ASSOCIATION BETWEEN ENDODONTIC INFECTION, ITS TREATMENT AND SYSTEMIC HEALTH: A NARRATIVE REVIEW

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Abstract:
Background: Endodontic infections can have a significant impact on systemic health, leading to a complex interplay between the endodontic microbiota, host immune response, and systemic diseases. The burden of endodontic disease on healthcare systems globally is substantial, with millions of root canal treatments performed each year. The presence of apical periodontitis, a consequence of root canal infection, can result in progressive bone resorption, periapical lesions, and potentially systemic complications. The relationship between endodontic infections and systemic health conditions has garnered increasing attention due to the potential risks posed by untreated infections. **Objective**: This review aims to examine the relationship between endodontic infections and systemic health conditions, evaluate the effectiveness of different treatment options in improving systemic health outcomes, identify potential risk factors for the development of endodontic infections, and explore the mechanisms by which these infections may contribute to systemic inflammation and disease. The research also delves into the occurrence of bacteremia after root canal treatment and the modulation of systemic inflammatory markers in response to endodontic interventions. **Conclusion**: The findings of this research underscore the importance of understanding and addressing the systemic implications of endodontic infections for enhanced patient care and public health. The review highlights the intricate relationship between endodontic microbiota, host immune response, and systemic diseases, emphasizing the need for comprehensive management of endodontic infections to mitigate potential systemic complications. By shedding light on the impact of apical periodontitis on conditions such as cardiovascular diseases, diabetes mellitus, and adverse pregnancy outcomes, this study contributes to the growing body of evidence linking oral health to overall systemic well-being. Moreover, the research emphasizes the potential role of endodontic interventions in reducing systemic inflammation and improving patient outcomes, underscoring the significance of proactive measures in addressing endodontic infections for better systemic health.

Keywords: apical periodontitis, systemic health, cardiovascular diseases, diabetes mellitus, pregnancy, autoimmune disorder, bacteremia.

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Introduction:

When a tooth becomes infected and causes pain, dentistry presents two treatment options. Despite the availability of extraction, many individuals prefer to save their teeth [1]. Endodontic treatment involves the meticulous removal of infected dental pulp and periradicular exudates using specialized tools and biocompatible substances, along with medications, to maintain the tooth's vitality. In healthy patients, the focus is primarily on the technical aspects of the procedure. However, when dealing with individuals with systemic illnesses who are under medical supervision, it is crucial to consider potential medical complications that may arise in the process of preserving the tooth [2].

There was a hypothesis suggesting that bacteria and toxins trapped in dentinal tubules could spread to other parts of the body, leading to various systemic diseases. Although this theory was later discredited due to lack of substantial evidence [3], recent studies have reignited interest in exploring the potential impact of endodontic diseases on overall health. Emerging research indicates that bacteraemia and low-grade systemic inflammation associated with apical periodontitis could have adverse effects on systemic health, such as increasing the risk of cardiovascular diseases, complications during pregnancy, and difficulties in managing diabetes. However, there is limited data on how conditions like diabetes mellitus or autoimmune disorders influence the prevalence and outcomes of endodontic treatments [4].

Moreover, there is strong evidence suggesting that successful root canal treatments can positively affect systemic health by reducing inflammation, thus dispelling the misconceptions related to the focal infection theory. While there is compelling evidence linking apical periodontitis to systemic health issues, further high-quality research is needed to solidify the benefits of endodontic treatments on overall health [5].

Objectives:

The main objectives of this review are:

1. To examine the relationship between endodontic infections and systemic health conditions.
2. To evaluate the effectiveness of different treatment options for endodontic infections in improving systemic health outcomes.
3. To identify potential risk factors for the development of endodontic infections and their impact on overall health.
4. To explore the mechanisms by which endodontic infections may contribute to systemic inflammation and disease.

