Evaluation of interleukin 10, interleukin 1-beta, and tumor necrosis factor-alpha gene polymorphisms in patients with periodontitis and healthy controls

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Abstract

Background: Chronic periodontitis (CP) is a prevalent infectious disease caused by an interplay between pathogens and immune responses. Gene polymorphisms are among the factors that affect susceptibility to CP. This study aimed to assess the association between CP and single nucleotide polymorphisms (SNPs) of interleukin-10 (IL-10), interleukin 1ß (IL-1ß), and tumor necrosis factor-a (TNF-a) genes.

Methods: A total of 87 patients with CP and 89 healthy controls were included in this study. Venous blood samples were obtained, and DNA was extracted and purified. Segments containing the relevant genes were amplified by polymerase chain reaction (PCR). Electrophoresis was performed after restriction fragment length polymorphism (RFLP) to determine genotype and allele frequencies.

Results: The CP group showed significantly different allele and genotype frequencies for three out of five SNPs: IL-10 — 592 C/A, IL-10 — 819 C/T, and IL-1ß + 3954 C/T ($p < 0.05$). Additionally, the frequency of the TNF-a — 857 AA genotype was significantly lower in patients compared with controls ($p = 0.034$); however, no significant differences were found in allele frequencies ($p > 0.05$). Logistic regression analysis revealed that carriers of IL-10 — 592 A allele and IL-1ß + 3954 T allele are at higher risk of CP ($p < 0.001$). Allele and genotype frequencies for TNF-a — 308 G/A did not differ significantly between patients and controls ($p > 0.05$).

Conclusions: This study showed specific genotypes of IL-10 — 592 C/A, IL-10 — 819 C/T, IL-1ß + 3954 C/T, and TNF-a — 857 G/A SNPs may be associated with an increased risk of CP development.

Keyword: Chronic periodontitis, Gene polymorphism, Interleukin-10, Interleukin-1beta, Tumor necrosis factor-alpha

Background

Periodontitis is one of the most common health conditions with an estimated prevalence of 10% among the adult population worldwide [1]. It is an infectious disease of the tissues supporting teeth, characterized by progressive destruction of the tissues leading to gingival recession and/or pocket formation, and in severe cases, loss of teeth [2]. It is an inflammatory condition driven by the interactions of immune response and pathogenic microorganisms present in dental plaque [3–5].

There are several risk factors including smoking, diabetes mellitus, socioeconomic variables, stress, and genetic predispositions [6]. Genetic variations are among the factors that predispose individuals to periodontitis [7, 8]. Gene polymorphisms are defined as variations in the

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sequence of DNA and may alter the function of the gene. These variations can affect gene expression when they are located in the promoter region. As a result, polymorphisms that affect the expression of inflammatory mediators, such as cytokines, may influence the initiation and progression of inflammatory diseases [9, 10].

IL-10, known as an anti-inflammatory cytokine, plays a complex role in the pathogenesis of chronic periodontitis (CP) [11, 12]. It decreases alveolar bone loss through downregulation of osteoclastogenesis mediated by T-helper 1 [11]. At the same time, it suppresses the innate response and thus, might contribute to bacterial persistence and the following chronic infection in the region [12]. Two detected single nucleotide polymorphisms (SNPs) in the promoter region of the IL-10 gene, including at positions -819 and -592, are reported to be associated with several diseases [13–16].

Pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), affect the development of periodontitis [17, 18]. Levels of these cytokines increase in the gingival crevicular fluid and saliva of patients with periodontitis [19–21]. IL-1β and TNF-α contribute to bone resorption through activation of osteoclasts and stimulation of the release of other mediators associated with bone destruction [17, 18]. Two variants of the TNF-α gene, one at position -857 and the other at -308, are documented to increase the risk of chronic diseases namely diabetes mellitus [10].

