

Review Article

Relationship of IL-1 β in Apical Periodontitis: A Systematic Review

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Abstract

Introduction: Apical periodontitis is an inflammatory process of the periradicular tissues, caused by infection and the presence of persistent microorganisms within the root canal system. When toxins released by microorganisms reach the periapex, innate and adaptive immune cells release significant amounts of various inflammatory mediators such as tumor necrosis factor, interleukin 6, interleukin 17, interferon gamma, interleukin 1 α and β , inducing periapical bone resorption.

Objective: Determine the relationship between the expression interleukin 1 β and the development of apical periodontitis.

Materials and methods: A systematic search was conducted in four electronic databases, PubMed, EBSCO Host, ScienceDirect and Wiley Online Library. Articles published from January 1, 2017, to May 10, 2022, were searched.

Results: 7 articles were included for the systematic review.

Conclusion: IL-1 β plays an important role in the development and progression of apical periodontitis.

Keywords: Apical Periodontitis; IL-1 β ; Periapical Granuloma; Periapical Cyst; Expression

Introduction

Apical periodontitis is an inflammatory process of the periradicular tissues, caused by infection and the presence of persistent microorganisms within the root canal system of the tooth [1-4]. It is commonly asymptomatic and sometimes diagnosed incidentally after a radiographic

study, showing an increase in periodontal ligament space and radiolucent areas in the periapical region [5,6]. If left untreated, it can develop into a chronic abscess with a sinus tract, periapical granuloma or periapical cyst, compromising the integrity of the tooth in the oral cavity [7,8]. Microorganisms play a key role in the development of pulp and periapical disease. When the pulp loses its vitality, mainly due to caries, periodontal disease, trauma, iatrogenic factors or previous pulp treatments, an environment conducive to their multiplication is created [9-11]. Anaerobic techniques have shown that the root canal microbiota is predominantly composed of more than 90% anaerobic bacteria belonging to the genera *Fusobacterium*, *Porphyromonas*, *Bacteroides*, *Eubacterium* and *Peptostreptococcus*, whose virulence and pathogenicity vary considerably [12]. Microbial interactions, which are an important part of the root canal microbiome, can be positive (synergistic) or negative due to specific microorganisms that alter the respiratory and nutritional environment within the root canal [13]. Individual species are less virulent and interact with pathogens due to factors such as interactions with other microorganisms present in the root canal, endotoxin release, synthesis of tissue-damaging enzymes and the ability to interfere with and neutralize host defenses. The infected root canal constitutes the main source of irritation for the periapical tissues. Within the canal, microorganisms are in strategic positions, protected from the host's defense cells. Typically, these intra-canal microorganisms organize themselves as biofilms that adhere to the root canal walls, making them resistant to chemical disinfectants, systemic antibiotics and the immune system. The World Health Organization defines it as "a proliferating and enzymatically active bacterial ecosystem generally

present in necrotic tissues." The presence of microorganisms living in the biofilm is 1000 times more resistant to antimicrobial agents in endodontic infections [14-23]. When toxins released by microorganisms (e.g., lipopolysaccharides, lipoteichoic acid) reach the periapex, many innate and adaptive immune cells release large amounts of various inflammatory mediators such as neuropeptides, cytokines, chemokines, Tumor Necrosis Factor (TNF- α), Interleukin 6 (IL-6), Interleukin 17 (IL-17), Interferon gamma (IFN- γ), interleukin 1 α and β , inducing periradicular bone resorption [24-29]. Interleukins are messengers of the immune system that allow for the coordination of responses to a wide range of physiological and pathological processes. Interleukins can inhibit or induce tissue inflammation and recruit immune cells. They bind to specific receptors on target cells and activate a signaling cascade that results in the expression of a set of genes necessary for a specialized response [30]. Most interleukins act on the same cell producing them (autocrine action) or on nearby cells (paracrine action) [31]. One of the main molecules involved in apical periodontitis is Interleukin-1 (IL-1) [32]. It belongs to one of the most described cytokine families, which includes a total of 8 cytokines, along with three receptor antagonists. The transcription of these molecules is activated by transcription factors of the NF- κ B family and the signaling is activated by various factors, primarily pathogen infection (pathogen-associated molecular patterns, PAMPs) through Toll-Like Receptors (TLRs), NOD-Like Receptors (NLRs), cytokines such as IL-6 and growth factors. Interleukin 1 β (IL-1 β) is a potent pro-inflammatory cytokine crucial for the host's activation in response to infections and injuries. It is also the most studied cytokine in the IL-1 family. As a pro-inflammatory cytokine, it helps activate the host's immune system in response to infections and injuries. There is evidence that these cytokines play an important role in the development of inflammation, as they are secreted by epithelial cells, NK cells, neutrophils, macrophages, mast cells, hepatocytes, etc [33]. IL-1 β is absent in cells under homeostasis conditions and is only expressed after the activation of lymphoid and myeloid cells [32]. For this to occur, IL-1 β must be synthesized from an inactive precursor called pro-IL-1 β , which has a weight of 31 kDa. The first expression of this inactive form occurs due to a secretion stimulus, but this initial stimulus is ineffective in inducing the processing and production of the active molecule. The cell must bind to another PAMP through a Pattern Recognition Receptor (PRR). Pro-IL-1 β is cleaved by caspase-1, derived from the inflammasome, giving rise to mature IL-1 β with a weight of 17 kDa, acquiring the ability to bind to its receptor (IL-1R1) present in endothelial, epithelial and leukocyte cells, resulting in increased expression of IL-1 β , IL-6, TNF- α and increased vascular permeability (Fig. 1) [31,34-37]. The purpose of this systematic review was to determine the relationship between IL-1 β expression and the development of apical periodontitis.

