorphisms in inflammatory factor-related genes such as TNF-α and IL-1β, as well as antioxidant genes such as glutathione S-transferase, may increase individual susceptibility to AP and CVD.[48,70,74] These gene polymorphisms could increase individual susceptibility to both CVD and AP, or delay the repair process of periapical lesions, by affecting the intensity of immune responses and the degree of inflammatory responses.[75] Environmental factors are equally important, with research confirming that traditional cardiovascular risk factors such as smoking and obesity are closely related to the risk of AP.[18,76]

In addition to the currently known mechanisms, future research needs to further explore the potential mechanisms by which CVD might influence AP. Firstly, the regulation of the neuro-immune-endocrine network may play an important role in this process. CVD may affect the progression of AP by affecting the function of the hypothalamic-pituitary-adrenal axis (HPA axis), leading to an exacerbation of systemic inflammatory responses.[66] Secondly, the effect of CVD-related coagulation function changes on AP. Abnormalities in platelet activation and the coagulation cascade not only affect microcirculation but may also influence the inflammatory response and repair process of periapical tissues by releasing factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β).[18] Finally, the changes in the function of endothelial progenitor cells (EPCs) in periapical tissues under CVD conditions. Studies have shown that patients with CVD have reduced numbers and impaired function of EPCs, which may affect the angiogenesis and tissue repair abilities of periapical tissues.[77] In-depth research on these potential mechanisms will help to more comprehensively understand the complex relationship between CVD and AP and provide a theoretical basis for developing new treatment strategies. The major pathways through which CVD may influence AP progression are summarized in Figure 2.

Summary and Interpretation of Evidence

This narrative review synthesizes emerging evidence regarding potential bidirectional associations between AP and CVD. While proposed biological mechanisms demonstrate plausibility and consistent associations have been observed across different study populations, the current evidence base remains fundamentally limited by methodological constraints and study design limitations. It is crucial to emphasize that most available data are observational and cannot demonstrate causality.

The available clinical evidence, derived predominantly from cross-sectional studies with sample sizes typically under 500 participants, suggests these associations may warrant clinical attention, particularly in patients with established cardiovascular risk factors. However, the observational nature of most studies precludes causal inference, and many mechanistic insights derive primarily from animal models whose clinical relevance remains uncertain. The wide variation in effect sizes reported across studies further reflects the heterogeneity and uncertainty inherent in current evidence.

Several key limitations characterize the existing literature. First, the lack of standardized diagnostic criteria for both AP severity and CVD endpoints across studies limits meaningful comparison and meta-analysis. Second, inadequate control for potential confounding variables such as smoking, diabetes, socioeconomic status, and oral hygiene practices could inflate observed associations. Third, the predominance of hospital-based studies introduces selection bias that may not reflect community-level relationships.

Despite these limitations, the biological plausibility of the proposed mechanisms and the consistency of associations across different study populations support continued investigation. The demonstrated reduction in systemic inflammatory markers following endodontic treatment provides the most compelling evidence for a potential causal pathway, though whether this translates to meaningful cardiovascular risk reduction remains unproven.

From a clinical perspective, current evidence supports heightened awareness of these potential associations without justifying major changes to established treatment protocols. Clinicians treating extensive AP might consider cardiovascular risk factors in treatment planning, particularly regarding healing expectations and follow-up protocols. Conversely, cardiovascular specialists could benefit from including oral health assessment in comprehensive

