Molecular Biology Reports (2021) 48:2285–2290
https://doi.org/10.1007/s11033-021-06253-9

ORIGINAL ARTICLE

Assessment of IL-10, IL-1ß and TNF-α gene polymorphisms in patients with peri-implantitis and healthy controls

Leila Saremi[1,2] · Marziyeh Shafizadeh[1] · Emran Esmaeilzadeh[3] · Mohammad Ebrahim Ghaffari[4] · Mohammad hosein Mahdavi[5] · Reza Amid[5] · Mahdi Kadkhodazadeh[1]

Received: 16 November 2020 / Accepted: 24 February 2021 / Published online: 10 March 2021
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Abstract

Peri-implantitis (PI) is a multifactorial condition caused by the interactions of pathogens and the host immune response. Previous studies have demonstrated a relationship between PI and specific gene polymorphisms, particularly cytokine genes involved in the pathogenesis of PI. This study aimed to evaluate the frequency of single nucleotide polymorphisms (SNPs) of interleukin-10 (IL-10), interleukin 1ß (IL-1ß), and tumor necrosis factor-α (TNF-α) genes in PI patients and healthy controls. A total of 50 patients with PI and 89 periodontally healthy controls were recruited for this study. Venous blood samples (5 cc) were collected, and DNA was extracted. After DNA purification, the relevant gene segments were amplified by polymerase chain reaction (PCR). Restriction fragment length polymorphism (RFLP) and electrophoresis were performed to assess the polymorphisms of the related genes. The analysis revealed that allele and genotype frequencies of IL-10 − 819 C/T, IL-10 − 592 C/A, and IL-1ß + 3954 C/T significantly differed between PI patients and healthy controls. The analysis revealed no significant association between TNF-α − 857 G/A and TNF-α − 308 G/A polymorphisms and PI. Our results indicated that specific gene polymorphisms of IL-10 − 819 C/T, IL-10 − 592 C/A, and IL-1ß + 3954 C/T may play a role in the pathogenesis of PI, and increase its risk of occurrence.

Keywords Peri-implantitis · Polymorphism · Interleukin · Tumor necrosis factor

Introduction

As dental implants are increasingly used for oral rehabilitation, peri-implant diseases are becoming a greater concern for dental clinicians. Peri-implantitis (PI) is an infectious disease of the tissues surrounding dental implants, characterized by progressive destruction of the supporting bone [1]. The mean prevalence rate of PI is reportedly 22% (CI: 14–30%) [2]. PI is an inflammatory condition caused by the interactions of pathogens with the host immune response.

Individual characteristics such as genetic variations are among the predisposing factors for dental implant complications [3, 4]. Gene polymorphisms refer to variations in the DNA sequence that may influence gene functions. Variations that involve regulation of inflammatory mediators, and primarily the promoter region of the gene, may affect the development of inflammatory diseases [5–7].

Pro-inflammatory cytokines appear to play an important role in the initiation and progression of PI [8]. Significant increase in concentration of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the peri-implant crevicular fluid of patients with PI has been documented in several studies [9]. IL-1β regulates the extracellular matrix degradation during inflammation. It also induces the production of prostaglandin E2, which also affects hard tissue degradation [10]. The allele T of IL-1β (+ 3954) polymorphism is associated with chronic periodontitis [5]. Similarly, TNF-α induces bone resorption either indirectly through the mediators or directly by promoting the proliferation and

✉ Mahdi Kadkhodazadeh
Kadkhodazadehmahdi@yahoo.com

1 Dental Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

3 School of Medicine, Aja University of Medical Sciences, Tehran, Iran

4 Dental Sciences and Research Center, Faculty of Dentistry, Guilan University of Medical Sciences, Rasht, Iran

5 Periodontics Department, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran

activity of osteoclasts [11]. There are two variants related to TNF-α gene: one at position -308 and the second at position -857, which have been shown to be correlated with periodontitis susceptibility [7].

On the contrary, anti-inflammatory cytokines such as interleukin-10 (IL-10) appear to protect the supportive tissues against destruction [12]. In fact, IL-10 exerts its protective role by inhibiting the production of pro-inflammatory mediators namely matrix metalloproteinases and receptor activator of nuclear factor-kappa-B ligand [12, 13]. Two types of single nucleotide polymorphisms (SNPs) in the promoter region of IL-10 gene have been detected at positions − 819 (C to T substitution) and − 592 (C to A substitution). SNPs in the promoter region of IL-10 gene have been reported to be associated with chronic periodontitis [6, 14].

To date, several studies have explored the relationship of the aforementioned gene polymorphisms with PI [15–17]; however, no study has been performed in this respect on the Iranian population. It is believed that ethnicity may affect how the potential risk factors influence the development of diseases. Thus, in the present study, we aimed to investigate the association of IL-10, IL-1ß, and TNF-α gene polymorphisms with the risk of PI in an Iranian population.