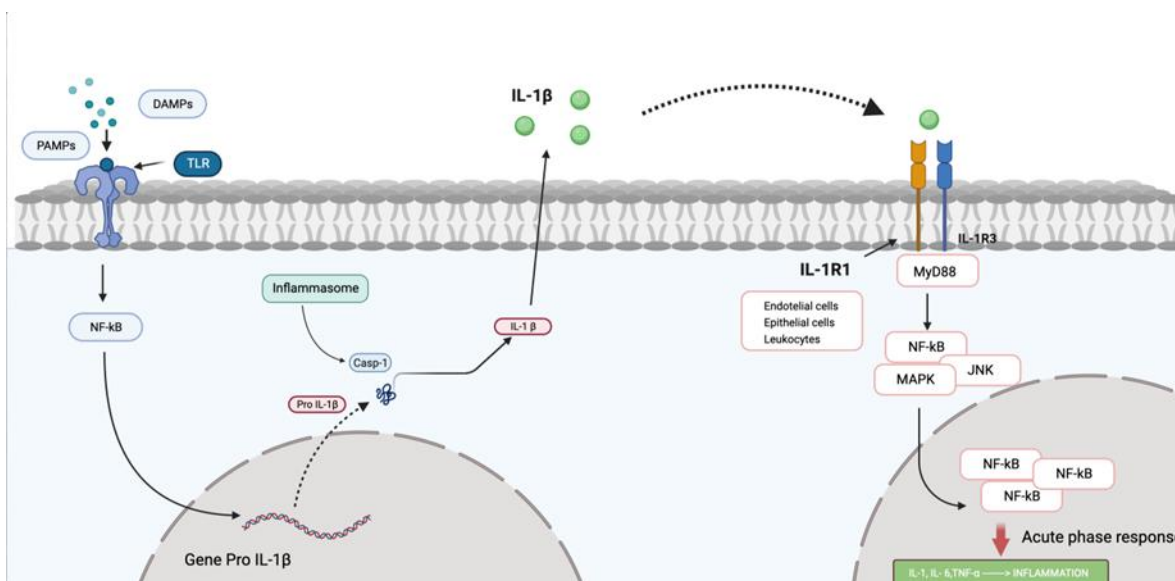


Figure 1: Expression of IL-1 β . The expression of interleukin is triggered by the initial contact between microorganisms and the receptor, leading to the first expression of IL-1 β . Once released into the extracellular environment and bound to its receptor, signaling occurs, resulting in increased recruitment of immune cells and higher expression of IL-1 β , IL-6 and TNF- α . This signaling cascade further amplifies the immune response and inflammatory processes associated with apical periodontitis.

Methodology

The first step in the systematic process of this review involved using the PICO methodology to formulate a clinical or research question. Studies were included that measured the expression of IL-1 β using immunohistochemistry, ELISA and qPCR and examined its relationship with the development of apical periodontitis.

PICO Strategy

Population (P): Patients with apical periodontitis

Intervention (I): IL-1 β

Comparison (C): Expression

Outcomes (O): Development of the disease

Protocol and Registration

The protocol of the current systematic review registered in the database of the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42023426010 and was performed according to the PRISMA guidelines.

Research Question

Is the expression of IL-1 β associated with the development of apical periodontitis?

Electronic Search

A systematic search of published articles was conducted from January 1, 2017, to May 10, 2022, using four different electronic databases: PubMed, EBSCO Host, ScienceDirect and Wiley Online Library.

Search Strategy

The keywords used were: "apical periodontitis" or "periapical lesions" or "apical lesion" and "interleukin 1 β " or "IL-1 β " MeSH terms and Boolean operators.

Inclusion Criteria

The inclusion criteria for the articles were as follows: studies conducted in humans, diagnosis of dental-origin apical periodontitis (granulomas, cysts, and/or abscesses), measurement of IL-1 β expression, a minimum sample size of 25. The considered articles were written in English and published between 2017 and 2022.

