

Polymorphisms of IL-17A and IL-17F in Periodontal Disease: A Case-Control Study



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Abstract

Background: Increased interleukin-17 (IL-17) leads to the production of proinflammatory mediators and increases local inflammation. Interleukin-17 may also promote receptor activator of nuclear factor kappa-B ligand (RANKL) expression on gingival fibroblasts, T cells, and B cells, resulting in alveolar bone resorption. Interleukin-17A and IL-17F levels in saliva and gingival crevicular fluid (GCF), were found to be elevated in periodontitis patients. Thus, IL-17A and IL-17F polymorphisms were hypothesized to be associated with a risk of periodontitis. **Methods:** The present study was conducted on 60 subjects, including 20 stage II grade B periodontitis patients, 20 stage III grade C periodontitis patients, and 20 healthy controls. Blood samples were drawn from the subjects and analyzed for IL-17A G-197A and IL-17F 7488T/C genetic polymorphisms using the TaqMan assay. **Results:** There was a significant statistical difference between the distribution of the different genotypes and the different alleles in the three groups for IL-17A G-197A with the A allele presence indicating a risk of periodontitis. **Conclusions:** Interleukin-17A G-197A polymorphism is significantly associated with different clinical forms of periodontitis in the Egyptian population. The A allele could be considered a risk factor for periodontal diseases.

Keywords: Interleukin-17; single nucleotide polymorphisms; gene polymorphisms; periodontitis risk.

Introduction

Periodontitis, one of the major causes of tooth loss, is an inflammatory disease affecting the integrity of tooth-supporting tissues. Although periodontal diseases are caused by bacteria present in periodontal sites, the host response plays a decisive role in the breakdown of the connective tissue and bone. The host response is influenced by different risk factors with the genetic factor being one of them.¹

According to the proceedings from the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, periodontitis is classified according to severity into four stages (I, II, III, and IV) and according to rate of progression into three grades (A, B, and C).² Periodontitis severity or even appearance might be regulated by the genetic control of cytokine function. Gene

polymorphisms of cytokines in different types of periodontitis have been investigated by several studies.³⁻⁵

Interleukin-17 (IL-17) is a cytokine with a family of six different molecules (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), with IL-17A and IL-17F being the well-recognized inflammatory mediators.⁶ Interleukin-17 has different biological activities on several cells, such as fibroblasts, endothelial cells, and epithelial cells, with a stimulator effect on osteoclastic bone resorption by inducing receptor activator of nuclear factor kappa-B ligand (RANKL) expression on osteoblasts and stimulating the differentiation and activation of osteoclasts.^{7,8} Interleukin-17 was found to control immune response activation so participating in the inflammatory response of the gingival tissue in periodontitis patients.⁹ Many studies have demonstrated the presence of IL-17 in

periodontal tissues, gingival crevicular fluid (GCF), saliva, and plasma of patients with periodontal disease.¹⁰⁻¹⁴

Recently, the search for genetic markers linked to periodontal disease severity and susceptibility has been receiving significant attention. Gene polymorphisms encoding host defense system molecules have been specifically targeted as possible genetic markers. Variation in an allele of a certain gene can cause different phenotypic presentations affecting molecule production.¹⁵

Interleukin-17A polymorphisms were found to partially influence red complex bacteria in periodontitis (formerly known as chronic periodontitis) patients by increasing the risk of *Tannerella forsythia* and *Prevotella intermedia* occurrence in sub-gingival pockets.¹⁶ IL-17F has a regulatory role in the immune response initiated by T-cells.¹⁷

In a recent meta-analysis, high levels of IL-17A and IL-17F were associated with rheumatoid arthritis suggesting a role of these cytokines in inflammatory disease. In addition, a significant association between IL-17F polymorphisms and the disease was found. This suggests that polymorphisms in these genes may affect periodontal disease progression.¹⁸ IL-17A and IL-17F genes are mapped on the same chromosome at position 6p12, and the polymorphisms of IL-17A G-197A and IL-17F 7488T/C have been associated with higher susceptibility to ulcerative colitis in addition to rheumatoid arthritis.¹⁹⁻²¹

Aiming to assess the risk, prevention, and treatment of periodontitis, determination of gene allelic variants is of great interest in periodontal research. Polymorphisms in cytokine genes may lead to an altered phenotype, and to different cytokine responses among individuals due to different phenotype presentations. This will affect the individual's susceptibility to disease as well as its progression and response to treatment.⁷

Thus, we hypothesized that IL-17A G-197A and IL-17F 7488T/C polymorphisms may be a risk factor for periodontitis. The aim of this pilot study was to detect IL-17A G-197A and IL-17F 7488T/C polymorphisms in stage II grade B and stage III grade C periodontitis patients within the Egyptian population and to analyze their relation to the disease.