Materials and methods

The present case–control study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU.rec.1389.92). This study was performed on 50 patients with PI, and 89 periodontally healthy controls. The patients were referred to the Department of Periodontics of Shahid Beheshti University of Medical Sciences, Tehran, Iran. The demographic and clinical data were collected, and written informed consent was obtained from all participants. Only Iranian participants were included, and the exclusion criteria were as follows: oral and periodontal diseases (except for dental caries), current orthodontic treatment, history of systemic diseases or any complication compromising the immune system, diabetes mellitus, HIV infection, hepatitis, chemotherapy, pregnancy, and lactation.

Healthy controls had at least 20 teeth with no symptom or history of periodontitis. In the case of having a dental implant, the sulcus depth had to be less than 4 mm, with no obvious bone loss on periapical radiographs. The patients with PI had no history of periodontitis and had at least one implant with a minimum of 12 months of loading. PI was diagnosed with the criteria of probing pocket depth > 5 mm, bleeding on probing with or without pus discharge, and evidence of at least 2 mm of bone loss on radiographs in at least one area.

After patient selection, 5 cc of venous blood was collected and transferred to Falcon tubes containing EDTA. A code was allocated to each patient, and the tubes were coded accordingly such that the lab technicians were blinded to the group allocations. Blood samples were stored at -40 °C. The nuclear and mitochondrial DNA was extracted based on the Miller's salting-out technique according to the instructions provided by the manufacturer in the DNA extraction kit (Bioneer, Cinnagen Company, Iran).

Following purification of DNA, the relevant gene segments were amplified. For the genotyping of each gene, the restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) process was performed. All the enzymes used in the present study were manufactured by Fermentas Company. The PCR products were then mixed with the restriction enzymes and Tango buffer, and the final volume was increased to 20 µL with sterile distilled water. The mixture was poured into half-microtiter micro tips for RFLP and incubated at 37 °C for 16 h (according to the manufacturer's instructions). After the incubation period, the solution was mixed with 2 µL of loading buffer, and loaded into wells of a polyacrylamide gel. Separately, a mixture of 0.5 µL marker (DNA ladder of 50 or 100 bp), and 10 µL sterilized distilled water was loaded into the first well to determine the size of DNA fragments. The period of electrophoresis was 20–30 min, and a voltage of 180 v was used. The gel was then removed from the device and stained with ethidium bromide or silver nitrate.

Statistical significance of the differences between the results was analyzed by the Chi-square and Fisher's exact tests. P-value < 0.05 was considered statistically significant. Logistic regression analysis was performed to identify the most prominent factors for the development of PI.

Results

This study was conducted on 50 patients with PI, and 89 healthy controls. The control group comprised periodontally healthy subjects without any dental implants. Demographic data and clinical characteristics of the subjects are presented in Table 1. There were no significant differences among the groups in terms of age or sex ($p = 0.42$ and $p = 0.97$, respectively). Table 2 summarizes the genotype and allele frequencies. In three out of five investigated genetic variations, allele and genotype frequencies significantly differed between PI patients and controls namely IL-10 − 819 C/T, IL-10 − 592 C/A, and IL-1ß + 3954 C/T. Based on the logistic regression analysis, IL-1ß + 3954 polymorphic CT/TT genotypes ($p < 0.001$) and IL-10 − 592 polymorphic CA/AA genotypes ($p = 0.002$) were significantly associated with higher risks of PI (Table 3).

In patients with PI, the frequency of CC, CT, and TT genotypes for IL-10 − 819 was 44%, 42%, and 14%, respectively (Table 2). These values were 60%, 39%, and 1%,

Table 1 Demographic data and clinical characteristics of the subjects

	Patients (n = 50)	Controls (n = 89)	P-value
Age (year)	42.2 ± 12.2	40.4 ± 13.5	0.424
Sex			
Male n (%)	24 (35.8)	43 (64.2)	0.972†
Female n (%)	26 (36.1)	46 (63.9)	
Probing depth (mm)	6.81 ± 0.52	1.83 ± 0.68	< .001
Bone loss (mm)	4.44 ± 1.89	0.17 ± 0.11	< .001

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

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

respectively, in healthy controls. The frequency of the TT genotype was significantly higher in patients with PI than in healthy controls (p = 0.002). For IL-10 − 592 C/A genotype distribution, the frequency of CC, CA, and AA genotypes in patients was 32%, 52%, and 16%, respectively. These values were 60%, 39%, and 1%, respectively, in healthy controls. The frequency of CC genotype was significantly lower in patients with PI (p = 0.002). Moreover, the frequency of AA genotype was significantly higher in patients compared with controls (p = 0.001). In patients with PI, the frequency of CC, CT, and TT genotypes for IL-1ß + 3954 C/T was 68%, 24%, and 8%, respectively. These values were 92%, 8%, and 0%, respectively, in healthy controls. The frequency of CC genotype was significantly lower in PI patients (p = 0.0002). Moreover, the frequency of CT and TT genotypes was

