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Influence of interleukin genetic polymorphism on apical periodontitis in human patients: A comprehensive review

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ABSTRACT. We examined the influence of interleukin genetic polymorphisms in individuals with apical periodontitis (AP). Based on the PICO strategy, searches were conducted in PubMed, SciELO, Web of Science, Medline, LILACS and EMBASE databases to answer a guiding question. The quality of studies and methodological rigor were assessed using the Critical Appraisal Skills Program Checklist and classification made according to levels of evidence. The search identified 292 studies, of which six were included based on the criteria. All evaluated the IL-1β polymorphism, of which three found a significant association with a protective and/or potentiating effect of IL-1β on AP. Two studies evaluated the IL-6 polymorphism, one of which identified a significant association. Three studies evaluated TNF-α polymorphism, of which two reported significant associations with AP. An association was also found in one study for IL-8 with AP. In conclusion, polymorphisms of several interleukins have been found to influence the risk and development of AP in humans. Some polymorphisms are more influential and have been more intensively studied than others, such as interleukin 1-β, followed by IL-6 and TNF-α. This influence of genotype can be expressively or mildly marked. Individuals presenting one or two copies of a particular allele appear to be at higher risk of developing

periapical lesions. These apparent associations of interleukins with AP merit further study.

Key words: Periapical periodontitis; Apical periodontitis; Periapical abscess; Polymorphism genetic; Interleukins

INTRODUCTION

Apical periodontitis (AP) involves inflammatory reactions caused by microbial colonization of the root canal system, which arises mainly due to pulp necrosis (Nair, 2006). It is a host response to recruit defense cells and mediators of the immune system to prevent the spread of infection to other sites (Cintra et al., 2016). Although microorganisms perform the main role in the etiology of AP, the presence of inflammatory cells, such as lymphocytes, macrophages and neutrophils in human periapical lesions shows that the immune response is directly involved in its pathogenesis (Gomez-Gallego et al., 2009; Salmond and Zamoyska, 2011; Quan et al., 2019).

The immune system is a sophisticated and interconnected set, which operates through cellular elements, protein substances and vascular alterations, pertinent and necessary factors for homeostasis. Such dynamics can establish the physiological process of tolerance, as well as the effective response of the host and its environment. Any dysregulation of this balance can result in disease (Kannarkat et al., 2013; Allen Reish and Standaert, 2015; Chen et al., 2017). The pathogenesis of AP is complex, for many mediators of inflammation are involved, and they act to regulate and determine the nature of the immune response. In other words, they exhibit pro- or anti-inflammatory properties (Siqueira and Roças, 2007; Burgener et al., 2010; Pak et al., 2012).

Inflammatory mediators or interleukins (IL) are responsible for a myriad of biological effects. Their local effects include increased leukocyte adhesion to endothelial walls, lymphocyte stimulation, neutrophil potentiation, prostaglandin and proteolytic enzyme production, enhanced bone resorption, and inhibition of bone formation (Nair, 2004; Küchler et al., 2018; Yang et al., 2018; Braz-Silva et al., 2019). The interleukins play an important role in the immunological intermediations. They are signaling molecules that, in a similar way to hormones, act in specific receptors on the surfaces of cell membranes, to stimulate or inhibit cell division, as well as stimulate the secretion of own molecules or induce apoptosis (Alam and Gosrka, 2003; Chaplin, 2003; Shlomchik and Weisel, 2012; Cantore et al., 2014).

The production of these mediators varies widely among individuals, due to genetic polymorphisms of the genes that transcribe them, which is defined as variations in the deoxyribonucleic acid (DNA) strand, present in greater than 1% of the population. Thus, Single Nucleotide Polymorphisms (SNP)— those in which there is a simple substitution of one nucleotide for another— are evaluated for their role in multifactorial and other inflammatory diseases (Pociot et al., 1992; Johnson et al., 2004; Balasubramanian et al., 2004). Besides potentiating or attenuating diseases, they cause several effects in periradicular responses, and may lead to alterations in the gene expression and activity levels, interfering in the balance of pro and anti-inflammatory interleukins (Martins and Falcão, 2000; Salles et al., 2018).

Identifying the functional role of SNP and their influence on disease susceptibility and severity not only increases the understanding of disease pathophysiology, but also allows to elucidate the host risk and susceptibility, to assists the diagnosis, to predicts the disease course, and to determine the treatment and prognosis in patients (Vernal et al., 2005). Thus, the present review was conducted in order to explore and summarize existing studies concerning the relationship and influence of genetic polymorphisms of interleukins with AP. Our hypothesis was that polymorphisms in gene promoters may or may not alter their expression profile, leading to a higher or lower production of their gene product, helping explain why individuals with the same disease manifest it differently.