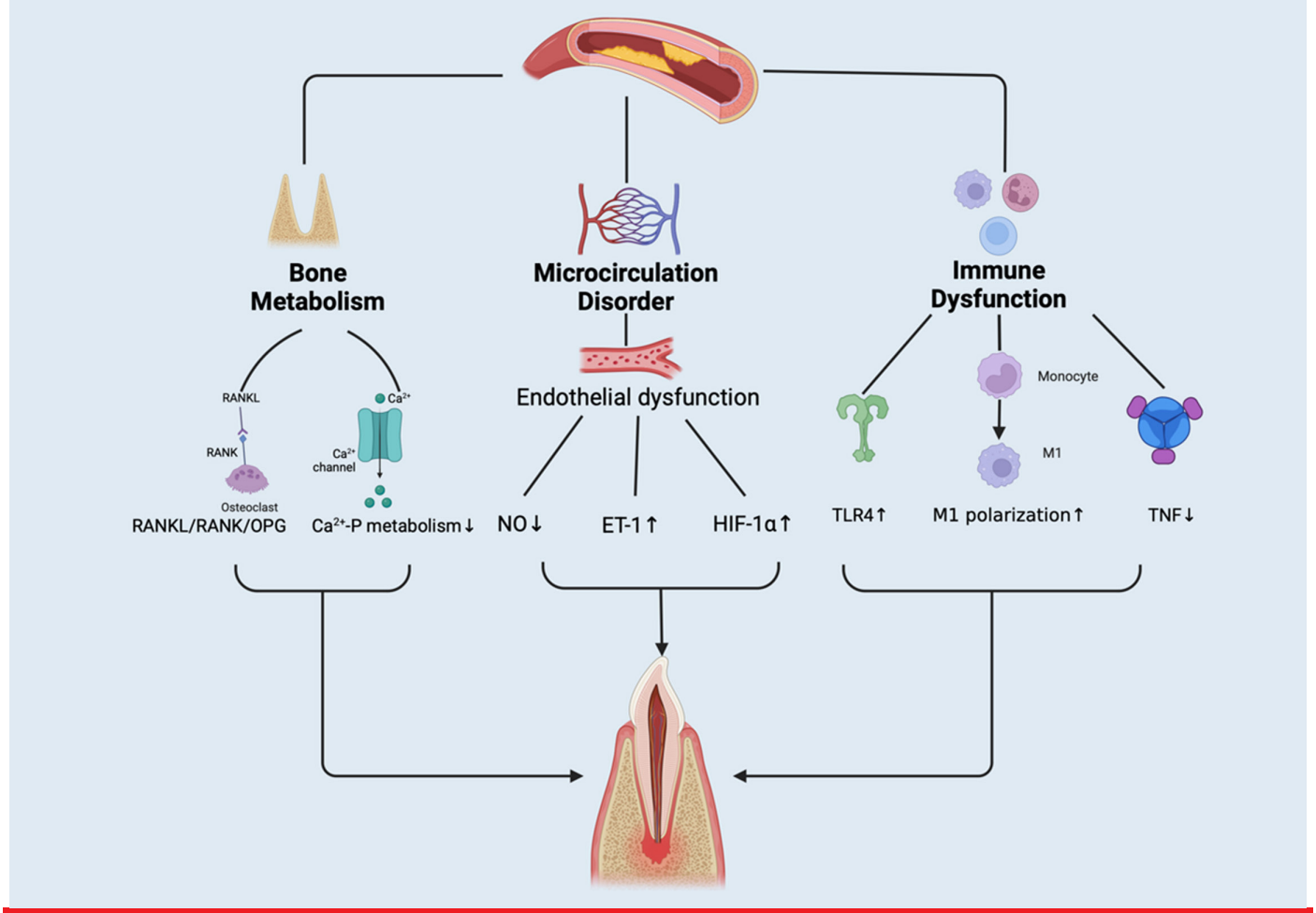

Figure 2.Mechanism diagram illustrating how CVD aggravates AP.

patient evaluation, though routine endodontic screening cannot be recommended based on current evidence.

The most critical need moving forward is for large-scale, prospective cohort studies with standardized outcome measures and adequate statistical power to detect clinically meaningful effects. Randomized controlled trials examining whether endodontic treatment reduces cardiovascular event rates in high-risk patients would provide definitive evidence for clinical decision-making. Until such evidence emerges, the integration of oral health considerations into cardiovascular risk assessment represents a reasonable clinical approach that acknowledges these potential relationships while maintaining focus on established, evidence-based preventive and therapeutic strategies.

In conclusion, while the concept of oral-systemic health connections continues to evolve, the specific relationship between AP and CVD requires substantially stronger evidence before translating into modified clinical practice guidelines. The current state of knowledge supports continued research investment while maintaining appropriate clinical vigilance for these potentially important associations.