Exclusion Criteria

We excluded literature reviews, animal studies, *in-vitro* studies, letters to the editor, studies examining the relationship between systemic diseases and apical periodontitis, studies involving drug administration without measuring expression or lacking specific methodology.

Elimination Criteria

Articles that failed to adhere to the code of ethics were eliminated.

Data Collection and Analysis

The relevant studies were individually analyzed and reviewed by two reviewers. For each study, a data collection form was utilized, which included the title, author, year, study design type, IL-1 β expression and corresponding results.

Results

During the literature search, a total of 29 articles were identified across the selected databases, including PubMed (17 articles), Wiley Online Library (3 articles), ScienceDirect (3 articles) and EBSCO Host (6 articles). Out of these, 6 duplicate articles were removed. After applying the inclusion criteria, 16 articles that did not meet the criteria were also eliminated. Ultimately, 7 articles were selected for a thorough reading, as illustrated in Fig. 2.

In the analysis, only human studies were considered. The characteristics of the included studies were categorized based on the author, year, study design, intervention, sample size in each group and mean results, as presented in Table 1.

Author and year	Type of study	Sample collection	Sample size	Methodology	Results	P-value
Popovska, et al., 2017	Transversal	Apical lesion	Group I: 25 Group I: 25 Group IIb: 15 Group III:15 Control: 5	ELISA	Group I: 9 pg/mL Group IIa: 14 pg/mL* Group IIb: 15 pg/mL Group III: 5 pg/mL* Control: Not detected	p=<0.05
Nikolic, et al., 2018	Transversal	Apical lesion	Experimental: 50 RANKL prevalence: 33 OPG prevalence: 17	qPCR	Relative gene expression: 0.01022 ± 0.01259 (0.00548) RANKL prevalence: 0.01212 ± 0.01422 (0.00809) OPG prevalence: 0.00653 ± 0.00766 (0.00333)	p=0.12
Kae Ishi, et al., 2021	Transversal	Apical lesion	Experimental: 25 Control: 5	qPCR	Experimental: 0.7* Control: 0	p=0.01
Tamura, el al., 2021	Transversal	Apical lesion	Experimental: 44 Control: 5	qPCR	Experimental: 0.27* Control: 0	p=<0.01
Dessaune Neto, et al., 2018	Transversal	Apical lesion	Cysts: 7 Granulomas: 20	Immunohistochemistry	Cyst - Focal: 57% - Mild-Moderate: 28.5 - Severe: 14.5% Granuloma - Focal: 70% - Mild-Moderate: 25% - Severe: 5%	There was no significant difference
Teixeira, et al., 2021	Transversal	Apical lesion	Adult patients Cysts: 15 Granulomas: 15 Young patients Cysts: 15 Granulomas: 15	Immunohistochemistry	Adult patients Cysts: 1.52 ± 0.46 * Granulomas: 1.40 ± 0.59 * Young patients Cysts: 0.32 ± 0.17 Granulomas: 0.60 ± 0.26	Cysts: young patients vs. adult patients: p=0.008 Granulomas: young patients vs adult patients: p=0.041

Thuller, et al., 2021	Transversal	Apical lesion	Smokers: 16 Non-smokers: 16	Immunohistochemistry	Smokers: 0.61* Non-smokers : 0.27	P=0.004
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Table 1: Characteristics of the included studies.