Etiology:

Endodontic infection, a complex polymicrobial infection, presents a distinct challenge due to the diverse nature of the endodontic microbiome and its interactions with the host, potentially posing risks for systemic diseases in other parts of the body [6]. Chronic apical periodontitis, a consequence of root canal infection, is characterized by persistent localized inflammation in periapical tissue, leading to progressive bone resorption and periapical lesion formation. Untreated cases may progress to sinus tract formation and cyst development. The pathogenesis of apical periodontitis involves the activation of both innate and adaptive immune responses, involving a variety of cells and inflammatory mediators, ultimately resulting in periapical tissue destruction and lesion formation [7].

The global burden of apical periodontitis is substantial, as evidenced by statistics from various regions. For instance, the National Health Service (NHS) in England and Wales reported that over 1 million teeth underwent root canal treatment between 2001 and 2004, with the procedure costing the NHS approximately GBP 50.5 million. In the United States, the American Association of Endodontists indicates that more than 15 million root canal treatments are performed annually. Similarly, in Europe, nearly 23 million endodontic procedures are carried out each year [8, 9]. A systematic review revealed a high global prevalence of apical periodontitis (affecting 5% of all teeth, with one periapical lesion per patient) and root canal treatment (involving 10% of all teeth, with two root canal treatments per patient) in the adult population. These findings underscore the commonality of root canal treatment as a prevalent oral health issue, which not only impacts systemic health but also places a significant financial burden on healthcare services worldwide [10].

Endodontic Disease and Systemic Impact:

In recent times, there has been a notable shift within the field of endodontics. Previously focused primarily on pain management, infection control, and tooth preservation, the discipline has now turned its attention towards understanding oral infections as potential risk factors for systemic complications. The ramifications of apical periodontitis, in particular, extend beyond mere dental implications, with a significant percentage of cases (60–80%) ultimately necessitating tooth extraction [11]. This resurgence of interest in the "Focal infection Theory" has reignited global attention on the potential correlation between oral cavity infections and systemic diseases, prompting

a reevaluation of their impact on overall health [11].

The influence of endodontic disease on a patient's health is multi-faceted, involving both the pathogenic effects of polymicrobial communities and the host immune responses. Specifically, the translocation of microbes from the root canal into the systemic environment can trigger immune responses that affect other tissues and organs within the body. Research has established links between apical periodontitis and a range of systemic diseases, including diabetes [12], hypertension [13], adverse pregnancy outcomes [14], skeletal infections, and coronary heart disease (CHD), which is the most prevalent form of cardiovascular disease (CVD) [15]. This association is attributed to an increased risk of bacteraemia [16], as well as the translocation of soluble microbial compounds, active inflammatory mediators, and haemostatic factors from the root canal into the systemic environment, leading to metastatic infection, injury, and inflammation. Consequently, this process can trigger low-grade systemic inflammation that affects other tissues and organs throughout the body [17].

Notably, apical periodontitis can manifest as a completely asymptomatic condition, often detected as an incidental finding on an intraoral radiograph in the form of a periapical radiolucency, with no discernible signs or symptoms such as pain, swelling, abscess, or sinus tract. Thus, it is important to recognize that not only symptomatic cases but also asymptomatic cases that go unnoticed for years may have a detrimental effect on a patient's general health. As a result, endodontic disease represents a significant global health burden [18].

Endodontic Bacteraemia:

Previous research has indicated the occurrence of bacteraemia subsequent to root canal therapy. These studies have determined that the likelihood of bacteraemia occurrence is heightened when root canal instrumentation extends beyond the root apex, as opposed to when it remains confined within the root canal system. Bender et al. (1960) demonstrated that bacteraemia resulting from root canal treatment is temporary, lasting for a maximum of 10 minutes post-instrumentation, as the body's immune system effectively eliminates the circulating microbes. Additionally, Baumgartner et al. (1976) found that bacteraemia did not manifest when root canal instrumentation was limited to the root canal itself [19].

