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

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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.1During 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.2Interleukins 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.3 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.4 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.4,5 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. TNFα 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.6 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

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more common among the control group with higher frequency of A1 allele in the same group. In addition, the frequency of A2 allele was higher in the case group compared to the control group, hence, the IL1RN genotype and the frequency of IL1RN allele were significantly different among the two study groups.7 Khoshhal et al (2011) examined the relationship between the polymorphisms in IL-4R gene at positions 375, 411, 478, and 406 and the severity of chronic periodontitis among the patients in Hamedan (Iran). These researchers found no significant difference in the frequency of individuals bearing this mutation among the three study groups who were suffering different stages of periodontitis.8 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.9 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.10
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.11same 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.12

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.13, 14
In 2009, Tabibzadeh et al investigated the correlation between smoking and IL-1β concentration in gingival crevicular fluid of patients with chronic periodontitis and healthy people in Tehran. The mean IL-1β concentration revealed a significant difference between smokers and non-smokers whereas the mean IL-1β concentrations for all affected sites of smokers and nonsmokers showed no significant difference although the mean IL-1β concentration in smokers was higher than that found for nonsmokers. When the healthy and affected sites in each group (smoker and nonsmoker) were compared alone, there was a significant difference in IL-1β concentration at affected sites in both groups. The authors concluded that higher concentration of IL-1β at affected sites, compared to normal sites, is indicative of a correlation between IL-1β concentration and periodontal degeneration.15In another study by Torkzaban et al in 2010, the polymorphisms of interleukin 10 gene in children (8-12 years) with gingivitis was investigated. This study which was aimed to study the H/L alleles at position -1082 and C/T alleles at position -819 of IL-10 gene revealed no significant difference between the genotypes within the study groups although the percentage frequency for the H allele, which affects the mutation, was higher in the case group compared to the control group. These researchers concluded that there is no association between the IL-10 gene polymorphism and gingivitis in 8-12-year-old children.16Interleukin 17 and the pathogenesis of periodontal diseases was the subject of another study conducted by Behfarnia et al in Isfahan (Iran) in 2009. This study showed that the mean concentration of IL-17 was significantly higher in the case group, compared to the control group.17Finally, Mellati et al in 2007 carried out a study to analyze the IL-10 gene polymorphism at position -1082 in patients with aggressive periodontitis among Iranian population and showed

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.19Several 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 diseas.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-4Rα 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 differences10 as it is well known that the racial variations play 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.27The 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 results 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.

References:

1-Kinane DF, Shiba H, Hart TC. The genetic basis of periodontitis, periodontal 2000. 2005; 39: 91-117

2- Gonzales JR, et all. J. Single-nucleotide polymorphisms in the IL-4 and IL-13 promoter region in aggressive periodontitis . J Clin Periodontal 2007; 34(6):473-479.

3- Tervonen T, et all. Polymorphisms in the CD14 and IL-6 genes associated with periodontal disease. J Clin Periodontol 2007; 34(5); 377-83.

4- Mariette X. Anti-cytokines in the treatment of inflammation. Rev Part 2003;53(5): 507-11.

5- Sorensen LK.et all.Aggressive periodontitis and chronic arthritis: Blood mononuclear cell gene expression and plasma protein levels of cytokines and cytokine inhibitors.J Periodontol 2009; 80(2): 282-9.

6- Kinane DF,et all. Analysis of genetic polymorphism at interleukin-10 and tumour necrosis factor F loci in early-onset peridontitis. J Periodontal Res 1999;34(7):379-386.

7- Association of Interleukin-1 Receptor Antagonist Gene Polymorphisms With Generalized Aggressive Periodontitis in an Iranian Population. Baradaran-Rahimi. J Periodontol 2010;81:1342-1346.

8- Association of Interleukin-4 Receptor Gene Polymorphism with Chronic Periodontitis. M. Khoshhal. Sci J Hamadan Univ Med Sci 2011; 18 (3):63-69).

9- The Effect of periodontal Treatment on IL-6 production of peripheral Blood Monocytes in Aggressive Periodontitis and Chronic Periodontitis Patients.M.Radvar.Iran.J.Immunol.June 2008,5 (2),100-106.

10-Polymorphism of IL-1α(-889) Gene and Its Association with Aggressive Periodontitis. Kiani. Iran J Allergy Asthma Immunol June 2009; 8(2): 95-98.