MATERIAL AND METHODS

This integrative review was composed of six steps: 1) elaboration of the guiding question; 2) literature search or sampling; 3) data collection; 4) critical analysis of the included studies; 5) discussion of the results; and 6) presentation of the integrative review (Whittemore and Knafl, 2005; Mendes et al., 2008). For the formulation of the research guiding question, the PICO strategy (Patient/population/disease; Intervention or issue of interest; Comparison, Intervention or issue of interest; Outcome) was used, (Page et al., 2020) and presented as, "What is the influence of interleukin genetic polymorphism in patients with apical periodontitis?"

Studies involving humans, clinical trials, case-control trials, editorial letters, historical reviews, case reports, and case series, which sought to evaluate the relationship and influence of genetic polymorphism of interleukins in humans with AP, were included. Unpublished manuscripts, duplicate articles, literature reviews, cell culture laboratory studies, animal studies, book chapters, theses, guidelines, and studies that did not evaluate the relationship and influence of genetic polymorphism of interleukins in humans with AP, were excluded. The electronic search was conducted in PubMed, Scientific Electronic Library Online (SciELO), Web of Science, Medical Literature Analysis and Retrieval System On-line (Medline) via Biblioteca Virtual em Saúde (BVS), Latin American and Caribbean Literature in Health Sciences (LILACS) via BVS, and EMBASE, from May 1 May 26, 2022, without restrictions on language and publication date. The Medical Subject Headings (MeSH) terms used in the search were "periapical periodontitis," "periapical abscess," "polymorphism, genetic," "polymorphism, single nucleotide," and "interleukins." In addition, MeSH synonyms and related terms were included. The Health Science Descriptor (*Descritores em Ciências da Saúde* – DeCS) terms used in the search were "periodontite periapical", “granuloma periapical", "abscesso periapical", "polimorfismo genético", "polimorfismo de nucleotídeo único", and "interleucinas". The Boolean operators "AND" and "OR" were applied to combine the terms.

Initially, the studies were selected by reading the title and abstract and evaluation of the eligibility criteria. If the title and abstract were unclear, the paper was read in its entirety to minimize the possibility of overlooking important studies. In addition, a manual search for additional studies was also performed in the reference lists of the included articles. The quality of the selected studies and methodological rigor were assessed using the *Critical Appraisal Skills Programme Case Control Study Checklist* (CASP) (CASP, 2018). In this evaluation, three broad questions are considered to evaluate a case control study, divided into sections (A, B and C). A 12-point scorecard based on CASP questions was created.

Each quality criterion was rated as "Yes" (1 point) or "No" or "Can't tell" (0 points). Regarding the effect, it was evaluated as "very statistically significant" (1 point) or "statically significant" (0 point), and regarding the estimation of the effect, "very precise" (1 point), "medium or low precise" (0 points). The articles were classified into two categories, according to the score achieved with the application of the instrument: A (10 or more points), studies of high methodological quality and reduced bias; B (9 points or less), studies of moderate methodological quality, but with increased potential bias. CASP does not aim to exclude studies due to poor methodological quality. Therefore, the exclusion criteria described above were the only ones considered to remove studies.

The classification of studies was performed according to the levels of evidence, as follows: I: systematic review or meta-analysis of clinical trials; II: Randomized controlled clinical trials; III: Non-randomized controlled clinical trials; IV: Case-control and cohort; V: Systematic review of descriptive and qualitative studies; VI: Descriptive or qualitative studies (Stetler et al., 1998). Following the analysis, data was extracted for interpretation and description of the results. These results were described in a narrative-descriptive way and synthesized in a synoptic table adapted from Ursi and Galvão (2006) with the following information: Title, author(s)/year, objectives, sample detailing, results, Recommendations/Conclusions and classification according to the level of evidence.

RESULTS

A total of 292 studies were identified in the databases, with eight duplicates and seven reviews removed. Of the 277 record articles being screened, eight remained for eligibility. Two articles were excluded because they were not directly related to the topic of the study. Therefore, six articles were included for the development of the review. Regarding quality, two studies were considered to have high methodological quality (Dill et al., 2015; Jakovljevic et al., 2020) and four studies (de Sá et al., 2007; Siqueira et al., 2009; Morsani et al., 2011; Amaya et al., 2013) were considered to have moderate quality (Supplementary 1). All of the selected studies were published in Endodontic Journals and were case-control studies published between the years 2007 and 2020. All articles selected for reading address the polymorphism of various interleukins, such as IL-1α, IL-1β, IL-6, TNF-α, IL-8, IL-10, IL-12 (Jakovljevic et al., 2020; Dill et al. 2015; Amaya et al., 2013; Morsani et al., 2011; Siqueira et al., 2009; de Sá et al., 2007), in the presence of AP (Supplementary 2).