Various investigations employing a culture-based methodology have revealed bacteraemia in approximately 3–20% of cases following non-surgical root canal therapy [20,21]. Nevertheless, many earlier studies were constrained by the sensitivity of the blood culture techniques utilized. Debelian et al. (1992, 1995) conducted research emphasizing that bacteraemia is linked not only to excessive instrumentation of the root canal beyond the apex but also to instrumentation confined within the root canal system [22]. Moreover, Debelian et al. (1995), through biochemical tests and antibiograms, established that the microorganisms isolated from the bloodstream originated from the root canal [23]. Subsequent studies employing electrophoresis, DNA hybridization, and phenotypic and genetic methodologies further corroborated the endodontic origin of bacteraemia-causing microorganisms [24,25]. The utilization of more sensitive identification techniques in these studies led to the detection of a significantly higher incidence of bacteraemia (ranging from 31% to 54%) post-root canal therapy compared to earlier reports. Pulsed field gel electrophoresis was also employed to demonstrate the genetic similarity between microbes identified in the blood and those present in the root canal. Given that more than half of the bacteria are not cultivable, the relatively lower detection rate in earlier studies following root canal therapy can be attributed to the reliance on a culture-based approach. Reis et al. (2016), utilizing a molecular approach (qPCR), identified bacteraemia post-non-surgical root canal therapy in all cases that had tested negative for bacteraemia using a culture-based approach [26].

Systemic Inflammatory Mediators:

Recent research suggests that apical periodontitis has the potential to influence the systemic levels of various inflammatory markers in the body, such as high-sensitivity C-reactive protein (hs-CRP), Interleukin-1β (IL-1β), IL-6, IL-12, IL-10, tumor necrosis factor (TNF-α), matrix metalloproteinases (MMP-8 and MMP-9), soluble vascular cell adhesion molecule 1 (sVCAM-1), endothelial leukocyte adhesion molecule (E-selectin), and intercellular adhesion molecule (ICAM), as well as Immunoglobulin (Ig) A, IgM, IgG, asymmetric dimethylarginine (ADMA), and complement-C3 levels in individuals [27]. This alteration in inflammatory markers could potentially lead to an increase in systemic inflammation. The implications of this are significant not only for cases of symptomatic apical periodontitis and failed root canal treatments but also for shedding light on the potential negative impact of asymptomatic apical periodontitis on overall systemic health. Furthermore, it underscores the

importance of successful endodontic treatment in mitigating these effects.

Studies involving interventions have demonstrated notable differences in inflammatory marker levels, including CRP, C3, and ADMA, between baseline measurements and subsequent follow-ups [28]. In a longitudinal interventional study conducted by Bakhsh et al. in 2022, it was observed that patients with apical periodontitis exhibited significantly higher pre-operative serum levels of IL-1β, hs-CRP, FGF-23, and ADMA compared to healthy controls, indicating a higher systemic burden associated with apical periodontitis. Following surgical or non-surgical root canal retreatment, one year post-treatment, there was a general reduction in the levels of these markers, suggesting a positive impact of the treatment on these markers [29]. The decrease in these biomarkers post-treatment appears to validate the efficacy of the current therapeutic approaches in endodontic treatment for suppressing systemic inflammation. This points towards the need for further research to explore the diagnostic potential of these biomarkers, which could complement existing objective criteria (clinical and radiological) in evaluating endodontic success. Additionally, these markers could serve as prognostic indicators of the systemic response to endodontic treatment in the future.

Apical Periodontitis and Cardiovascular Diseases:

Cardiovascular diseases (CVDs) encompass a range of conditions impacting the heart and blood vessels, such as coronary heart disease, cerebrovascular disease, stroke, hypertensive heart disease, cardiomyopathies, myositis, rheumatic heart disease, atrial fibrillation, flutter, congenital heart disease, valvular heart disease, peripheral artery disease, deep vein thrombosis, thromboembolic disease, and transient ischemic attack [30]. CVDs pose a significant global health and economic challenge, being the primary cause of death worldwide and accounting for approximately 30% of total global mortality. Projections indicate a potential 10% rise in CVD incidence over the next two decades, leading to a threefold surge in healthcare expenditures [30].

Research has indicated a potential link between endodontic infection and coronary heart disease, the most prevalent form of cardiovascular illness representing 49% of the overall CVD burden [31, 32].

