

Apical periodontitis, atherosclerosis, and hypertension: correlation between inflammatory mechanisms and systemic repercussions - integrative review

Periodontite apical, aterosclerose e hipertensão, correlação entre mecanismos inflamatórios e repercussões sistêmicas - revisão integrativa

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ABSTRACT

Background: Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide and are closely associated with chronic inflammatory processes and endothelial dysfunction. Apical periodontitis, an infectious inflammation affecting the tissues surrounding the dental apex, has been investigated for its potential systemic implications, particularly regarding hypertension and atherosclerosis. **Objective:** This study aimed to analyze, through an integrative literature review, the relationship between apical periodontitis, arterial hypertension, and atherosclerosis, with emphasis on the underlying inflammatory mechanisms. **Material and Methods:** This integrative review was conducted with searches in the Medline database via PubMed and Lilacs via the Virtual Health Library (VHL), using the descriptors “cardiovascular diseases and endodontics”. After screening and applying inclusion and exclusion criteria, 21 studies were selected for qualitative analysis. **Results:** The findings suggest that apical periodontitis may contribute to systemic inflammation through the release of inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, biomarkers involved in the pathophysiology of arterial hypertension and atherosclerosis. Experimental and clinical studies indicated that periapical infections might exacerbate endothelial dysfunction, change lipid metabolism, and compromise the efficacy of biomaterials used in endodontic treatments, particularly in hypertensive patients. **Conclusion:** In conclusion, apical periodontitis appears to act as a modulating factor for cardiovascular risk, highlighting the need for an integrated approach between oral health and systemic health. Controlled clinical studies and longitudinal research are still necessary to establish possible synergistic relationships and guide evidence-based clinical practices.

KEYWORDS

Apical periodontitis; Cardiovascular diseases; Endodontics; Inflammation; Oral health.

RESUMO

Contexto: As doenças cardiovasculares representam a principal causa de morbidade e mortalidade mundial, estando associadas a processos inflamatórios crônicos e a disfunções do endotélio vascular. A periodontite apical, inflamação infecciosa que acomete os tecidos ao redor do ápice dental, tem sido investigada pelo seu possível impacto sistêmico, especialmente na hipertensão arterial e na aterosclerose. **Objetivo:** O estudo objetivou analisar, por meio de uma revisão integrativa da literatura, a relação entre periodontite apical, hipertensão arterial e aterosclerose, com ênfase nos mecanismos inflamatórios envolvidos. **Material e Métodos:** Realizou-se essa revisão integrativa com buscas nas bases de dados Medline via PubMed e Lilacs via Biblioteca Virtual em

Saúde (BVS), utilizando os descritores “Doenças cardiovasculares e endodontia”. Após triagem e aplicação de critérios de inclusão e exclusão, foram selecionados 21 artigos para análise qualitativa. **Resultados:** Os resultados sugerem que a periodontite apical pode contribuir para o desencadeamento da inflamação sistêmica por meio da liberação de mediadores inflamatórios como interleucina 6, fator de necrose tumoral alfa e proteína C reativa, biomarcadores envolvidos na fisiopatologia da hipertensão arterial e da aterosclerose. Estudos experimentais e clínicos indicaram que infecções periapicais podem agravar a disfunção endotelial, alterar o metabolismo de lipídios e comprometer a eficácia de biomateriais utilizados em tratamentos endodônticos, particularmente em pacientes hipertensos. **Conclusão:** Em conclusão, a periodontite apical parece atuar como fator modulador do risco cardiovascular, ressaltando a necessidade de uma abordagem integrada entre saúde bucal e saúde sistêmica. Estudos clínicos controlados e pesquisas longitudinais ainda são necessários para estabelecer possíveis relações sinérgicas e orientar condutas clínicas fundamentadas em evidências.

PALAVRAS-CHAVE

Periodontite apical; Doenças cardiovasculares; Endodontia; Inflamação; Saúde bucal.

