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Investigating the Relationship Between IL-6 Gene (Rs1800795) Polymorphism and Chronic Periodontitis in an Iranian Population

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Objectives Chronic periodontitis is the most common type of periodontitis and a multifactorial disease in which a set of factors such as microbial plaque, environment, systemic conditions and genetics play a role in its development. Periodontal destruction occurs due to the host's immune response to microbial stimulation, which can lead to tooth loss. The purpose of the present study is to investigate the correlation between IL-6 gene polymorphism (rs1800795) and chronic periodontitis in an Iranian population.
Method This case-control analytical study was conducted on 54 patients with chronic periodontitis and 66 healthy individuals referred to the dental clinics of Shahid Beheshti, Zanjan, and Mashhad universities of medical sciences. After clinical examination and classification of subjects, blood samples (10 cc) were taken. The genomic DNA was extracted using salting-out method. The desired variant was amplified using PCR-RFLP method. Reaction products were analyzed after electrophoresis with 1% agarose gel. Data were analyzed with Pearson's chi-square and Hardy-Weinberg equilibrium tests, and $P<0.05$ was considered as the significant level.
Results The frequency of GG, GC, and CC genotypes was 41%, 44%, and 15%, in the patient group, and 36%, 42%, and 21%in the control group, respectively. There was no significant difference between the two groups in terms of the distribution of any of the inheritance patterns ($P>0.05$).
Conclusion The present study showed no relationship between IL-6 gene polymorphism (rs1800795) and chronic periodontitis in the studied population.
Keywords Interleukin-6; Chronic periodontitis; Polymorphism

Introduction

Periodontitis refers to chronic inflammation of the tooth-supporting tissues with a microbial origin, and its most common form is the chronic type. It is characterized in three groups of slight, moderate, and severe in terms of severity. [1] The prevalence of this disease in American adults above 30 years of age is up to 42%, and is severe in 7.8% of patients. [2] Treatments include mechanical plaque removal, training proper hygiene [3], and conservative surgical interventions. [4] If left untreated, it would progress and bone resorption due to it can lead to loss of the teeth.[3] Accordingly, it will cause functional, aesthetic, psychological, social, and economic problems for patients. [5] The immune system response to the bacteria present in the plaque and their products leads to production of inflammatory cytokines such as TNFα, IL-2, IL-1, and IL-6, and their activity results in degradation of connective tissue and bone. [6,7] Thus, the polymorphism in the genes encoding these cytokines and their receptors may be involved in increased susceptibility to incidence or lack of incidence of periodontal disease. [8] IL-6 is one of the important inflammatory mediators with both pro-inflammatory and anti-inflammatory effects. [9]

Researchers in different studies have examined the correlation between polymorphism in IL-6 plus its receptor and presence of chronic periodontitis, and they have presented variable results regarding presence or absence of correlation. Taker et al. (2017) in Turkey, found that IL-10 polymorphism is correlated with chronic and aggressive periodontitis, while IL-6 polymorphism is associated with aggressive periodontitis. [10] Zhang et al. (2014) in China, found that the polymorphism of IL-6 gene plus its receptor is involved in susceptibility to develop chronic periodontitis. [11] Kalburgi et al. (2010) in an Indian population, discovered that presence of a type of IL-6 genotype in individuals might increase the susceptibility to develop chronic periodontitis, while presence of another genotype would have protective effects against this disease. [12] Chatzopolous et al. (2018) in Greece, did not find any significant correlation between IL-6 gene polymorphism and risk of developing periodontitis; however, they found a correlation between a special genotype of IL-10 gene and higher risk of disease progression. [13]

Given the different results of previous studies and failure to find a suitable relationship between IL-6 gene polymorphism and chronic periodontitis, the aim of this research was to investigate the correlation between polymorphism of IL-6 gene and chronic periodontitis in patients referring to clinics covered by Shahid Beheshti, Zanjan, and Mashhad Universities of medical sciences in 2021. The results of this research may contribute to prepare well-documented information based on academic research for better evaluating periodontal disease,

determining the risk of disease development, and better screening.