Apical Periodontitis and Diabetes Mellitus:

Diabetes mellitus (DM) is a multifaceted metabolic syndrome affecting various systems within the body. It is characterized by disruptions in the metabolism of carbohydrates, proteins, and lipids, primarily stemming from either a significant lack of insulin production due to pancreatic β-cell dysfunction (type 1) or resistance to insulin in the liver and muscles (type 2). This metabolic disorder can impact the immune system by triggering the overproduction of pro-inflammatory cytokines by monocytes and polymorphonuclear neutrophils while simultaneously reducing the release of growth factors by macrophages. These immune system alterations predispose individuals to chronic inflammation, tissue degradation, and reduced tissue repair capabilities. Over time, diabetes can lead to dysfunction in vital organs such as the kidneys, nerves, eyes, blood vessels, and the heart, contributing to increased morbidity and mortality rates [33].

As of 2019, diabetes was estimated to affect approximately 463 million adults globally, with projections suggesting this number could rise to around 700 million by 2045. The chronic systemic inflammation associated with diabetes results in changes in the levels of inflammatory markers such as TNF-α, IL-1α, IL-1β, CRP, and IL-6 in the bloodstream, which can negatively impact the healing process in periapical regions. Furthermore, diabetes hinders collagen production, disrupts matrix protein degradation, and impairs tissue remodeling, all of which contribute to delayed wound healing [34].

Research conducted by Garber et al. (2009) [35] demonstrated impaired wound healing in diabetic rats undergoing direct pulp capping with mineral trioxide aggregate (MTA), exhibiting reduced dentin bridge formation and heightened pulpal inflammation. Additionally, existing literature strongly suggests that individuals with diabetes exhibit a higher prevalence of apical periodontitis, larger periapical lesions, and increased incidence of periapical infections compared to non-diabetic counterparts. In a retrospective study by Segura-Egea et al. (2005), it was found that patients with diabetes had a greater likelihood of untreated periapical lesions and unsuccessful endodontic treatments. Moreover, patients with diabetes receiving insulin therapy showed a tendency towards symptomatic periradicular disease and increased incidences of flare-ups following endodontic procedures [36].

Apical Periodontitis and Pregnancy:

Periodontal diseases have been demonstrated to impose a significant burden on pregnant individuals as a result of the systemic inflammatory stress they induce. Research has shown that molecules such as Prostaglandin E2 (PGE-2) and TNF-α originating from inflamed periodontal

tissues in pregnant women have the ability to traverse to the placenta and amniotic fluid, thereby playing a role in the occurrence of preterm birth. Recent investigations have also delved into the connection between apical periodontitis and adverse pregnancy outcomes. Studies have revealed that the presence of a periapical lesion in women postpartum has been linked to a heightened risk of a shortened pregnancy duration, intrauterine growth restriction, and preterm birth. Notably, Khalighinejad et al. (2017) identified maternal apical periodontitis as a potent independent predictor of preeclampsia [37], a prevalent adverse pregnancy outcome characterized by hypertension and proteinuria occurring after the 20th week of gestation [38], and a leading cause of maternal mortality. In a recent systematic review, Jakovljevic et al. (2021) critically assessed the existing body of evidence regarding the association between maternal apical periodontitis and adverse pregnancy outcomes. The authors concluded that, based on the available evidence of 'Fair' and 'Good' quality, a positive correlation was discernible between maternal apical periodontitis and adverse pregnancy outcomes [39]. Consequently, it is plausible to propose that the risk of preeclampsia and low birth-weight preterm birth could potentially be mitigated through the timely identification and treatment of any sources of inflammation, including apical periodontitis, prior to pregnancy.

Conclusion:

In conclusion, the research highlights the significant impact of endodontic infections on systemic health. The review emphasizes the complex interplay between endodontic microbiota, host immune response, and systemic diseases. It underscores the potential risk factors, the burden of endodontic disease on healthcare systems, and the emerging evidence linking apical periodontitis to conditions such as cardiovascular diseases, diabetes mellitus, and adverse pregnancy outcomes. Furthermore, the article discusses the occurrence of bacteremia after root canal treatment, the modulation of systemic inflammatory markers, and the potential role of endodontic interventions in reducing systemic inflammation. Overall, the research underscores the importance of understanding and addressing the systemic implications of endodontic infections for improved patient care and overall public health.

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