INTRODUCTION

Cardiovascular diseases (CVD) represent the leading cause of global morbidity and mortality, affecting millions of people annually. These diseases comprise a heterogeneous group of conditions that affect the heart and blood vessels, including coronary artery disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, and venous thrombosis [1]. Among these conditions, two clinically significant events—ischemic heart disease and stroke—share a common etiological factor: atherosclerotic vascular disease, characterized by a low-grade chronic inflammatory process and progressive endothelial dysfunction [2].

Arterial hypertension, defined by persistently elevated blood pressure levels, is associated with metabolic and hormonal alterations and may also contribute to cardiac and vascular hypertrophy. Due to the magnitude of the problem, its diagnosis and management have undergone constant refinement, particularly in view of its correlations with other systemic and local health factors, such as oral infections [3].

In recent years, the relationship between oral infections and systemic diseases has been significantly investigated, with a focus on the impact of apical periodontitis on cardiovascular health [4-6]. Apical periodontitis is a periapical inflammatory response to pulp infection that can potentially lead to the destruction of periradicular bone tissue [7]. Although traditionally considered a local condition, increasing evidence suggests that the inflammation associated with apical periodontitis can have systemic effects, contributing to the progress of atherosclerosis and increasing the risk of adverse cardiovascular events [8].

The biological plausibility of this association is supported by several mechanisms, including hematogenous dissemination of microorganisms, systemic immune activation, and elevated levels of inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP), which play a central role in the pathophysiology of atherosclerosis [9]. Moreover, studies demonstrate that individuals with chronic oral infections exhibit alterations in lipid metabolism, and a greater predisposition to thrombotic events and increased blood pressure levels [7,10].

Within this context, understanding the relationship between endodontic infections and cardiovascular risk becomes essential for the adoption of integrated preventive and therapeutic strategies. This article aims to review the available scientific evidence and observe whether there is a correlation between apical periodontitis and the development of atherosclerosis and hypertension or vice versa, considering the systemic and local inflammatory mechanisms. Moreover, it provides updated insights to guide researchers and clinicians in evidence-based decision-making.

METHODOLOGY

This review was developed following established methodological guidelines for integrative reviews [11-13], with the aim of synthesizing and critically analyzing the available evidence on the association between apical periodontitis and cardiovascular diseases, specifically hypertension and atherosclerosis. The research question was developed and refined using the PEO question framework, identifying three core elements: population, exposure, and outcome.

Search strategy

The bibliographic search was conducted in Medline databases via PubMed platform and Lilacs via Virtual Health Library (VHL), considering their scope and relevance to the biomedical field. The descriptors “cardiovascular diseases” and “endodontics” were used, and applied in the fields of title, abstract, and main subject. No language or publication date filters were established to maximize the accuracy of the search and include all relevant studies.

Eligibility criteria - Inclusion criteria

1. Original research conducted in humans or animal models;
2. Studies that directly investigated the association between apical periodontitis and cardiovascular diseases (hypertension and/or atherosclerosis);
3. Availability of the full text a translatable language;
4. Observational, experimental, or clinical study designs.

Exclusion criteria

1. Literature reviews, systematic reviews, meta-analyses and overviews;
2. Articles unavailable for full access;
3. Studies that did not directly investigate the relationship between apical periodontitis and cardiovascular events.

Study selection process

The initial search retrieved 431 records. Duplicate removal was carried out using the Rayyan software, resulting in 417 unique articles. Study selection followed three sequential steps: (1) preliminary screening of titles; (2) abstracts analysis based on eligibility criteria, and (3) full reading of the eligible texts. After this process, 83 articles were selected for full reading, culminating in the final inclusion of 21 studies that met all the established criteria (Figure 1).

Data analysis

The data extracted from each study included the author, year of publication, country of origin, central theme, methodology employed, main results, and conclusions. The information was organized into a synthesis matrix, allowing for a critical comparative analysis of the findings, with a focus on identifying patterns, divergences, and gaps in the literature (Table I).