Methods and Materials

In this analytical study of case-control type, with sequential referral of patients to healthcare centers and medical dental clinics covered by Shahid Beheshti, Zanjan, and Mashhad Universities of medical sciences, sampling was done non-randomly. In this study, based on the inclusion criteria, 54 patients with chronic periodontitis were chosen as the case group and 66 patients who were healthy and disease-free, as the control group.

Clinical phase

Three calibrated senior students of general dentistry (one in each of the Tehran, Zanjan, and Mashhad cities) performed clinical examinations and blood sampling, each under supervision of an experienced periodontist. For the categorization of the subjects into case and control groups, first clinical examinations were done using Williams periodontal probe. The Clinical Attachment Level (CAL) and Probing Depth (PD) levels were measured at the six points around the teeth (mesiobuccal. midbuccal distobuccal, distolingual, midlingual and mesiolingual) using Williams probe, and presence or absence of Bleeding On Probing (BOP) was investigated. Those with BOP and CAL greater than 3 mm and PD 4 mm and above were assigned into the case, while the others were assigned to the control groups. After selecting the patients and healthy individuals according to the inclusion and exclusion criteriasmoking) (and systemic diseasesas well as acquiring informed consent and assuring them about their information confidentiality, 10 ml of venous blood sample was taken from each subject, and kept in Ethylene Diamine Tetra Acetic acid (EDTA) tube to be transferred to the laboratory. In order to prevent bias in the study and to blind the individuals, one code was given to each patient, and was also written on the tube of samples. Thereafter, all samples were sent for laboratory investigation, determining gene sequence, and examining presence or absence of correlation with the patient's disease.

Laboratory phase

At this stage, genome DNA was extracted from the blood samples using salting out method via columnar DNA extraction kit (Pars tous Iran Co.). The IL-6-(rs1800795) variant inside IL-6 gene was replicated using PCR-RFLP technique. For this purpose, the desired Single Nucleotide Polymorphism (SNP) was searched from the relevant section in NCBI database, whereby the sequence of interest was found, and the primers required for replication of this region was designed by Oligo Primer Analysis Software v. 7. The prepared sequence, after confirmation of specificity through blasting in NCBI database, was ordered to the Pishgam biotechnology company , Iran. The sequence of the utilized primers is reported in Table 1.

Table 1- The nucleotide sequence of utilized primers

5'-ATG CCA AGT GCT GAG TCA CTA-3'	Forward primer
5'-GGA AAA TCC CAC ATT TGA TA-3'	Reverse primer

PCR

In this study, for gene sequence amplification, three minutes of denaturation was done at 94°C, along with 30 cycles at 94°C for 30 min, annealing at 57°C for 50 min, extension at 72°C for 40 s, and final extension at 72°C for 3 min.

One of the samples underwent electrophoresis using ABI 3730xl system (Macrogen, Korea) to confirm the RFLP-PCR results. Exposure of DNA pieces to the NIaIII limiting enzyme was done according to the relevant product. The DNA piece with C allele was broken to two 117- and 109-base pair pieces, while the piece with G allele remained unbroken with 226 base pairs (Figure 1).

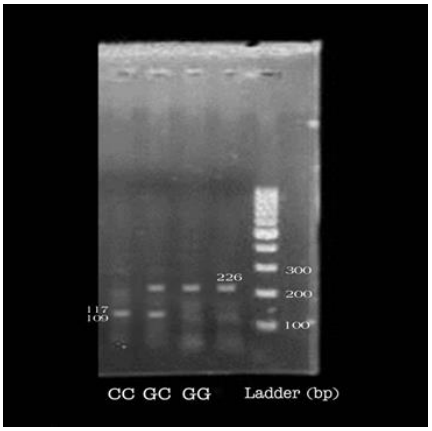

Figure 1: Electrophoresis particles

Using chi-square test, the concordance of gene frequencies with Hardy-Weinberg equilibrium was evaluated. The correlations between the genotype frequencies and the type as well as the severity of periodontitis were investigated in three models of inheritance including dominant, recessive, and codominant using Pearson's chi-square test. The P-value was corrected through multiplication by the number of SNPs, whereby those lower than 0.05 were considered significant. The results have been expressed as odds ratio (OR) and confidence interval 95%. The patients have been matched with the control group in variables such as BMI. The obtained data were analyzed by SNP Stats online software (www.snpstats.net).

