Investigating the effect of genetic factors on periodontal diseases among Iranian population

Jalaloddin Hamissi, Shaghayegh Pishkari, Adeleh Ghoudosi

Background: Periodontitis is a multifactorial disease in which the host's immune system and genetic factors greatly influence the pathogenesis of the disease. Polymorphism in cytokines genes and the associated receptors is considered as a potential genetic risk factor for the occurrence of periodontal diseases.

Objective: The aim of this study was to investigate the correlation between the polymorphism in interleukins genes and the incidence of periodontitis.

Materials & Methods: This was a literature review covering all studies over the correlation between the interleukins genes polymorphism and the existence of periodontitis which were performed during the last 10 years in Iran.

Results & Conclusion: Lack of correlation between the polymorphism in IL-1RN, IL-1α(889), TNF-α(-308), IL-1β(+3954), IL-4R(375), IL-4R(411), IL-4R(478), IL-4R(406), IL-10(-1082), and IL-10 genes and periodontitis among the study populations brings doubt to the usefulness of these candidate genes, as risk makers in various types of periodontitis. However, polymorphisms associated with IL-1RN, IL-6, IL-1β, IL-8 and IL-17 genes are suggested to be used as risk markers in diagnosing periodontitis.

Keywords: Periodontal diseases, Interleukin, Polymorphism, Genotype.
**Introduction**

Periodontitis is a multifactorial disease initiated by a microbial dental plaque although its further progression and severity depend on environmental factors, acquired diseases, and genetic susceptibility. Destruction of dental supporting (connective) tissues, loose teeth and even loss of teeth are among the most important complications of this disease. 

During the inflammation of gingival tissues, in addition to related pathogenic bacteria, the immune reactions against bacteria also affect the severity of damage to gingiva. Among these, the cytokines that regulate the immune responses, play an important role in this clinical condition. Since the production of different cytokines, similar to other cellular factors, is under genetic control, therefore, the status of the genes involved in the production of cytokines could indirectly influence the severity of gum disease. 

Interleukins are considered as important members of cytokines. Interleukin-10 (IL-10) which is also known as human cytokine synthesis inhibitory factor (CSIF), is secreted by TH2 and active macrophage cells and inhibits the majority or all cytokines generated by TH1 cells, thus the immune system and genetic factors are obviously involved in the process of periodontal diseases and the occurrence of mutation in the promoter region of some genes could affect the production of these cytokines as seen in patients with gingivitis and IL-10 polymorphism who are more susceptible to develop periodontitis. 

The most proinflammatory cytokines are IL-1α, IL-1β, and TNF-α that produce similar effects with synergistic properties. These cytokines are also engaged in the incidence of fever, regulation of coagulation system, and suppression of stem cells division in the bone marrow. 

TNF-α, in addition to activating the chemotaxis mechanism in inflammatory cells, stimulates the synthesis of IL-1, IL-6, and IL-8 and increases the generation of products by T and B lymphocytes. Proinflammatory cytokines promote the synthesis and expression of adhesion molecule on the endothelium of inflammatory cells such as neutrophils, monocytes, and fibroblasts, leading to local vasodilatation, chemotactic activity, and inflammation. 

The secretion of TNF-α is regarded as the host’s most important response against the active component of gram negative bacteria i.e. LPS or endotoxin, which is mostly produced by mononuclear macrophages and is produced at higher concentration when these cells are stimulated by interferon gamma (IFNγ), IL-1, and IL=17. TNFa is also produced by antigen-activated T cells, activated natural killer cells (NK), and activated mast cells. As periodontitis is a multifactorial and inflammatory disease, a hypothesis over the genetic similarity of this disease with many other inflammatory and autoimmune diseases such as asthma, atopy, lupus erythematosus, and rheumatoid arthritis has been proposed. 

The present study was aimed to investigate the correlation between the genetic risk factors and the development of periodontitis through a comprehensive literature review over the studies published within the last 10 years in Iran.