All studies have evaluated, beside others, the polymorphism of IL-1β (Jakovljevic et al., 2020; Dill et al. 2015; Amaya et al., 2013; Morsani et al., 2011; Siqueira et al., 2009; de Sá et al., 2007). Jakovljevic et al (2020) found that the IL-1β polymorphism -511 C/T exerted a protective effect in both heterozygotes and homozygotes. The presence of polymorphism decreases the risk of developing AP in homozygotes and heterozygotes, leading to a 2- to almost 9-fold decrease in AP risk in CT and TT genotypes, respectively. Dill et al (2015) found that polymorphism in IL-1β showed a single allele and genotype AA association in subjects with deep caries and periapical lesions. Morsani et al (2011) found a strong association in the case group and the presence of a genotype comprising at least one polymorphic T allele 2 of IL-1β. The presence of the polymorphism increased the risk of persistent AP sevenfold compared to those without the polymorphism.

Two studies have evaluated the polymorphism of IL-6 (Dill et al., 2016; de Sá et al., 2007). De Sá et al (2007) found a significant association between the GG genotype and the G allele of the IL-6 gene polymorphism -174 G/C, in women and in individuals ≤ 35 years old, with the presence of symptomatic odontogenic abscess. Three studies evaluated the polymorphism in TNF-α (Jakovljevic et. al, 2020; de Sá et al., 2007; Amaya et al., 2013). Jakovljevic et al (2020) identified that the TNF-α -308 G/A polymorphism increased susceptibility to AP for heterozygotes, GA genotype and homozygotes, AA genotype, in carriers of the variant A allele, showing that the TNF-α -308 G/A polymorphism is associated with increased risk of AP. De Sá et al (2007) identified a strong inverse correlation between TNF-α and patients with symptomatic odontogenic abscess, speculating that patients carrying the AA genotype may express a protective phenotype against the disease was reported.

Severa; authors studied the polymorphism of the pro inflammatory IL-8 and anti-inflammatory IL-10 and IL-12 (Amaya et al., 2013; de Sá et al., 2007). Only Amaya et al (2013) found significant differences in the distribution of the A -251 allele of IL8/CXCL8, AA or AT and TT, wild-type genotype (no polymorphism). The A allele was associated with chronic non-suppurative AP, revealing that the risk of developing this form is higher in homozygotes, AA or heterozygotes, AT.

For identification of interleukin genotypes, four studies performed them by simple buccal swabs, (de Sá et al., 2007; Morsani et al., 2011; Dill et al., 2015; Jakovljevic et al., 2020). Two studies were conducted through blood studies (Siqueira et al., 2009; Amaya et al., 2013). One study used part of the lesions for genotyping (Jakovljevic et al., 2020).

DISCUSSION

Genetic polymorphisms are alterations in the DNA chain itself caused by different combinations of nucleotides that can change the genetic code in a way that affects gene transcription, exacerbating or attenuating diseases. In AP, genes contribute to functional alterations in the apical periodontium by varying protein production. Many interleukins and their genetic polymorphisms are known, and they can act by inducing bone resorption, inhibiting neoformation, stimulating osteoclasts, as well as acting in a protective or anti-inflammatory manner. Thus, this review aims to provide a summary of the scientific evidence in the literature about the relationship between genetic alterations and their repercussions on the phenotype, as well as gaps in knowledge and the need for new studies.

The studies evaluated are consistent regarding the role of IL-1β as an important pro-inflammatory cytokine involved in the pathogenesis of AP, as well as its function in bone metabolism in the periapical region. Regarding biallelic genetic polymorphisms, it is suggested that this effect is potentiated. Monocytes from people homozygous for IL-1β, TT genotype, produce four times more IL-1β than heterozygous cells, CT genotype, and twice as much as wild-type, CC genotype. This increased production may contribute to perpetuating the inflammatory response found in the periapical area of a tooth (Pociot et al., 1992). A case-control study that evaluated the IL-1β gene polymorphism in the pathogenesis of endodontic failure, observed a strong association between recurrent AP and the presence of the IL-1β polymorphism +3954 C/T - regardless of the genotype, whether heterozygous or homozygous - evidencing that the presence of the T allele increased the risk of recurrent AP by 7-fold, compared to individuals without polymorphism (Morsani et

al., 2011). A case-control study hypothesized that polymorphisms in cytokine genes might contribute to an individual's increased susceptibility to apical tissue destruction in response to deep caries. The authors identified an association of an allele and genotype of IL-1β polymorphism in individuals with deep caries and periapical lesions, agreeing with findings in the literature (Bian et al., 2012).