RESULTS

The systematic search yielded 21 studies that addressed the relationship between apical periodontitis and cardiovascular diseases, specifically atherosclerosis, and hypertension. The articles were published between 2009 and 2024 and involved research conducted in diverse countries, including the United States, Spain, Brazil, Italy, Germany, India, and the United Kingdom, reflecting a growing and global interest in the topic (Table I).

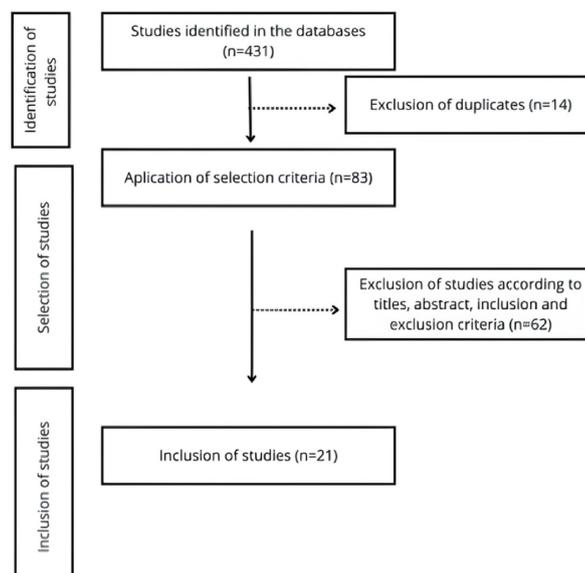


Figure 1 - Illustration of the research methodology, selection, and inclusion of studies for the construction of the article's results.

Table I - Summary of Studies on Apical Periodontitis, Hypertension, and Atherosclerosis