The relationship between several SNPs and periodontitis has been questionable and more clinical data are needed to draw a reliable conclusion in this regard [22, 23]. Furthermore, it is proved that the association between gene polymorphisms and periodontitis differs based on race [24, 25]. However, there is relatively little evidence available on the Iranian population. Therefore, this study aimed to assess the association between IL-1β, IL-10, and TNF-α gene polymorphisms and CP in an Iranian population. As genetic predisposition seems to be different for various forms of periodontitis [23], this study focused on the chronic form.

Materials and methods

The present case-control study was conducted at the Department of Periodontics, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The study protocol was approved by the ethics committee (IR.SBMU.DRC. REC.1399.099). Written informed consent was obtained from all patients and demographic data were collected. The study was conducted on 87 patients with CP and 89 periodontally healthy controls. Only Iranian individuals were included and the following exclusion criteria were applied: oral diseases other than dental caries, ongoing

orthodontic treatment, smoking, history of systemic diseases or medications affecting the immune system, pregnancy, lactation, diabetes mellitus, HIV infection, hepatitis, and chemotherapy.

Individuals in the control group were selected based on the criteria of having a minimum of 20 teeth with no history or current symptoms of periodontitis. The patients had at least five teeth in each quadrant, except for the third molars. CP was diagnosed based on the radiographic and clinical evaluation with the following criteria: probing pocket depth > 3 mm, clinical attachment loss ≥ 3 mm, and bleeding on probing of at least three teeth at two quadrants.

For genotype determination, a 5 cc venous blood sample was obtained from each participant and stored in EDTA-coated tubes at -40 °C. A code was assigned to each tube and the respective patient so that the lab technicians were blinded to the group allocation. DNA was extracted using Miller's salting-out technique, following the guidelines of the DNA extraction kit manufacturer (Bioneer, Cinnagen Company, Iran).

After the purification of DNA, segments containing the relevant gene were amplified. Restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) was conducted to determine genotype frequencies. Following the PCR, products were combined with specific restriction enzymes (Fermentas, Thermo Fisher Scientific, Waltham, U.S.) (Table 1), Tango buffer, and sterile distilled water, to reach the final volume of 20 μL. The solution was then incubated in half-microtiter micro tips for RFLP at 37 °C for 16 h (following the manufacturer's guidelines). Following the incubation, the mixture was combined with 2 μL loading buffer and poured into the polyacrylamide gel's wells. The first ladder served as a marker for the determination of DNA fragments' length. For this purpose, 0.5 μL marker solution (50 or 100 base pair DNA ladder) was mixed with 10 μL sterilized distilled water and poured into the first well. Electrophoresis was completed within 20–30 min at a voltage of 180 v. After the electrophoresis, the polyacrylamide gel was stained with 0.1% silver nitrate or 0.5 μg/ml ethidium bromide.

Data analysis was performed using SPSS Statistics 22.0 (IBM, Armonk, USA). Distribution normality was assessed with the Shapiro-Wilks test and graphical approach. Chi-square or Fisher's exact test was applied to assess the statistical significance of the differences, which was set at P value < 0.05.

Results

This study was performed on 87 patients with periodontitis and 89 healthy controls. Table 2 demonstrates demographic data and the outcomes of clinical examination

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Table 1 Primer sequence, restriction enzyme, and cut sequences for each gene

Gene	Primer	Restriction enzyme	Allele		Cut sequence
IL-10 — 592 C/A	(F: 5´ GGTGAGCACTACCTGACTAAGC 3´) (R: 5´ CCTAGGTCACAGTGACGTGG 3´)	Rsal	Wild	C	412 bp
			Mutant	A	236 bp, 176 bp
IL-10 — 819 C/T	(F: 5´ CCAGATATGAAGAAGTCCTG 3´) (R 5´ TGGGGGAAGTGGGTAAGAGT 3´)	Rsal	Wild	C	443 bp, 116 bp
			Mutant	T	559 bp
IL-1ß + 3954 C/T	(F; 5´TCAGGTGTCCTCGAAGAAATCAAA 3´) (R: 5´ GCTTTTTTGCTGTGAGTCCCG 3´)	Taq I	Wild	C	97 bp, 85 bp
			Mutant	T	182 bp
TNF-α — 308 G/A	(F: 5´ ATCCAAGACAACACTACTAA 3´) (R: 5´ TAAATATCCTCAAAGTTCC 3´)	Nco I	Wild	G	87 bp
			Mutant	A	107 bp
TNF-α — 857 C/T	(F: 5´ ATCCAAGACAACACTACTAA 3´) (R: 5´TAA ATATCCTCAAAGTTCC 3´)	Tai I	Wild	C	18 bp, 109 bp
			Mutant	T	127 bp