Future Research Directions and Clinical Implications

Future Research Directions

Clinical Research Priorities

Current evidence limitations highlight several key areas requiring investigation. Large-scale, multi-center prospective cohort studies with sample sizes exceeding 1000 participants and follow-up periods of at least 5 years are essential to establish temporal relationships and clinical significance. These studies must implement standardized diagnostic criteria for both AP severity and cardiovascular endpoints while adequately controlling for shared risk factors such as smoking, diabetes, and socioeconomic status.

Well-designed randomized controlled trials examining whether endodontic treatment reduces cardiovascular risk markers would provide crucial evidence for clinical decision-making. Given ethical constraints regarding cardiovascular outcomes, alternative study designs such as propensity score-matched cohorts may be necessary to evaluate treatment effects on surrogate endpoints.

Mechanistic Research Advancement

Multi-omics approaches should be employed to comprehensively characterize the molecular mechanisms

underlying AP-CVD associations. Single-cell RNA sequencing can illuminate cellular heterogeneity within periapical lesions, while spatial transcriptomics may reveal tissue-specific gene expression patterns contributing to systemic inflammation.

Microbiome research should advance beyond 16S rRNA sequencing to utilize metagenomic and metatranscriptomic approaches for species-level identification and functional characterization. Long-read sequencing technologies offer improved accuracy for microbial community analysis. Bacterial translocation studies using advanced tracing techniques could provide direct evidence for systemic dissemination of oral pathogens.

Animal Model Development

Animal model selection should align with specific research objectives. For investigating overall AP effects on cardiovascular health, ligature-induced periodontitis models are recommended. When studying bacterial translocation via oral-gut pathways, gavage models may better isolate bacterial effects from local inflammatory responses. Chronic disease models rather than acute interventions should be employed to better reflect human pathophysiology.

Clinical Implications

Risk Assessment Integration

Clinical practice might incorporate cardiovascular risk stratification in endodontic treatment planning, particularly for patients over 50 years or those with multiple risk factors. This could include routine blood pressure measurement, review of cardiovascular medications, and communication with physicians when indicated. However, these recommendations require validation through prospective clinical studies before implementation as standard practice.

Multidisciplinary Collaboration

Healthcare systems should develop standardized protocols for multidisciplinary communication between dental and cardiovascular specialists. This includes establishing referral pathways, shared care protocols, and integrated electronic health records to facilitate comprehensive patient management. Training programs should emphasize the potential oral-systemic health connection for both dental and medical professionals.

Treatment Modifications

For patients with known CVD, endodontic treatment planning should account for potential healing complications and may benefit from extended follow-up periods. Consideration should be given to the cardiovascular effects of commonly used medications: while angiotensin receptor blockers may have protective effects, beta-blockers and calcium channel blockers might adversely affect treatment outcomes through effects on calcium-phosphorus metabolism.

Ethics Committee Approval: Not applicable. This article is a narrative review based exclusively on previously published studies and does not involve new human or animal research or identifiable patient data; therefore, institutional ethics committee approval was not required.

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REFERENCES

1. Pietrzycka K, Radwanski M, Matinlinna JP, Lukomska-Szymanska M. The prevalence of root canal treatment, periapical status, and coronal restorations in elderly patients in the Polish population. *Heliyon*. 2024;10(17):e35584. [CrossRef]
2. Bender IB. Factors influencing the radiographic appearance of bony lesions. *J Endod*. 1997;23(1):5-14. [CrossRef]
3. Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. *Int Endod J*. 2021;54(5):712-735. [CrossRef]
4. Luo X, Wan Q, Cheng L, Xu R. Mechanisms of bone remodeling and therapeutic strategies in chronic apical periodontitis. *Front Cell Infect Microbiol*. 2022;12:908859. [CrossRef]
5. Karamifar K, Tondari A, Saghiri MA. Endodontic periapical lesion: an overview on the etiology, diagnosis and current treatment modalities. *Eur Endod J*. 2020;5(2):54-67. [CrossRef]
6. Öçbe M, Çelebi E, Öçbe ÇB. An overlooked connection: oral health status in patients with chronic diseases. *BMC Oral Health*. 2025;25(1):314. [CrossRef]
7. Camponogara JG, De Ferreira TGM, Pelissari TR, Anversa AM, Moreira CHC, Bier CAS. Demographics, smoking status, and systemic health factors associated with apical periodontitis in a Brazilian rural population: a cross-sectional study. *Clin Oral Investig*. 2023;27(12):7319-7325. [CrossRef]
8. Dos Santos VC, Kublitski PMO, da Silva BM, Gabardo MCL, Tomazinho FSF. Periapical lesions associated with demographic variables, dental conditions, systemic diseases, and habits. *J Contemp Dent Pract*. 2023;24(11):864-870. [CrossRef]
9. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *Circulation*. 2019;140(11):e596-e646. [CrossRef]
10. World Health Organization. Cardiovascular diseases (CVDs); 2021. Accessed December 23, 2024. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
11. Hansson GK, Robertson AKL, Söderberg-Nauclér C. Inflammation and atherosclerosis. *Annu Rev Pathol*. 2006;1:297-329. [CrossRef]