Table 2 Association of polymorphisms in IL-10, IL-1ß, and TNF-α genes with risk of peri-implantitis

	Allele/Genotype	Patients n (%)	Controls n (%)	P-value*	Odds Ratio (95% CI)
	IL-10 − 819 C/T				
Allele s	C	65 (65%)	141 (79%)	**0.009**	2.052(1.187–3.548)
	T	35 (35%)	37 (21%)		
Genotypes	CC	22 (44%)	53 (60%)	0.078	0.534(0.265–1.075)
	CT	21 (42%)	35 (39%)	0.758	1.117(0.552–2.26)
	TT	7 (14%)	1 (1%)	**0.003**†	14.326(1.708–120.161)
	IL-10 − 592 C/A				
Alleles	C	58 (58%)	141 (79%)	**< 0.001**	2.76(1.612–4.723)
	A	42 (42%)	37 (21%)		
Genotypes	CC	16 (32%)	53 (60%)	**0.002**	0.32(0.154–0.663)
	CA	26 (52%)	35 (39%)	0.148	1.671(0.831–3.363)
	AA	8 (16%)	1 (1%)	**0.001**†	16.762(2.03–138-409)
	IL-1ß + 3954 C/T				
Alleles	C	80 (80%)	171 (96%)	**< 0.001**	6.107(2.481–15.032)
	T	20 (20%)	7 (4%)		
Genotypes	CC	34 (68%)	82 (92%)	**< 0.001**	0.181(0.068–0.48)
	CT	12 (24%)	7 (8%)	**0.008**	3.699(1.35–10.14)
	TT	4 (8%)	0 (0%)	**0.015**†	
	TNF-α − 308 G/A				
Alleles	A	80 (80%)	152 (85%)	0.246	1.462(0.769–2.779)
	G	20 (20%)	26 (15%)		
Genotypes	GG	4 (8%)	4 (5%)	0.394	1.848(0.442–7.734)
	GA	12 (24%)	18 (20%)	0.604	1.246(0.543–2.856)
	AA	34 (68%)	67 (75%)	0.355	0.698(0.325–1.499)
	TNF-α − 857 G/A				
Alleles	G	39 (39%)	50 (28%)	0.061	0.611(0.364–1.026)
	A	61 (61%)	128 (72%)		
Genotypes	GG	8 (16%)	10 (11%)	0.422	1.505(0.552–4.099)
	GA	23 (46%)	30 (34%)	0.152	1.675(0.825–3.404)
	AA	19 (38%)	49 (55%)	0.054	0.5(0.247–1.015)

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 3 Logistic regression analysis of risk factors associated with peri-implantitis susceptibility

Genes	Odds ratio (95% CI)	Wald test (P-value*)
Sex	0.99 (0.49–1.97)	0.972
IL-10 — 819 CT + TT	1.87 (0.93–3.78)	0.078
IL-10 — 592 CA + AA	3.13 (1.51–6.49)	**0.002**
IL-1ß + 3954 CT + TT	5.51 (2.08–14.60)	**< 0.001**
TNF-α — 308 GA + AA	0.54 (0.13–2.26)	0.458
TNF-α — 857 GA + AA	0.66 (0.24–1.81)	0.422

95% CI = 95% Confidence Interval

*Statistically significant values are presented in bold

significantly higher in patients compared with controls ($p = 0.008$ and $p = 0.007$, respectively). The difference in frequency of other genotypes was not statistically significant between the patient and control groups. As shown in Table 2, there was no significant difference in allele and genotype frequencies for TNF-α — 857 G/A and TNF-α — 308 G/A between PI patients and healthy controls ($p > 0.05$).

Discussion

PI is among the most common complications of implant-supported dental restorations [18, 19]. Thus, it is imperative to assess the risk factors influencing the development of PI. In this study, we evaluated IL-10 — 819, IL-10 — 592, IL-1ß + 3954, TNF-α — 308, and TNF-α — 857 gene polymorphisms in an Iranian population with PI. Previous studies have elucidated the contributing role of TNF-α and IL-1ß pro-inflammatory cytokines in bone resorption [10, 11, 20]. Increased concentrations of these factors in the gingival crevicular fluid of individuals with PI have been reported in several studies [9, 21, 22]. IL-10 is an anti-inflammatory cytokine, and alteration in its concentration in peri-implant tissues has been a controversial topic [23–25]. However, its protective role in the supporting hard tissue has been well documented [12, 13, 26, 27]. The association between the SNPs of TNF-α, IL-1ß and IL-10 and several inflammatory diseases including periodontitis has been reported in various studies [6, 7, 14, 28–30].