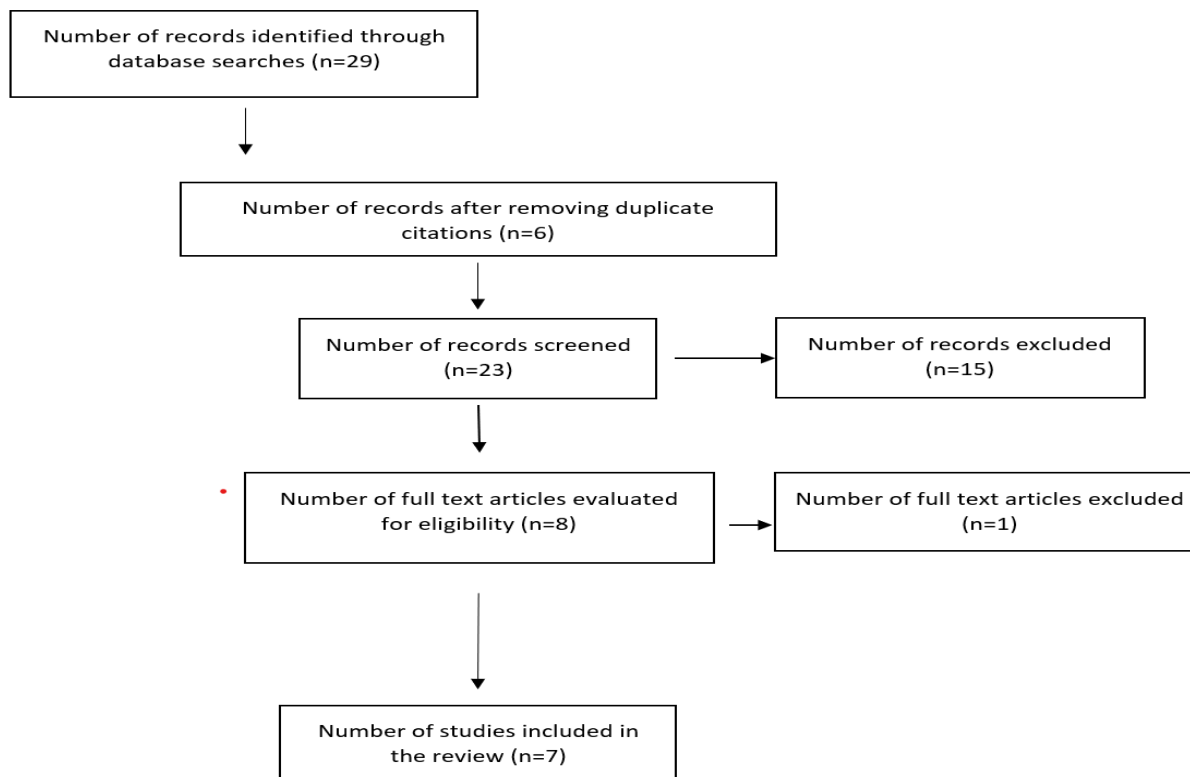


Figure 2: Inclusion and exclusion strategy.

Discussion

All the studies included in this systematic review obtained samples through apical surgery and/or dental extractions, ensuring complete removal of the affected tissue for analysis. Various variables such as granulomas, cysts, lesion size and symptomatology were analyzed, yielding different results depending on the variable under study. One study showed that IL-1 β is generally associated with the chronic stage of apical periodontitis [38]. Immunohistochemistry revealed focal and weak/moderate expression of IL-1 β in both the cyst and granuloma groups. However, no significant differences were found between the patients' symptoms and IL-1 β expression, nor was a correlation established with the destruction of periapical bone tissue as measured by cone beam computed tomography. In contrast, a study made by ELISA to measure IL-1 β expression demonstrated a trend of lower expression in smaller lesions and higher expression in larger lesions [29]. Nonetheless, cases of large lesions with low expression and small lesions with high expression of IL-1 β were also observed, suggesting the need for a larger sample size to verify these findings. Similarly, the study by did not find a correlation between cytokine expression and symptoms [38]. IL-1 β expression has also been assessed through Real-Time Polymerase Chain Reaction (RT-PCR) using apical lesions and healthy gingival tissue as a control group. In this regard, Ishii, Tamura found significantly higher mRNA expression of IL-1 β in periapical granulomas compared to the control group ($p < 0.01$) [39]. Tamura, Miyata corroborated these findings, demonstrating higher IL-1 β expression in periapical granulomas compared to the control group, thus emphasizing the importance of this interleukin in the development of periapical pathogenesis [40]. Other molecules, such as RANKL and OPG, can interact with IL-1 β . The presence of RANKL was associated with higher expression of IL-1 β (0.01212 ± 0.01422) compared to OPG expression (0.00653 ± 0.00766). As apical periodontitis is characterized by bone resorption, molecules involved in osteoclastogenesis like RANKL play a crucial role in IL-1 β expression (Nikolic, Jakovljevic. Various factors may interact with the development of apical periodontitis [41]. Teixeira, Ferreira compared two groups based on age, evaluating age as a factor in the progression of apical periodontitis through immunohistochemistry [27]. They found increased expression of IL-1 β in elderly patients compared to young patients,

which aligns with a prevalence study, reporting a higher prevalence of apical periodontitis in elderly individuals. Smoking was also examined as a factor associated with higher IL-1 β expression using immunohistochemistry and a statistically significant difference ($p=0.04$) was found, suggesting that osteoclastic and inflammatory responses could be linked to tobacco consumption [42]. However, similar to the study by no significant difference in lesion size was observed between the studied groups (Thuller, Armada) [28,38]. Further investigation regarding the potential relationship between IL-1 β overexpression and lesion size would be an important step in understanding its role in bone loss.

Conclusion

IL-1 β is a crucial factor in the development and advancement of apical periodontitis. However, its association with symptoms remains unclear and further evidence is required to ascertain its impact on lesion size. While the studies examined in this systematic review underscore the significance of this cytokine in apical inflammation, it is important to acknowledge that there are other cytokines that may also play a significant role in the establishment and progression of apical periodontitis.

Conflict of Interest

There are no potential conflicts of interest to declare in this systematic review.

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Author Contributions

All authors contributed equally for this paper.

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