12. Tomás I, Diz P, Tobías A, Scully C, Donos N. Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. *J Clin Periodontol*. 2012;39(3):213-228. [CrossRef]
13. Sanz M, Del Castillo AM, Jepsen S, et al. Periodontitis and cardiovascular diseases. Consensus report. *Glob Heart*. 2020;15(1):1. [CrossRef]
14. Naderi S, Merchant AT. The association between periodontitis and cardiovascular disease: an update. *Curr Atheroscler Rep*. 2020;22(10):52. [CrossRef]
15. Fu WT, Zhu QK, Li N, et al. Clinically oriented CBCT periapical lesion evaluation via 3D CNN algorithm. *J Dent Res*. 2024;103(1):5-12. [CrossRef]
16. Hamedy R, Shakiba B, Pak JG, Barbizam JV, Ogawa RS, White SN. Prevalence of root canal treatment and periapical radiolucency in elders: a systematic review. *Gerodontology*. 2016;33(1):116-127. [CrossRef]
17. Cintra LTA, Gomes MS, Da Silva CC, et al. Evolution of endodontic medicine: a critical narrative review of the interrelationship between endodontics and systemic pathological conditions. *Odontology*. 2021;109(4):741-769. [CrossRef]
18. Berlin-Broner Y, Febbraio M, Levin L. Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature. *Int Endod J*. 2017;50(9):847-859. [CrossRef]
19. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. *Int Endod J*. 2015;48(10):933-951. [CrossRef]
20. Dorn BR, Harris LJ, Wujick CT, Vertucci FJ, Progulske-Fox A. in vitro by Invasion of vascular cells *Porphyromonas endodontalis*. *Int Endod J*. 2002;35(4):366-371. [CrossRef]
21. Niazi SA, Bakhsh A. Association between endodontic infection, its treatment and systemic health: A narrative review. *Medicina (Kaunas)*. 2022;58(7):931. [CrossRef]
22. An GK, Morse DE, Kunin M, Goldberger RS, Psoter WJ. Association of radiographically diagnosed apical periodontitis and cardiovascular disease: A hospital records-based study. *J Endod*. 2016;42(6):916-920. [CrossRef]
23. Chauhan N, Mittal S, Tewari S, Sen J, Laller K. Association of apical periodontitis with cardiovascular disease via noninvasive assessment of endothelial function and subclinical atherosclerosis. *J Endod*. 2019;45(6):681-690. [CrossRef]
24. Petersen J, Inglehart MR. Endodontic treatment and atherosclerosis: is there a connection? *J Am Dent Assoc*. 2011;142(6):668-674. [CrossRef]
25. Costa TH, de Figueiredo Neto JA, de Oliveira AE, Lopes e Maia Mde F, de Almeida Souza LM. Association between chronic apical periodontitis and coronary artery disease. *J Endod*. 2014;40(2):164-167. [CrossRef]
26. Malvicini G, Marruganti C, Abu Leil M, et al. Association between apical periodontitis and secondary outcomes of atherosclerotic cardiovascular disease: a case-control study. *Int Endod J*. 2024;57(3):281-296. [CrossRef]
27. Milojevic Samanovic A, Jakovljevic V, Vasovic M, et al. Cardiac, biochemical and histopathological analysis reveals impaired heart function in hypertensive rats with apical periodontitis. *Int Endod J*. 2021;54(9):1581-1596. [CrossRef]
28. Cabanillas-Balsera D, Areal-Quecuty V, Cantiga-Silva C, et al. Prevalence of apical periodontitis and non-retention of root-filled teeth in hypertensive patients: systematic review and meta-analysis. *Int Endod J*. 2024;57(3):256-269. [CrossRef]
29. Leão TSS, Tomasi GH, Conzatti LP, Marrone LCP, Reynolds MA, Gomes MS. Oral inflammatory burden and carotid atherosclerosis among stroke patients. *J Endod*. 2022;48(5):597-605. [CrossRef]