However, in discordance, we found evidence that the IL-1β polymorphism -511 C/T exerted a protective effect in both heterozygotes and homozygotes, i.e., it decreased the risk of developing AP, leading to a 2- to almost 9-fold decrease in the risk of AP in the CT and TT genotypes, respectively (Jakovljevic et al., 2020). Also, some of the studies included in our review found no positive association or differences in the presence of IL-1β polymorphism and AP (de Sá et al., 2007; Siqueira et al., 2009; Amaya et al., 2013). Such differences can be explained by the diversity of studies, sample size, as well as ethnic variety of the populations.

IL-6 is an important pro-inflammatory cytokine in bone resorption (Moreira et al., 2007). De Sá et al. (2007) found a significant association between the GG genotype and the G allele of the polymorphism at the -174 G/C locus of the IL-6 gene in women and individuals ≤35 years old with symptomatic odontogenic abscesses. In agreement, the increased expression of the IL-6 polymorphism is associated with periodontal disease severity in Brazilian individuals (Moreira et al., 2007).

TNF-α is a potent pro-inflammatory immune mediator of acute and chronic inflammatory responses and can increase bone resorption (de Sá et al., 2007). In the studies by Jakovljevic et al. (2020), under asymptomatic conditions, the TNF-α polymorphism -308 G/A increased susceptibility to AP for heterozygotes and homozygotes (GA and AA) in carriers of the variant A allele. A strong inverse correlation was detected between TNF-α and patients with symptomatic odontogenic abscesses (de Sá et al., 2007). While the first identified increased susceptibility, the latter identified a protective effect. It can be suggested that TNF-α potentiates effects in chronic or asymptomatic episodes and has a protective effect in acute or symptomatic episodes.

Also, it is necessary to study the relationship of the AP polymorphism to other proinflammatory interleukins, such as IL-17. Reports indicate that IL-17 levels are elevated in cases of periodontitis and chronic periapical lesions (Johnson et al., 2004; Takahashi et al., 2005; Vernal et al., 2005; Colić et al., 2009). A study conducted in mice that evaluated the role of IL-17A in periapical lesions suggested that IL-17 would be involved in the process of periapical lesion formation (Oseko et al., 2009). Studies of the polymorphism of this gene in patients with underlying inflammatory disease AP are scarce. Most reports associated the IL-17 gene polymorphism with periodontal and other immunoinflammatory diseases (Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis) (Fishman et al., 1998; Bian et al., 2012; Farmohammadi et al., 2019), showing the need for further research with these objectives.

The clinical implications of this review consisted of the synthesizing of several studies in humans that allow the screening of interleukin genotypes through simple cheek swabs, blood studies, or using part of the lesions and verifying, through the analyzed genetic material, the presence of a high-risk allele (homozygous or heterozygous genotype). Thus, specific designs can be elaborated to mimic the consequences arising from polymorphic genes. In other words, it becomes possible to recognize the patient's status regarding the disease even before starting endodontic treatment.

The limitations of this study include the fact that there are few studies regarding the relationship and influence of genetic polymorphisms in interleukins in humans with AP. Besides, the primary studies have a small sample size, and the ethnic diversity of the populations studied may cause bias. Moreover, none of the gene polymorphisms analyzed was associated with the clinical characteristics of the periapical lesions, which makes it suggestive for the scientific community to research this pathology associated with heredity, including clinical-radiographic aspects such as the relationship with lesion dimensions, bone loss, and presence of pain, with regard to pro-inflammatory interleukins, as they stimulate resorption and pathological bone loss in the presence of the disease. The relatively small sample size of the patients evaluated in the studies, added to the ethnic variations of the populations, shows the need for further studies.

CONCLUSIONS

Genetic factors, especially interleukin polymorphisms, whether pro- or anti-inflammatory, influence the risk and development of AP in humans, as a microbial disease. This influence is more or less marked with regard to the. Therefore, individuals presenting one or two copies of a specific allele appear to be at higher risk of developing periapical lesions.

The polymorphism of several interleukins is involved in these processes. Some are more influential than others, such as interleukin 1-β. Since it is the most predominant form found in human periapical lesions, it was the one that showed the most association and influence on the severity of AP in the studies evaluated, followed by IL-6 and TNF-α. Other interleukins need to be further studied, such as IL-17, which has been suggested to be associated with the pathogenesis of the disease but is still little studied due to genetic polymorphism.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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