This study has been approved by the ethics committee of dental sciences research center of Shahid Beheshti

University of medical sciences with the ethics code of IR.SBMU.DRC.REC.1400.161.

Results

Overall, this case-control study was done on 120 samples including 66 healthy individuals (55%) and 54 patients with chronic periodontitis (45%). Thirty (55.5%) of the patients and 34 (51.5%) of the healthy subjects were male and the rest were female. No significant difference was found between the patient and control groups regarding gender (P-value>0.05).

Hardy-Weinberg equilibrium (HWE) in the control group was established based on the genotype and allele distribution of IL-6 (rs1800795) polymorphism (p-value=0.32). The allele and genotype distribution of the intended IL-6 polymorphism can be seen in Tables 2 and 3, respectively.

Table 2- The allele distribution of IL-6 gene polymorphism in patients and healthy subjects

translate	Healthy	Chronic Periodontitis	Total
G	76 (58%)	68 (63%)	144 (60%)
C	56 (42%)	40 (37%)	96 (40%)

Table 3- Frequency of IL-6 gene polymorphisms in patients and healthy subjects

Genotype	Healthy	Chronic Periodontitis	Total	P value
G/G	24(36%)	22(41%)	46(38%)	
G/C	28 (41.5%)	24 (44%)	52 (44%)	0.65
C/C	14 (21.5%)	8 (15%)	22(18%)	

The genotype frequency of the polymorphism alongside investigation of different types of inheritance models can be seen in Table 4. The frequency of GG, GC, and CC genotypes in patients was 41%, 44%, and 15%, while being 36%, 42%, and 21% in the control group; no significant difference was observed between the two groups in any of the inheritance models. The frequency of G allele was 63% and 58% in the patient and control groups, while that of C allele was 37% and 42% in the patient and control groups, and again no significant difference was seen between the two groups. In the codominant model, the odds ratio of the mutated homozygote to normal homozygote (CC/GG) was calculated 1.60 (0.56 - 4.56 CI 95%). The odds ratio of heterozygote to normal heterozygote (GC/GG) was calculated 1.07 (0.48 - .37 Cl %95). The odds ratios of the two other models and their lack of significance are observed in Table 4.

Table 4- The frequency of IL-6 gene polymorphisms in patients and healthy subjects while considering different inheritance models

Inheritance models	Genotype	Patients	Control	OR (95% CI)	P-value
Codominant	G/G†	22 (40.7%)	24 (36.4%)		
	G/C	24 (44.4%)	28 (42.4%)	1.07 (0.48-2.37)	0.65
	C/C	8 (14.8%)	14 (21.2%)	1.60 (0.56-4.56)	
Dominant	G/G	22 (40.7%)	24 (36.4%)		0.62
	G/C-C/C	32 (59.3%)	42 (63.6%)	1.20 (0.57-2.52)	
Recessive	G/G-G/C†	46 (85.2%)	52 (78.8%)		0.36
	C/C	8 (14.8%)	14 (21.2%)	1.55 (0.60-4.02)	

†: Reference group

Discussion

In the present study, we investigated the contribution of Rs1800795 gene polymorphism to the susceptibility of developing chronic periodontitis in an Iranian population. According to the findings, the ratio of healthy subjects and patients with chronic periodontitis among men and women was almost the same, and there was no relationship between gender and periodontitis. No significant difference was observed either between case and control groups regarding genotype and allele distribution of the polymorphism in this gene locus while considering three inheritance models of dominant, recessive, and codominant.