**Materials & Methods**

The present research was attempted to thoroughly examine all studies associated with the correlation between the interleukins genes polymorphism and periodontitis reported within the last 10 years from Iran. In a case-control study by Baradaran-Rahimi et al (2010) the association between several numbers of tandem repeat polymorphism in IL1RN gene and generalized aggressive periodontitis (GAgP) among patients in Mashhad (Iran) was investigated. The authors showed that the presence of A1A2 genotype in the control group was considerably lower than the case group and that the A1A1 genotype was engaged in the incidence of fever, regulation of coagulation system, and suppression of stem cells division in the bone marrow. 

**References**

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In a case-control study by Houshmand et al. (2012) in Hamedan, there was a significant difference in the incidence of periodontitis among adults with periodontitis in Mashhad (Iran). They found no significant relationship between the three types of IL-1α (-889) genotypes and the presence of periodontitis. There was no association between the two alleles (1 and 2) of IL-1α (-889) gene in the control group. Also, no correlation between the absence or presence of alleles 1 and 2 and the incidence of periodontitis was observed.

In a study by Ebadian et al. (2009) the effect of proinflammatory cytokines gene polymorphism in generalized aggressive periodontitis was investigated. This study was aimed to examine the impact of single nucleotide polymorphisms (SNP) of IL-1β gene at position 3954, IL-1α (-889), and TNF-α (-308) on incidence of periodontitis among Iranian population. This case/control study showed that there was no significant difference between the polymorphisms of IL-1β at position 3954, IL-1α (-889), and TNF-α (-308) and aggressive periodontitis when genotypes and alleles were examined both in patients with periodontitis and healthy individuals. They concluded that the occurrence of polymorphism in IL-1β gene at position 3954, IL-1α (-889), and TNF-α (-308) should not be considered as markers for detecting genetic susceptibility to aggressive periodontitis in Iranian/Khorasani population and Iranian/Zahedani population.

In another study by Radvar et al. (2008) over the effect of periodontal treatment on IL-6 production by peripheral monocytes in patients with aggressive and chronic periodontitis, it was shown that the level of IL-6 in the aggressive and chronic periodontitis groups was significantly higher than that found in the control (healthy) group. Also, Kiani et al. (2009) investigated the correlation between the IL-1α (-889) gene polymorphism and the incidence of aggressive periodontitis in a case-control study on adult individuals with periodontitis in Mashhad (Iran). They found no significant relationship between the 3 types of IL-1α (-889) genotypes and the presence of periodontitis. There was no association between the two alleles (1 and 2) of IL-1α (-889) gene in the control group. Also, no correlation between the absence or presence of alleles 1 and 2 and the incidence of periodontitis was observed.

In case-control study by Houshmand et al. (2012) in Hamedan, there was a significant difference in the genotype frequencies of C1633T (P < 0.05) polymorphism of IL-8 gene between the aggressive and chronic periodontitis. The same as none of the investigated SNPs in the IL8 gene was individually associated with periodontitis, some haplotypes can be protective against CP in the Czech population.
that there was no significant difference in the frequency of genotype between the two case (with aggressive periodontitis) and control (healthy individuals) groups. Also, there was insignificant difference in allele frequency between the two study groups. The authors concluded that the presence of nucleotide polymorphism in IL-10 gene at position -1082 is not associated with the development of aggressive periodontitis.18