30. Chauhan N, Mittal S, Tewari S, Sen J, Laller K. Effect of endodontic treatment on endothelial dysfunction and subclinical atherosclerosis-a prospective intervention study. *Clin Oral Investig*. 2023;27(9):5617-5625. [CrossRef]
31. Jiménez C, Garrido M, Pussinen P, et al. Systemic burden and cardiovascular risk to Porphyromonas species in apical periodontitis. *Clin Oral Investig*. 2022;26(1):993-1001. [CrossRef]
32. Jakovljevic A, Fransson H, Bakhsh A, et al. Endodontic treatment modifies circulatory inflammatory mediator levels: A systematic review with meta-analysis. *Int Endod J*. 2024;58(2):171-192. [CrossRef]
33. Bergandi L, Giuggia B, Alovisi M, et al. Endothelial dysfunction marker variation in young adults with chronic apical periodontitis before and after endodontic treatment. *J Endod*. 2019;45(5):500-506. [CrossRef]
34. Bhardwaj S, Tewari S, Laller K, Kumar A, Arora M. Impact of apical periodontitis and non-surgical root canal treatment on serum inflammatory biomarkers in patients with cardiovascular disease with apical periodontitis: a prospective interventional study. *Cureus*. 2025;17(7):e87723. [CrossRef]
35. Siqueira JF, Rôças IN. Present status and future directions: microbiology of endodontic infections. *Int Endod J*. 2022;55(suppl 3):512-530. [CrossRef]
36. Jiménez-Sánchez MC, Cabanillas-Balsera D, Areal-Quecuty V, Velasco-Ortega E, Martín-González J, Segura-Egea JJ. Cardiovascular diseases and apical periodontitis: association not always implies causality. *Med Oral Patol Oral Cir Bucal*. 2020;25(5):e652-e659. [CrossRef]
37. Liljestrand JM, Mäntylä P, Paju S, et al. Association of endodontic lesions with coronary artery disease. *J Dent Res*. 2016;95(12):1358-1365. [CrossRef]
38. Gan G, Lu B, Zhang R, et al. Chronic apical periodontitis exacerbates atherosclerosis in apolipoprotein E-deficient mice and leads to changes in the diversity of gut microbiota. *Int Endod J*. 2022;55(2):152-163. [CrossRef]
39. Gan G, Lin S, Luo Y, et al. Unveiling the oral-gut connection: chronic apical periodontitis accelerates atherosclerosis via gut microbiota dysbiosis and altered metabolites in apoE−/− mice on a high-fat diet. *Int J Oral Sci*. 2024;16(1):4. [CrossRef]
40. Koren O, Spor A, Felin J, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci U S A*. 2011;108(suppl 1):4592-4598. [CrossRef]
41. Matos-Sousa JM, Chemelo VS, Frazão DR, et al. Is there any association between the presence of biomarkers and apical periodontitis? A systematic review. *Front Immunol*. 2024;15:1366954. [CrossRef]
42. Chen S, Ma D, Xiao S, Li P, Lei H, Huang X. Effects of chronic apical periodontitis on the inflammatory response of the aorta in hyperlipemic rats. *Clin Oral Investig*. 2021;25(6):3845-3852. [CrossRef]
43. Georgiou AC, Cornejo Ulloa P, Van Kessel GMH, Crielaard W, Van der Waal SV. Reactive oxygen species can be traced locally and systemically in apical periodontitis: a systematic review. *Arch Oral Biol*. 2021;129:105167. [CrossRef]
44. Liang S, Tian X, Wang C. Nanozymes in the treatment of diseases caused by excessive reactive oxygen specie. *J Inflamm Res*. 2022;15:6307-6328. [CrossRef]
45. Hernández-Ríos P, Pussinen PJ, Vernal R, Hernández M. Oxidative stress in the local and systemic events of apical periodontitis. *Front Physiol*. 2017;8:869. [CrossRef]
46. Su W, Liao C, Liu X. Angiogenic and neurogenic potential of dental-derived stem cells for functional pulp regeneration: a narrative review. *Int Endod J*. 2025;58(3):391-410. [CrossRef]