Table 2 Demographic data and clinical characteristics of the subjects

	Patients (N = 87)	Controls (N = 89)	P value*
Age (year)	41.8 ± 12.2	40.4 ± 13.5	0.471
Sex			0.651
Male N (%)	42 (47.7%)	46 (52.3%)	
Female N (%)	45 (51.1)	43 (48.9)	
Probing depth (mm)	5.95 ± 0.75	1.83 ± 0.68	**<.001**
Bone loss (mm)	5.34 ± 0.85	0.17 ± 0.11	**<.001**

Age, probing depth and bone loss are presented as mean ± standard deviation

Analyzed with the Pearson Chi-Square test, the remaining values were analyzed with the t-test

*Statistically significant values are presented in bold

of individuals. No significant differences were found between the two groups in terms of age or sex ($p = 0.471$ and $p = 0.651$, respectively). Genotype and allele frequencies are depicted in Table 3. Patients showed significantly different allele and genotype frequencies in three out of five gene polymorphisms: IL-10 — 592 C/A, IL-10 — 819 C/T, and IL-1ß + 3954 C/T ($p < 0.05$). In addition, AA genotype frequency of TNF-α — 857 gene was significantly lower in patients ($p = 0.034$). Based on logistic regression analysis, CA and AA carriers of IL-10 — 592 gene, and CT and TT carriers of IL-1ß + 3954 gene were more likely to present periodontitis ($p < 0.001$, Table 4).

In the CP group, the frequency of CC, CA, and AA genotypes for IL-10 — 592 C/A was reported to be 32%, 53%, and 15%, respectively. These values were 60%, 39%, and 1%, respectively, in the control group. The frequency of CC genotype was significantly lower in patients compared with the controls ($p < 0.001$). The frequency of AA genotype was significantly higher in patients ($p = 0.011$). For IL-10 — 819 C/T, the frequency of CC, CT, and TT genotypes was 23%, 52%, and 25%, respectively, in patients, and 51%, 39%, and 10%, respectively, in controls.

In patients, CC genotype was significantly less frequent ($p < 0.001$), while TT genotype was significantly more frequent ($p = 0.008$). In addition, the frequency of CC, CT, and TT genotypes for IL-1ß + 3954 C/T was 71%, 23%, and 6%, respectively, in patients, and 92%, 8%, and 0%, respectively, in controls. In patients, the frequency of CC genotype was significantly lower (< 0.001) and the frequency of CT genotype was significantly higher ($p = 0.005$). for TNF-α — 857 gene, AA genotype frequency was 39% in patients and significantly higher in controls (55%, $p = 0.034$). However, there was no statistically significant difference in allele frequencies between the groups. The genotype and allele frequencies of TNF-α — 308 G/A did not significantly differ between the groups ($p > 0.05$).

Discussion

Several cytokines are involved in the inflammatory and immune response of connective tissue [26]. These cytokines can be associated with the onset and progression of inflammatory diseases including periodontitis [27–29]. Gene polymorphisms that are located in the promoter region can affect cytokine expression and thus, the risk of periodontitis. Therefore, the identification of such polymorphisms contributes to a better understanding of the molecular drives of periodontitis as well as its risk factors. Our outcomes showed that the CC genotype of IL-10 — 592, IL-10 — 819, and IL-1ß + 3954 genes and AA genotype of TNF-α — 857 gene have significantly lower frequency among CP patients. In contrast, IL-10 — 819/ TT and IL-1ß + 3954/ CT genotypes had significantly higher prevalence among these patients. This data suggest a link between the latter genotypes and periodontitis development, in a way that they might make the supportive tissue susceptible to destruction.