Our results showed that IL-10 — 819/ TT, IL-10 — 592/ AA, IL-1ß + 3954/ TT, and IL-1ß + 3954/ CT genotypes had significantly higher prevalence in patients with PI than the control group. Such data suggest that there might be an association between these genotypes and development of PI, as they may predispose the peri-implant hard tissue to degradation.

IL-10 — 592/CC and IL-1ß + 3954/CC were the most prevalent genotypes in healthy controls. Previous studies have shown higher expression of IL-10 in diseased periodontal tissues as it relates to the lower severity of disease [13, 31]. Since IL-10 protects the hard tissue from breakdown, it may be concluded that IL-10 — 592/ CC genotype results in higher expression of IL-10 in the tissues. Previous studies have shown that carriers of the CC genotype express a significantly higher level of IL-10 mRNA compared with CA and AA genotypes [14, 32], which supports our findings.

The allele T in both heterozygote and homozygote genotypes of IL-1ß + 3954 was associated with an increased risk of PI. It is confirmed by the fact that the T allele is correlated with the secretion of IL-1ß, which in part results in more tissue destruction [29]. Our results suggest that the T allele increases the risk of PI occurrence under a dominant model.

The association between IL-10 — 819/CT SNP and several diseases has been documented, including Behcet's disease, lung cancer, and Alzheimer's disease [33–36]. Based on a meta-analysis performed in 2018, no association exists between this polymorphism and periodontitis [37]. However, based on our results, the frequency of IL-10 — 819/ TT was significantly higher in patients with PI than the control group; while, there was no significant difference between the patients and controls for the CC and CT genotypes. This finding suggests an association between IL-10 — 819/ CT SNP and PI under a recessive model.

As mentioned earlier, the association between TNF-α— 857 G/A and — 308 G/A polymorphisms and periodontitis has been documented in several studies. Nonetheless, in our study, no correlation was found between these SNPs and PI. Although the frequency of AA genotype in — 857 G/A was greater in healthy controls, it was not statistically significant. Mo et al., in a meta-analysis assessed the correlation of — 308 G/A and PI and reported no significant association [15]. The difference between the results on periodontitis and PI may be due to the different nature of these diseases. However, the negative results for PI could also be related to the small sample size, as a limited number of studies have evaluated the association of SNPs with peri-implant complications [38].

To the knowledge of the authors, only two studies have assessed the relationship of implant complications and IL-10 SNPs [39, 40], and both of them failed to find a significant association. The controversy between the results of previous studies and ours may be due to the fact that our study was performed on PI patients; while, previous studies evaluated patients with failed implants. Since implant failure may occur as a result of a variety of conditions, factors affecting it may not be necessarily the same as those responsible for PI.

Our results regarding IL-1ß + 3954 SNP are consistent with a recent study performed on a Chinese population [41]. They similarly found a significantly higher frequency of TT and CT genotypes in patients ($p = 0.03$ and $p = 0.041$,

respectively), and a lower frequency of CC genotype in healthy controls. They also declared that TT carriers had a significantly higher plaque index, peri-implant pocket depth, and clinical attachment level. Liao et al. evaluated the association of implant failure and IL-1ß + 3954 in a meta-analysis. They showed no significant relationship between implant failure and IL-1ß + 3954; however, they found that a composite genotype of IL-1A (-889) and IL-1ß + 3954 increased the risk of implant failure and PI. This finding highlights the multifactorial nature of PI.

There are several limitations to this study that should be addressed. Primarily, genetic studies should be performed on a large, randomly selected sample size to be representative of the general population. Moreover, they should be designed prospectively. These could not be done in this study since it was a clinic-based study. Further studies are required to confirm the current findings. Additionally, the criteria for PI should be consistent across studies, which are not, due to different definitions available for PI. This may complicate the comparison of studies and drawing a final conclusion in future reviews.

In conclusion, the present study found a significant association between IL-10 − 819 C/T, IL-10 − 592 C/A, and IL-1ß + 3954 C/T SNPs and PI; although no statistically significant association was noted between TNF-α − 308 G/A and TNF-α − 857 G/A SNPs and PI.

Author's contribution All the authors have substantial contributions to the conception or design of the work, revising and drafting the work.

Funding This work was supported by a grant from Shahid Beheshti University of Medical Science Grant No. 0000.

Data availability All data and materials of the work are available behind the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This work was approved by ethical committee of Shahid Beheshti University of Medical Science.

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