Author / Year / Country	Methodology	Main Results	Conclusion
Caplan et al., 2009 – United States [14]	Community-based study using medical histories and endodontic treatment records	Potential association between apical periodontitis and atherosclerosis	Oral health should be considered in cardiovascular assessment; further studies are needed
Segura-Egea et al., 2010 – Spain [15]	40 hypertensive patients compared with 51 controls; periapical radiographic evaluation	75% of hypertensives had apical periodontitis vs. 61% of controls; not statistically significant	Suggests influence; more research needed
Segura-Egea et al., 2011 – Spain [16]	100 hypertensive patients (50 smokers, 50 non-smokers)	92% of smokers had apical periodontitis vs. 44% of non-smokers; greater treatment needs in smokers	Correlation between hypertension, smoking, and apical periodontitis; no direct link between apical periodontitis and hypertension
King et al., 2012 – United States [17]	Normotensive patients with pulpal necrosis treated endodontically; measured blood pressure and postoperative pain	Correlation between systolic blood pressure and postoperative pain	Monitoring blood pressure may help control endodontic pain
Inchingolo et al., 2013 – Italy [18]	Measured d-ROMs (derivatives of Reactive Oxygen Metabolites) and BAP (Biological Antioxidant Potential) before and after endodontic treatment	Decrease in reactive oxygen metabolites after treatment	Endodontic treatment helps restore systemic redox balance
Vidal et al., 2016 – Brazil [9]	170 severe hypertensive patients evaluated clinically and via biomarkers (CRP, IL-6, fibrinogen)	Higher levels of inflammatory markers in patients with apical periodontitis	Chronic apical periodontitis leads to persistent systemic inflammation
Martins et al., 2016 – Brazil [19]	24 hypertensive and normotensive rats assessed for response to mineral trioxide mineral aggregate (MTA)	Hypertensive rats showed less mineralization	Hypertension impairs biological response to MTA
Martins et al., 2016 – Brazil [10]	Hypertensive and normotensive mice assessed for cytokines and bone resorption	Hypertensive mice showed more osteoclasts; similar cytokine levels and lesion size	Hypertension may modulate bone resorption
Tong, Wang, Chang, 2019 – Taiwan [20]	72,630 patients with apical periodontitis vs. 72,630 without; cardiovascular risk analysis	No overall increased risk; increased risk of atherosclerosis in men with apical periodontitis	Significant association between apical periodontitis and cardiovascular risk only in men
Cosme-Silva et al., 2019 – Brazil [21]	Induced hypertension in rats; analysis of immune response and biomineralization after endodontic treatment	Hypertension affected circulation, immunity, and pH, compromising endodontic materials	Hypertension impairs biocompatibility and biomineralization
Chauhan et al., 2019 – India [22]	120 men (60 with apical periodontitis, 60 without); endothelial function and carotid intima-media thickness assessment	Lower flow-mediated dilation and greater carotid thickness in patients with apical periodontitis	Indications of increased cardiovascular risk in patients with apical periodontitis
Conti et al., 2020 – Brazil [7]	40 rats divided into four groups (control, apical periodontitis, atherosclerosis, both)	Apical periodontitis increased triglycerides and worsened inflammation and bone loss when combined with atherosclerosis	Apical periodontitis exacerbates systemic inflammation and worsens atherosclerosis
Cowan et al., 2020 – United States [23]	Longitudinal study with 6,638 ARIC (Atherosclerosis Risk in Communities) patients	No significant correlation between prior endodontic treatment and cardiovascular disease	History of endodontic treatment is not associated with increased cardiovascular risk
Katz and Rotstein, 2021 – United States [24]	Clinical evaluation of 1,200 hypertensive and normotensive patients	Higher prevalence of periapical abscesses in hypertensive patients	Possible association between hypertension and dental infections
Poornima et al., 2021 – India [4]	50 patients; CRP measured before and after root canal treatment	Significant reduction in CRP after treatment	Root canal treatment can reduce systemic inflammation associated with apical periodontitis
Chauhan et al., 2023 – Germany [25]	Evaluation of endothelial function, carotid thickness, and inflammatory markers before and after endodontic treatment	Significant improvements in endothelial function, reduction in carotid thickness, and CRP	Treatment of apical periodontitis may improve subclinical cardiovascular parameters
Sebring et al., 2023 – United States [26]	Case-control study with 797 myocardial infarction patients and 796 controls; analysis of inflammatory endodontic disease	Combination of endodontic diseases increased infarction risk; isolated diseases did not	Combined oral inflammation may increase cardiovascular risk
Agger et al., 2023 – Norway [6]	20 apical periodontitis samples and 20 healthy bone samples; inflammatory cytokine analysis	Increased chronic inflammatory cytokines in apical periodontitis; cardiovascular disease did not alter this profile	Cardiovascular diseases do not alter the inflammatory response in apical periodontitis

Table I - Continued...

Author / Year / Country	Methodology	Main Results	Conclusion
Al-Abdulla et al., 2023 – United Kingdom [5]	70 patients with chronic apical periodontitis underwent retreatment or periapical surgery; analysis of CRP, ADMA (Asymmetric Dimethylarginine), MMP-2, blood glucose, and lipid profile	Significant reduction in biomarkers and improvement in metabolic parameters after two years	Successful endodontic treatment correlates with improved cardiovascular biomarkers
Malvicini et al., 2024 – Italy [27]	65 patients (33 with apical periodontitis, 32 without); vascular and lab exams	Higher IL-6 and TNF-alpha in patients with apical periodontitis; oral pathogens detected	Apical periodontitis may be a risk factor for atherosclerosis; further research on treatment impact is needed
Garrido et al., 2024 – Chile [28]	Pre- and post-treatment study with 29 patients; inflammatory biomarker analysis	Reduced CRP levels; other biomarkers unchanged	Treatment of apical periodontitis reduced systemic inflammation associated with atherosclerosis

Of the selected studies, eight directly investigated the association between apical periodontitis and arterial hypertension, nine explored the correlation between apical periodontitis and atherosclerosis, and four analyzed serum inflammatory biomarkers related to both cardiovascular conditions. Both acute and chronic manifestations of apical periodontitis were considered.