47. Lin Y, Wang J, Bu F, et al. Bacterial extracellular vesicles in the initiation, progression and treatment of atherosclerosis. *Gut Microbes*. 2025;17(1):2452229. [CrossRef]
48. Jakovljevic A, Nikolic N, Carkic J, et al. Association of polymorphisms in TNF-α, IL-1β, GSTM and GSTT genes with apical periodontitis: is there a link with herpesviral infection? *Int Endod J*. 2020;53(7):895-904. [CrossRef]
49. Conti LC, Segura-Egea JJ, Cardoso CBM, et al. Relationship between apical periodontitis and atherosclerosis in rats: lipid profile and histological study. *Int Endod J*. 2020;53(10):1387-1397. [CrossRef]
50. Willershausen B, Kasaj A, Willershausen I, et al. Association between chronic dental infection and acute myocardial infarction. *J Endod*. 2009;35(5):626-630. [CrossRef]
51. González-Navarro B, Segura-Egea JJ, Estrugo-Devesa A, et al. Relationship between apical periodontitis and metabolic syndrome and cardiovascular events: A cross-sectional study. *J Clin Med*. 2020;9(10):3205. [CrossRef]
52. Martins CM, Sasaki H, Hirai K, Andrada AC, Gomes-Filho JE. in vitro and in vivo studyRelationship between hypertension and periapical lesion: an . *Braz Oral Res*. 2016;30(1):e78. [CrossRef]
53. Katz J, Rotstein I. Prevalence of periapical abscesses in patients with hypertension: A cross-sectional study of a large hospital population. *J Endod*. 2021;47(7):1070-1074. [CrossRef]
54. Minty M, Lê S, Canceill T, et al. Low-diversity microbiota in apical periodontitis and high blood pressure are signatures of the severity of apical lesions in humans. *Int J Mol Sci*. 2023;24(2):1589. [CrossRef]
55. Lin SK, Kok SH, Lee YL, et al. Simvastatin as a novel strategy to alleviate periapical lesions. *J Endod*. 2009;35(5):657-662. [CrossRef]
56. Ideo F, Manca MF, Niazi S, Mannocci F, Bardini G, Cotti E. The role of systemic statins in the inception and healing of apical periodontitis: a systematic review. *BMC Oral Health*. 2023;23(1):730. [CrossRef]
57. Şehirli AÖ, Aksoy U, Sibai A, Orhan K, Sayıner S. Effects of N-acetyl-L-cysteine against apical periodontitis in rats with adriamycin-induced cardiomyopathy and nephropathy. *Int Endod J*. 2024;57(2):195-207. [CrossRef]
58. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of viridans group streptococcal infective endocarditis: A scientific statement from the American Heart Association. *Circulation*. 2021;143(20):e963-e978. [CrossRef]
59. Lockhart PB, Tampi MP, Abt E, et al. Evidence-based clinical practice guideline on antibiotic use for the urgent management of pulpal- and periapical-related dental pain and intraoral swelling: a report from the American Dental Association. *J Am Dent Assoc*. 2019;150(11):906-921.e12. [CrossRef]
60. Shimizu H, Nakagami H, Osako MK, et al. Prevention of osteoporosis by angiotensin-converting enzyme inhibitor in spontaneous hypertensive rats. *Hypertens Res*. 2009;32(9):786-790. [CrossRef]
61. Gao W, Wang D, Shi Y, et al. Potential cardiovascular disease treatment by natural drugs targeting the HIF-1α factor and its pathway. *Comb Chem High Throughput Screen*. 2025;28(17): 2971-2988. [CrossRef]