The role of IL-10 in periodontitis progression is a complicated issue. Its protective role of the supporting

Table 3 Association of IL-10, IL-1ß, and TNF-*a* polymorphisms with risk of periodontitis

Allele/Genotype	Patients *N* (%)	Controls *N* (%)	*P* value*	Odds ratio (95% CI)
IL-10 — 592 C/A				
Alleles				
C	102 (59%)	141 (79%)		
A	72 (41%)	37 (21%)	**< 0.001**	2.69(1.68–4.31)
Genotype				
CC	28 (32%)	53 (60%)	**< 0.001**	0.322(0.174–0.598)
CA	46 (53%)	35 (39%)	0.071	1.731(0.952–3.149)
AA	13 (15%)	1 (1%)	**0.011**	9.486(1.204–74.727)
IL-10 — 819 C/T				
Alleles				
C	85 (49%)	125 (70%)		
T	89 (51%)	53 (30%)	**< 0.001**	2.47(1.594–3.826)
Genotypes				
CC	20 (23%)	45 (51%)	**< 0.001**	0.292(0.152–0.559)
CT	45 (52%)	35 (39%)	0.099	1.653(0.909–3.006)
TT	22 (25%)	9 (10%)	**0.008**	3.009(1.297–6.981)
IL-1ß + 3954 C/T				
Alleles				
C	144 (83%)	171 (96%)		
T	30 (17%)	7 (4%)	**< 0.001**	5.089(2.171–11.931)
Genotypes				
CC	62 (71%)	82 (92%)	**< 0.001**	0.212(0.086–0.521)
CT	20 (23%)	7 (8%)	**0.005**	3.497(1.395–8.768)
TT	5 (6%)	0 (0%)	0.560[†]	-
TNF-*a* — 308 G/A				
Alleles				
A	136 (78%)	152 (85%)		
G	38 (22%)	26 (15%)	0.079	1.633(0.943–2.831)
Genotypes				
GG	7 (8%)	4 (5%)	0.330	1.859(0.524–6.593)
GA	24 (28%)	18 (20%)	0.252	1.503(0.747–3.023)
AA	56 (64%)	67 (75%)	0.115	0.593(0.309–1.138)
TNF-*a* — 857 G/A				
Alleles				
G	66 (38%)	50 (28%)		
A	108 (62%)	128 (72%)	0.050	0.639(0.408–1)
Genotypes				
GG	13 (15%)	10 (11%)	0.466	1.388(0.574–3.357)
GA	40 (46%)	30 (34%)	0.096	1.674(0.91–3.077)
AA	34 (39%)	49 (55%)	**0.034**	0.524(0.287–0.954)

95% CI = 95% Confidence Interval

[†] Analyzed with the Fisher's exact test, the remaining values were analyzed with the Chi-square test

*Statistically significant values are presented in bold

Table 4 Logistic regression analysis of risk factors associated with periodontitis susceptibility

Predictive factors	Odds ratio (95% CI)	Wald test (*P* value*)
Sex	0.87 (0.37–1.85)	0.960
IL-10 − 592 CA + AA	4.01 (2.39–7.37)	**< 0.001**
IL-10 − 819 CT + TT	1.80 (0.86–3.71)	0.071
IL-1ß + 3954 CT + TT	5.58 (2.16–14.68)	**< 0.001**
TNF-*α* − 308 GA + AA	0.50 (0.09–2.22)	0.450
TNF-*α* − 857 GA + AA	0.58 (0.16–1.74)	0.415