The methodological approaches varied widely, encompassing observational clinical trials, cohort and case-control studies, experimental animal models, and laboratory-based research. Human studies commonly employed periapical radiographic evaluation, measurement of inflammatory biomarkers (such as C-reactive protein, interleukin-6, TNF-alpha), and assessments of endothelial function and carotid thickness.

Overall, the findings indicated that apical periodontitis is associated with elevated levels of systemic inflammatory biomarkers and changes in subclinical cardiovascular parameters, such as increased carotid intima-media thickness and endothelial dysfunction. Experimental studies in hypertensive animal models have shown that arterial hypertension can negatively modulate inflammatory processes, leading to compromised inflammatory responses and reduced bone repair following apical periodontitis.

Moreover, several studies have demonstrated that effective endodontic treatment contributed to the reduction of systemic inflammatory markers and the improvement of vascular parameters, suggesting that controlling endodontic infection may have a positive impact on cardiovascular health. However, some cohort studies reported that a history of previous endodontic treatments, in isolation, was not statistically significantly associated with an increased cardiovascular

risk, highlighting the multifactorial complexity involved.

Although there is a strong trend in the literature suggesting a correlation between apical periodontitis and cardiovascular diseases, the authors emphasize the need for more longitudinal studies, with larger samples and rigorous control of confounding variables, to strengthen the scientific evidence in this area.

DISCUSSION

Research into the bidirectional relationship between systemic conditions and oral health has gained considerable momentum in recent years. For instance, studies have demonstrated that individuals with type 2 diabetes and periodontal disease can exhibit elevated levels of oxidative stress markers, such as malondialdehyde (MDA), alongside reduced activity of antioxidant enzymes, such as superoxide dismutase (SOD), and elevated levels compared to diabetic individuals without periodontal disease [29]. In addition, it has been observed that the highest levels of IL-10, an anti-inflammatory cytokine, are found in patients with periodontitis, followed by those with both periodontitis and type 2 diabetes mellitus [30]. This increase in oxidative stress is not limited to periodontal disease but is also observed in cases of apical periodontitis, reinforcing the hypothesis that oral inflammatory processes can significantly contribute to systemic imbalances [5,6].

Apical periodontitis is mainly caused by bacterial colonization of the root canal system. These microorganisms release toxins and metabolic products that activate the host immune system, leading to the local production of pro-inflammatory

cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) [5,6,27]. Once released into the systemic circulation, these mediators stimulate hepatic synthesis of C-reactive protein (CRP) and fibrinogen [9]. CRP is an inflammatory marker that rises in the presence of chronic infections, while fibrinogen is related to coagulation and vascular inflammation [22].

The resulting chronic inflammation can affect endothelial function, leading to vascular dysfunction and increased blood pressure. Elevated fibrinogen can contribute to the formation of clots and increased blood viscosity, worsening the cardiovascular risk in hypertensives. It is important to emphasize that the association between apical periodontitis and hypertension has been considered modest, indicating that endodontic infections can intensify systemic inflammation in individuals with severe hypertension, but do not act in isolation as a determining factor [9].

Clinical findings support this interpretation. In one study involving 40 hypertensive patients and 51 controls, periapical status was evaluated using the Periapical Index (PAI) [31]. Although apical periodontitis was observed in 75% of hypertensive patients compared to 61% of the controls, the difference was not statistically significant, suggesting that additional systemic and behavioral factors influence oral health in this population [7].

Animal studies provide complementary evidence. Research on Wistar rats demonstrated that apical periodontitis was associated with elevated triglyceride levels, and when combined with experimentally induced atherosclerosis (via a modified diet), this effect was markedly intensified [31]. These findings are consistent with the observations of Vidal et al. (2016), who demonstrated that conditions such as an unregulated diet, hypertension, and arteriosclerosis can exacerbate the systemic and local inflammatory processes.