Discussion & Conclusion

Cytokines may be present at high concentrations in gingival crevicular fluid and periodontal tissues and affect the destruction of periodontal tissues and bone. Therefore, the presence of polymorphism in these cytokines and their associated receptors is regarded as susceptibility to develop periodontal diseases.19 Several researchers (Torkzaban et al, Dashash et al) compared patients with gingivitis and healthy people for the difference in frequency of IL-10 alleles at positions -1082, 819, and 592 and reported that the presence of allele A could be considered as a risk factor for the development of gingivitis and that the presence of IL-10 polymorphism at promoter site could efficiently influence the pathogenesis of gingivitis.16,20 In contrast, lack of any significant correlation between IL-10 concentration and periodontal disease among German, Finnish, Iranian, and Icelander populations is claimed by other researchers (Bable et al, Tervonen et al, Mellati et al, and Viana et al).18,21,22,23 In similar studies by Ebadian et al and McGuire et al, the rate for loss of tooth in individuals with IL-1β polymorphism was about 2.7 times higher than those without polymorphism.24 Also, Meisel et al found a significant relationship between the IL-1β polymorphism and the rate for tooth loss.25 Wagner et al also reported an association between the IL-1β (3954) and IL-1α (-889) polymorphisms and chronic periodontitis.26 Likewise, Tabibzadeh et al showed a relationship between IL-1 concentration and periodontal degeneration.15 In a study by Kiani no association between IL-1α (-889) polymorphism and periodontal disease was established. They also found that the presence or absence of alleles 1 and 2 has no effect on periodontal disease and that the allele 2 of IL-1β (3953) polymorphism is without any impact on periodontal disease.10 Armitage et al reported that there was no difference in IL-β and IL-1α gene polymorphism between patients with periodontitis and healthy individuals.27 The results of a study by Khoshhal et al was consistent with that of Donati et al in which the distribution of genotype frequency in IL-4Ra of Swedish population showed no significant difference between the two study (case and control) groups.8,28 Also, the genotype frequency in Caucasian and Japanese populations as well as the alleles frequency in Japanese individuals showed insignificant difference between the patients and healthy groups.29 However, in a study by Gonzales et al, a significant difference in single nucleotide polymorphism (SNP) at positions -590 and -39 between the patients with aggressive periodontitis and healthy persons was reported.30 Finally, Atanasovska et al investigated the correlation between IL-4 gene polymorphism and periodontal diseases in Macedonian population in 2011 and concluded that the cytokine gene polymorphism of IL-4 (-33) and IL-4 (-1098) is associated with the incidence of periodontal diseases.31

In a case-control study by Houshmand et al (2012) in Hamedan, there was a significant difference in the genotype frequencies of C1633T (P < 0.05) polymorphism of IL-8 gene between the aggressive and chronic periodontitis.11 As well as none of the investigated SNPs (rs4073, rs2227307, rs2227306, and rs2227532) in the IL8 gene was individually associated with periodontitis, some haplotypes can be protective against CP in the Czech population.12 Kadkhodazadeh et al (2013) reported that The CC genotype of IL17 polymorphism (rs10484879) may contribute to the pathogenesis of peri-implantitis and periodontitis. The association of IL-17 polymorphism with PI and CP is a promising finding that may help in future similar studies on other ethnicities and larger study populations.32

Considering the studies mentioned above it could be concluded that the lack of correlation between the polymorphisms of IL-1RN, IL-1α (-889), TNF-α (-308), IL-1β (+3954), IL-4R (375), IL-4R (411), IL-4R (478), IL-4R (406), IL-10 (-1082), and IL-10 genes and periodontal disease, emphasized in many studies including those mentioned earlier, makes it difficult to consider these genes as risk markers for various types of periodontitis. Hence, the authors recommend that the polymorphisms of IL-1RN, IL-6, IL-1β, IL-8 and IL-17 gene to be regarded as risk markers in the detection of periodontal diseases. The most important factor that affects the results of
different studies could be the racial differences as it is well known that the racial variations play an important role in the susceptibility to periodontal disease. Also, the difference between the alleles frequency due to racial variations could justify the necessity for performing similar studies among different populations. The benefits of confirming a correlation between genetic factors and periodontal diseases include the early diagnosis of patients who are at risk of developing disease because of genetic susceptibility which could lead to preventive therapy in these individuals. The identification of genetic elements involved in the process of periodontitis, in addition to well-known factors, could also result in effective therapeutic recommendations such as considering more maintenance sessions. Eventually, the recognition of young people who are not affected by periodontitis at present but strongly at risk of developing severe periodontitis in the future because of genetic susceptibility, could pave the way for faster therapeutic measures to prevent the progression of the disease.

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