62. Wang X, Wu Z, Zhang Y, Lian B, Ma L, Zhao J. Autophagy induced by hypoxia in pulpitis is mediated by HIF-1α/BNIP3. *Arch Oral Biol*. 2024;159:105881. [CrossRef]
63. Huang HY, Wang WC, Lin PY, Huang CP, Chen CY, Chen YK. The roles of autophagy and hypoxia in human inflammatory periapical lesions. *Int Endod J*. 2018;51(suppl 2):e125-e145. [CrossRef]
64. Lima RB, Da Silva A, Silva CMPC, Nelson-Filho P, Da Silva LAB, Da Silva RAB. The role of toll-like receptor 4 in the pathogenesis of periapical lesions in experimental models: a scoping review. *Rev Odontol Bras Central*. 2024;33(92):81-101. [CrossRef]
65. Rider D, Furusho H, Xu S, et al. Elevated CD14 (cluster of differentiation 14) and toll-like receptor (TLR) 4 signaling deteriorate periapical inflammation in TLR2 deficient mice. *Anat Rec (Hoboken)*. 2017;300(11):1986-1996. [CrossRef]
66. Biancardi VC, Bomfim GF, Reis WL, Al-Gassimi S, Nunes KP. The interplay between angiotensin II, TLR4 and hypertension. *Pharmacol Res*. 2017;120:88-96. [CrossRef]
67. Zhu L, Shang J, Li Y, et al. Toll-like receptors mediate opposing dendritic cell effects on Treg/Th17 balance in mice with intracerebral hemorrhage. *Stroke*. 2024;55(8):2126-2138. [CrossRef]
68. de Carvalho MS, de Almeida-Junior LA, Silva-Sousa AC, et al. Absence of tumor necrosis factor Receptor 1 inhibits osteoclast activity in apical dental resorption caused by endodontic infection in mice. *J Endod*. 2022;48(11):1400-1406. [CrossRef]
69. Dai B, Wang ZZ, Zhang H, Han MX, Zhang GX, Chen JW. Antihypertensive properties of a traditional Chinese medicine GAO-ZI-YAO in elderly spontaneous hypertensive rats. *Biomed Pharmacother*. 2020;131:110739. [CrossRef]
70. Pramusita A, Kitaura H, Ohori F, et al. Salt-sensitive hypertension induces osteoclastogenesis and bone resorption via upregulation of angiotensin II Type 1 receptor expression in osteoblasts. *Front Cell Dev Biol*. 2022;10:816764. [CrossRef]
71. Aoki M, Kawahata H, Sotobayashi D, et al. Effect of angiotensin II receptor blocker, olmesartan, on turnover of bone metabolism in bedridden elderly hypertensive women with disuse syndrome. *Geriatr Gerontol Int*. 2015;15(8):1064-1072. [CrossRef]
72. Song Y, Li X, Huang D, Song H. Macrophages in periapical lesions: potential roles and future directions. *Front Immunol*. 2022;13:949102. [CrossRef]
73. Shi M, Guo K, Liu Y, et al. Role of macrophage polarization in periodontitis promoting atherosclerosis. *Odontology*. 2024;112(4):1209-1220. [CrossRef]
74. Kim SJ, Kim MG, Kim KS, Song JS, Yim SV, Chung JH. Impact of glutathione S-transferase M1 and T1 gene polymorphisms on the smoking-related coronary artery disease. *J Korean Med Sci*. 2008;23(3):365-372. [CrossRef]
75. Zahiu SG, Fratila O. Assessment of systemic condition and smoking impact over incidence of apical periodontitis. *Cureus*. 2024;16(2):e55250. [CrossRef]
76. Blair P, Flaumenhaft R. Platelet α-granules: basic biology and clinical correlates. *Blood Rev*. 2009;23(4):177-189. [CrossRef]
77. Fadini GP, Losordo D, Dimmeler S. Critical reevaluation of endothelial progenitor cell phenotypes for therapeutic and diagnostic use. *Circ Res*. 2012;110(4):624-637. [CrossRef]