Experimental investigations by Martins et al. (2016) and Cosme-Silva et al. (2019) analyzed the impact of hypertension on the tissue response and the mineralization capacity of Mineral Trioxide Aggregate (MTA) in animal models [19,21]. In hypertensive rats, a significant reduction in the formation of mineralized dentin around the MTA was observed, compared to normotensive rats. This may have relevant clinical implications, indicating that hypertensive patients may exhibit compromised tissue response in endodontic treatments.

Hypertension can harm dental biomaterials, as it alters the pH balance in the periapical microenvironment, compromising the curing and chemical reaction of materials like MTA and Biodentine®. Furthermore, hypertension affects micro-regional blood flow, impairing tissue healing and the local immune response, favoring the persistence of microorganisms responsible for apical periodontitis.

Another important point to consider is the impact of antihypertensive medications on oral health. The use of diuretics, ACE (angiotensin-converting enzyme) inhibitors, beta-blockers, and calcium channel blockers can reduce saliva production, causing xerostomia and promoting bacterial growth, increasing the risk of cavities and subsequent periapical infections. Moreover, these medications can delay healing, affecting the body's response to dental infections [21].

Cohort studies have also provided relevant information about the association between apical periodontitis and cardiovascular diseases [20,24]. In general, self-reported history of endodontic treatment was not independently associated with an increased risk of cardiovascular disease. However, it was observed that men with chronic apical periodontitis had a significantly higher risk of developing atherosclerosis, although this risk was strongly associated with lifestyle factors such as diet and health habits.

This review has some limitations that should be acknowledged. The number of available studies directly addressing the association between apical periodontitis and cardiovascular events remains limited, which reduces the robustness of the conclusions. Most studies included relied on cross-sectional or animal model designs, which restricts the ability to establish causality. In addition, variability in diagnostic criteria for apical periodontitis and cardiovascular outcomes may have introduced heterogeneity in the findings, and the exclusion of articles without full-text access may have led to the omission of potentially relevant data.

It is also important to note that the findings across studies were not entirely consistent. While some investigations demonstrated a significant association between apical periodontitis and cardiovascular markers such as elevated triglycerides and increased inflammatory mediators, others did not observe a statistically significant correlation between hypertension and the presence of apical

periodontitis. These discrepancies may be explained by differences in study design, sample size, and population characteristics, as well as by the influence of confounding factors such as diet, smoking, and systemic comorbidities. Animal models provide valuable mechanistic insights, but their extrapolation to humans should be made with caution. Future longitudinal and well-controlled clinical studies are needed to clarify these conflicting results and to better define the extent to which apical periodontitis contributes to cardiovascular disease risk.

CONCLUSION

The analyzed data suggest that apical periodontitis may contribute to systemic inflammation, exacerbating disorders such as hypertension and atherosclerosis, especially in individuals with other risk factors. Although the direct cause-and-effect association between apical periodontitis and cardiovascular diseases cannot be inferred, it is possible that there is a synergistic correlation since the process of chronic infection can exacerbate endothelial and metabolic changes. Moreover, hypertension can compromise the tissue response to endodontic treatments, impairing tissue regeneration. The effective treatment of apical periodontitis has been shown to reduce inflammatory markers, reinforcing its potential role in protecting cardiovascular health. However, more studies are needed to fully clarify these relationships.

Author's Contributions

GERM, AHT: Conceptualization. GERM, VMMJ, AKSS: Methodology. GERM: Formal Analysis. GERM, AHT: Investigation. GERM: Data Curation. VMMJ: Visualization. AHT: Supervision. GERM, AKSS: Writing – Original Draft Preparation. HVC, VPTP, MMBB, AHT: Writing – Review & Editing.

Conflict of Interest

No conflicts of interest declared concerning the publication of this article.

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Regulatory Statement

The integrative review was conducted using a search strategy in electronic databases. The search was restricted to publications in peer-reviewed journals in which the original work had received approval from an ethics committee.

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