Extensive analyses have been performed on gene polymorphism and its effects on various biological and immunological processes such as inflammatory reactions, autoimmune diseases, and response to infectious agents. Some believe that polymorphisms either alone or in combination with other factors can function as a protective factor against progression of some diseases. In contrast, there are some theories noting the role of gene polymorphism as a disease-predisposing factor. The polymorphisms of IL-6 gene have long been of interest and investigated as an important inflammatory cytokine in periodontal diseases. Nevertheless, the current findings about correlation between IL-6 gene polymorphism and chronic periodontitis disease are contradictory.

Several studies have achieved findings similar to the present study results. In the study by Cirelli et al. [14] in 2020 on a Brazilian population, the effect of similar polymorphism on developing periodontitis and type II

diabetes mellitus was investigated. Similar to us, they did not find any relationship between the afore-mentioned polymorphism and susceptibility of developing periodontitis alone. However, they stated that those with CC genotype are 80% less susceptible to develop diabetes, and periodontitis concurrently. In 2017, Taker et al. [10] in Turkey investigated the effect of several gene polymorphisms including the discussed polymorphism on the susceptibility to develope chronic and aggressive periodontitis. According to their study, GG genotype would increase the risk of developing the aggressive form of the disease, but no relationship was found between this polymorphism and the chronic form of the disease. The latter finding is in line with the present study results. In addition, Yani et al. [15] in 2013 reached findings similar to our study on an Italian population. In another study in Brazil in 2012, again Stephani et al. [16] examining a smaller sample size, including 21 controls and 21 cases did not find any relationship between IL-6 polymorphism and chronic periodontitis. In this regard, some studies have also been done on Iranian population, which concur with our study findings. For example, Sanchuli et al. [17] in 2012 explored the effect of IL-6-174G/C gene polymorphism on developing chronic periodontitis in a Sistan-Baluchestan population. Their study had 100 control and 100 cases, in which, similar to our study, no significant difference was observed regarding allele and genotype distribution between the two groups. In 2016, again Heydari et al. [18] in a study investigated quantitative properties of interdental papilla in patients with chronic periodontitis and its association with polymorphism of 174G/C-IL-6 gene. They did not find significant differences between the examined features of papilla in patients with different genotypes. Accordingly, they concluded that the afore-mentioned polymorphism is unlikely to have any association with the disease development.

Meanwhile, the findings obtained from the recent study are in contrast to the results of a study done by Gabriella et al. [19] (2014) in Brazil. In their study with a larger sample size including 134 chronic periodontitis patients and 196 healthy subjects, GC genotype was expressed as a protective factor against development of disease. They also showed that there was no significant relationship between salivary concentration of IL-6 and different genotypes when comparing the two groups. Thus, they postulated that higher salivary concentration of IL-6 in patients has reasons other than genetics such as poor oral hygiene and extent of bacteria. Similarly, in 2010, Kalburgi et al. [12] also showed that there was an association between IL-6 (-174G/C) gene polymorphism and chronic periodontitis in a population in southern India. According to their study, G allele had a significantly higher distribution in the patients. In the afore-mentioned study, which examined 15 patients and 15 healthy controls, the frequency of G allele was 76.6% and 26.6% in patients and control groups respectively. They stated that GG genotype is effective on the development and progression of periodontal disease. In another study in 2012 by Scapoli et al. [20] on an Italian population to explore the relationship between polymorphism of five genes and chronic periodontitis, again they found different results compared to ours. They showed that those with both genotypes containing C allele (CC, CG) in the IL6-174G polymorphism had a low risk for developing the disease. Thus, possibly C allele has a protective role against the disease. Further, Tervilato [21], Tronen [22], Costa et al. [6] observed a kind of relationship between IL-6-174G gene polymorphism and susceptibility to develope chronic periodontitis.