11- Evaluation of IL-8 gene polymorphisms in patients with periodontitis in Hamedan, Iran. Houshmand B, Hajilooi M, Rafiei A, Bidgoli M, Soheilifar S. Dent Res J (Isfahan). 2012 Jul-Aug; 9(4): 427–432

12-Haplotype Analysis of Interleukin-8 Gene Polymorphisms in Chronic and Aggressive Periodontitis. Petra Borilova Linhartova, Jan Vokurka, Hana Poskerova, Antonin Fassmann, and Lydie Izakovicova Holla. Mediators Inflamm. 2013; 2013: 342351

13- Association between TNF-α (– 308 G → A) Gene Polymorphism and Chronic Periodontitis. Solhjoo S, Mahmoudzadeh Sagheb H , Heidari Z, Hashemi M , Rigi Ladez M.Zahedan Journal of Research in Medical Sciences. 2014, 16(2): 10-14.

14- Analysis of Proinflammatory Cytokines Gene Polymorphisms in Generalized Aggressive Periodontitis (GAgP). Ebadian AR, Radvar M, Arab HR, TavakkolAfshari J, Sargolzaei N, et al. J Mash Dent Sch 2009; 33(3): 231-40.

15- Relationships between smoking & IL-1β concentrations in chronic periodontal patients . Tabibzadeh .Journal of Dental School Shahid

Beheshti University of Medical Sciences, 2009; 26 (4) :375-381

16- Evaluation of Polymorphism of IL-10 in Children with Gingivitis. TorkZaban. J Mash Dent Sch 2010; 34(1): 7-14.

17- Interleukin 17 and the pathogenesis of periodontal disease.P.Behfarnia.9th Annual Congress of Iranian Academy of Periodontology 9- 11 December – 2009 Tehran – Iran

18- Mellati E, et all. Analysis of-1082 IL-10 gene polymorphism in Iranian patients with generalized aggressive periodontitis. Med Sci Monit 2007; 13(11): CR510-14.

19- Meisel P, et all. Smoking and polymorphisms of the interleukin-1 gene cluster (IL-1 a, IL-1 |3, and IL-1RN) in patients with periodontal disease. J Periodontol 2002; 73(1): 27-32.

20- Dashash M, et all. Interleukin-10 haplotype frequencies in children with gingivitis. J. Periodontol 2006; 77(9): 1503-9.

21- Babel N, et al. Analysis of tumor necrosis factoralpha,transforming growth factor-beta, interleukin-10, IL-6 and interferon-gamma gene polymorphisms in patients with chronic periodontitis. J Periodontol 2006; 77(12); 1978-83.

22- Tervonen T, et all. Polymorphisms in the CD14 and IL-6 genes associated with periodontal disease. J Clin Periodontol 2007; 34(5); 377-83.

23- Methylation pattern of IFN-_ and IL-10 genes in periodontal tissues. Immunobiology 216 (2011) 936– 941. Viana MB

24- McGuire MK, Nunn ME. Prognosis versus actual outcome. IV the effectiveness of clinical parameters and IL-1genotype in accurately predicting prognoses and tooth survival. J Periodontol 1999; 70(1): 49-56.

25- Meisel P, et all. Smoking and polymorphisms of the interleukin-1 gene cluster (IL-1 a, IL-1 |3, and IL-1RN) in patients with periodontal disease. J Periodontol 2002; 73(1): 27-32.

26- Wagner J, et al. Prevalence of OPG and IL-1 gene polymorphisms in chronic periodontitis. J Clin Periodontol 2007; 34(10): 823-7.

27- Armitage GC, et all. Low prevalence of a periodontitis-associated interleukin-1 composite genotype in individuals of Chinese heritage. J Periodontol 2000; 71(2): 164-71

28- Donati Met all. Association of the -159 CD14 gene polymorphisms and lack of association of the -308 TNFA and Q551R Il-4RA polymorphisms with sever chronic periodontitis in Swedish Caucasians. J Clin Periodontol. 2005; 3(5)2:474-479.

29- Gonzales JR,et all. Interleukin-4 gene polymorphisms in Japanese and Caucasian patients with aggressive periodontitis. J Clin Periodontol2004; 31(5): 384- 389.

30- Gonzales JR, et all. Single-nucleotide polymorphisms in the IL-4 and IL-13 promoter region in aggressive periodontitis. J Clin Periodontol 2007; 34(6):473-479

31- IL4 gene polymorphisms and their relation to periodontal disease in a Macedonian population. Atanasovska-Stojanovska. A. Atanasovska-Stojanovska et al. / Human Immunology 72 (2011) 446–450

32- IL-17 Gene Polymorphism Is Associated with Chronic Periodontitis and Peri-implantitis in Iranian Patients: A Cross-Sectional Study. Kadkhodazadeh M, Baghani Z, Ebadian AR, Youssefi N, Mehdizadeh AR, Azimi N. Immunological Investigations, 2013; 42(2): 156–163.

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