95% CI = 95% Confidence Interval

*Statistically significant values are presented in bold

bone has been documented, which is due to the suppression of osteoclastogenesis [11, 30–32]. IL-10 also inhibits macrophage activation as well as pro-inflammatory cytokines such as IL-1, TNF, and IL-6 [33–35]. As a result, it limits the extent and period of inflammatory and immune response and can contribute to the persistence of bacteria and chronic infection in the region [12, 36, 37]. This is consistent with the studies that have shown higher levels of IL-10 in the gingival crevicular fluid of periodontitis patients [20]. Our results showed that the A allele of the IL-10 − 592 gene is significantly associated with CP. Considering the higher expression of IL-10 in periodontitis patients, it can be inferred that the C allele is associated with a higher expression of IL-10. In a systematic review and meta-analysis by Mashhadiabbas et al. (2021), the A allele was proved to increase risks of CP (p = 0.034), which supports our findings. To the knowledge of the authors, only one study other than the present one has evaluated IL-10 − 592 C/A SNP in the Iranian population, which has reported no significant association [38].

Previous studies have shown a significant relationship between IL-10 − 819 C/T SNP and several diseases, including Alzheimer's disease, lung cancer, and Behcet's disease [13–16]. We demonstrated that the T allele of the IL-10 − 819 gene is associated with higher risks of periodontitis. This is consistent with the outcomes of our previous study on peri-implantitis [39]. In contrast, Mashhadiabbas et al. [25] reported no significant association between risks of chronic and aggressive periodontitis with IL-10 − 819 C/T SNP. Differences between our outcomes and the previous studies might be attributed to racial differences [24, 25].

A significantly higher level of IL-1 *β* has been documented in patients with periodontitis, which decreases by clinical improvement following treatment [40]. We showed that carriers of the T allele of the IL-1ß + 3954 gene are at a higher risk for CP. Based on the latest meta-analysis on this subject by Citterio et al., the association between IL-1ß + 3954 C/T and CP has been questionable because of the methodological inconsistency of relevant studies [22]. For improvement of the methodological quality, Citterio et al. [22] suggested multicentric studies with sufficiently powered samples, stricter criteria for the groups, and adjustment for confounders.

We found no significant association between TNF-*α* − 308 G/A SNP and CP. In contrast to our findings, a recent meta-analysis by Zhang et al. [23] has reported an association between chronic and aggressive periodontitis with the A allele, particularly in the Asian subgroup. However, none of the included studies had been performed on the Iranian population with CP, which highlights the importance of inter-racial differences. To the best of our knowledge, only one similar study has been performed on Iranian patients, which indicates no significant relationship between aggressive periodontitis and TNF-*α* − 308 G/A SNP [41].

For TNF-*α* − 857 G/A SNP, our analysis revealed a significantly lower frequency of AA genotype in CP patients; however, no significant differences were observed in terms of allele frequencies. Xu et al. [42] in a meta-analysis in 2020 found no association between TNF-*α* − 857 G/A SNP and CP susceptibility.

There are several limitations to this study. Genetic studies should be conducted on a large scale, multi-center settings, with randomly selected samples, to be representative of the target population. In addition, such studies can yield better results if they are conducted prospectively. These could not be carried out in this study as it was primarily a clinic-based investigation. Therefore, more studies are required to corroborate the current results. This is particularly true for SNPs with inconsistent results across the studies, including IL-10 − 819 C/T, TNF-*α* − 308 G/A, and TNF-*α* − 857 SNPs. Finally, it should be noted that genetic susceptibility to CP is affected by a combinational effect of hundreds or thousands of genes, in addition to the environmental and epigenetic factors, which could be considered potential confounders [6]. Limited access to patients with CP made it challenging to evaluate the response to treatment in each genotype in terms of statistical power. It is highly recommended to assess the treatment responses in each genotype in future studies with larger sample sizes to overview and achieve the best therapeutic approaches for each genotype.

Conclusions

In conclusion, this study demonstrated a significant association between IL-10 − 592 C/A, IL-10 − 819 C/T, IL-1ß + 3954 C/T, and TNF-*α* − 857 G/A SNPs and CP;

however, no statistically significant relationship was found between TNF-*α* ─ 308 G/A SNP and CP.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethics committee (IR.SBMU.DRC.REC.1399.099) at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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