Considerable contradictions are observed among the results obtained in various studies across different populations and even sometimes in the same nationalities. Furthermore, if there is any relationship between type of relevant genotype and disease progression, again there is no consensus among researchers. It is known that periodontal disease has a multifactorial nature and in spite of the attempts made by us and other researchers in matching the samples as much as possible and eliminating other confounding factors, some issues inevitably remain out of control. Some factors are intrapersonal, cellular, molecular, functional, and the structural differences, most of which are still unknown to us and each would affect the health and integrity of the periodontal fibers in a different way and can set the ground for pathogenicity of the bacterial agents or fight with them. Explanation of part of these differences can also lie in the method adopted in different studies; issues such as differences in the inclusion and exclusion criteria, age as well as socioeconomic differences of the examined populations all can explain at least part of these differences. For example, Gabriella et al. [19], to achieve the genomic DNA, utilized oral mucosal epithelial cells obtained through scraping in a larger sample size. Evidently, in the present study in which we used venous blood sample, we faced numerous problems regarding ethics, clinical practice, and approval by patients, and this issue was one of the reasons behind our smaller sample size. Further, in their study, smokers were also present, and elimination of these subjects from our study would increase the internal validity of ours, though it reduces the external validity. Another feature of their study was examining the salivary level of IL-6. Nevertheless, their study had been done only on one population of Brazil in one region (Northeastern); however, in our study in addition to the subjects being Iranian, we also dealt with three different centers at three different points across the country, which has increased the racial diversity in our subjects. The small sample size in some studies can also be another reason behind this lack of congruence among results. For example, in the study by Kalburgi [12] only three subjects had been investigated;

definitely, no generalizable genetic conclusion can be drawn from this sample size. Furthermore, in the study by Scapoli [20], the inclusion and exclusion criteria have not been mentioned clearly, but cigarette smokers have not been excluded from the study. Factors such as the extent of observing personal hygiene by subjects that has been effective on gingivitis, considering their culture and level of education, should not be ignored. The differences in results can also be related to racial and ethnic differences. The similar results in studies performed on Iranian populations and in the present study can confirm this issue and be a guide for conducting further studies with a special attention to racial differences alongside genetics. Nevertheless, the opposite is also observed in discordant results of studies done in Brazil [14, 16, 19] and Italy. [15, 20] Possibly, if in this study, as with another study performed in 2018 on the polymorphism of vitamin D receptor and vitamin D binding protein [23], we could group periodontitis patients in terms of severity (mild, moderate, and severe) and investigate the correlation with each degree of the disease, more different results would have been obtained. Nevertheless, it does not mean that in our study we were necessarily seeking a significant correlation. However, the relationship between the afore-mentioned polymorphism and a special severity of the disease could have been investigated, and this could somehow reduce the noted discrepancies. Nevertheless, many similar papers such as the study by Gabriella [19] and Scapoli [20] have not found the relationship between polymorphism and disease severity. Alternatively, in the study by Cirelli [14] who performed this investigation, the results between the moderate and severe periodontitis groups showed no significant difference regarding genotype distribution.

Using the results of the present study, now lack of relationship between this polymorphism and developing chronic periodontitis in the Iranian population could be justified more confidently. One of the limitations in this study was difficulty of blood sampling, considering the dire conditions of COVID-19 pandemic and attracting patient cooperation under these conditions. Further, if we could first instruct oral hygiene measurements, and then took samples from the patient, perhaps we could achieve more accurate results since the inflammation could not cause false positive results in that case.

Definitely, if in future studies sampling is done with a larger sample size and across the national level and if they are done per region or province basis, more generalizable results for the entire Iranian population could be achieved. It is suggested that future studies be performed with an accuracy greater than the present research and by categorizing the severity of disease, gene loci related to other interleukins, and sequencing. Unfortunately, due to financial, human, and time constraints, these issues were unfeasible for us.

Conclusion

In this study, no association was found between IL-6 gene polymorphism and chronic periodontitis. It is suggested that future studies investigate this issue with a larger sample size and using a more accurate method across wider geographical areas and other races.

Conflict of Interest

No Conflict of Interest Declared ■

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