Materials and Methods

The study was conducted on 60 subjects, including 20 stage II grade B periodontitis patients (group I), 20 stage III grade C periodontitis patients (group II), and 20 healthy controls (group III). The protocol was approved by the Research Ethics Committee of the Faculty of Oral and Dental Medicine, Cairo University, and the methods were carried out in accordance with the committee's relevant guidelines and regulations. Informed consent was obtained from participants prior to inclusion in the study. Complete records of the periodontal examination, diagnosis, treatment, and recommended follow-up were maintained. All study participants were from the Egyptian population. Systemic diseases that correlate with periodontal disease such as polymorphonuclear leukocyte (PMN) and monocyte defects, HIV infection, or diabetes mellitus were excluded from the present study. Individuals with a history of antimicrobial therapy, periodontal surgery, or smoking within the 6 months prior to initiation of the study, and pregnant and lactating females were also excluded.

Inclusion criteria for group I and II patients as well as patient grouping was in accordance with the clinical and radiographic criteria described in the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.²

The patients' periodontal condition was assessed in all groups. It included the following: plaque index (0-3, in accordance with Silness and Loe), gingival index (0-3, in accordance with Loe and Silness), periodontal probing depth (in accordance with Caton et al.), and clinical attachment level (in accordance with Glavind and Loe).²²⁻²⁵ Radiographic examination was used to aid the diagnosis.

I. Blood Sample Collection

Three milliliters of blood were collected from each subject in ethylenediaminetetraacetic acid (EDTA) tubes using venipuncture at the antecubital fossa. The tubes were maintained in ice and transported to the biochemistry lab at the Faculty of Medicine, Cairo University, where they were stored at -70°C until all samples were collected. All collected samples were given a specific serial number and patient information was not shown on the sample labels.

II. Genotyping of IL-17A and IL-17F

DNA was isolated from the whole blood using a DNA extraction kit. Genotyping of single nucleotide polymorphisms (SNPs) in IL-17A G-

197A (rs2275913) and IL-17F 7488T/C (rs763780) was based on polymerase chain reaction (PCR) using TaqMan assays.^a Reaction mixture and conditions were designed according to the manufacturer’s instructions and fluorescence was measured using the rotor gene apparatus.

III. Statistical Analysis

Sample size was calculated using a power analysis that was based upon the results of Cheng et al.²⁵ The effect size was found to be 0.82, using an alpha (α) level of 0.05 (5%), and a beta (β) level of 0.20 (20%) i.e. power = 80%. The minimum estimated sample size was 18 subjects per group, for a total of 54 subjects. The sample size was increased to 20 subjects per group to compensate for the use of non-parametric tests. Sample size was calculated using the G*Power computer software (version 3.1.9.2).

Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). Age data showed normal (parametric) distribution while data for clinical parameters showed non-normal (non-parametric) distribution. Data were presented as mean and standard deviation (SD) values.

For parametric data, the one-way analysis of variance (ANOVA) test was used to compare between the mean age values in the three groups. Tukey’s post-hoc test was used for pair-wise comparisons when ANOVA was significant. For non-parametric data, the Mann-Whitney U test was used to compare between the clinical parameters of the different groups. The

Kruskal-Wallis test was used to compare between clinical parameters among different genotypes. Dunn’s test was used for pair-wise comparisons when the Kruskal-Wallis test was significant.

Qualitative data were presented as frequencies and percentages. Chi-square test (or Fisher’s exact test when applicable) was used for comparison of qualitative data. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to study the association between genotypes and periodontitis. Confidence intervals for the odds ratios that included a “1” indicated a non-statistically significant association between the studied variables.

The Hardy-Weinberg equilibrium was calculated using the Court-Lab – HW calculator.

The significance level was set at $P \leq 0.05$. Statistical analysis was performed using IBM SPSS Statistics Version 20 for Windows.

Results

I. Demographic Data

The stage II periodontitis group showed the highest mean age which was of statistical significance. The control group showed a significantly lower mean age, and the stage III periodontitis group showed the lowest mean age which was of statistical significance.

There was no statistically significant difference regarding gender distribution in the three groups (Table 1).

Table 1. Descriptive statistics and results of one-way ANOVA and Chi-square tests for comparison between demographic data in the three groups

Demographics	Stage II Grade B Periodontitis (N=20)	Stage III Grade C Periodontitis (N=20)	Control (N=20)	P Value
Age (Mean ± SD)	45.4 ± 8.5 ^A	24.9 ± 5.6 ^C	31 ± 4.5 ^B	<0.001*
Female Gender [N(%)]	10/20 (50%)	11/20 (55%)	11/20 (55%)	0.935
Male Gender [N(%)]	10/20 (50%)	9/20 (45%)	9/20 (45%)	

*Significant at $P \leq 0.05$; different superscripts in the same row indicate statistically significant differences according to Tukey’s test.

^a Thermo Fisher Scientific, Waltham, MA, USA

II. Genotype Data

A. Comparison Between the Three Groups

As regards to gene rs2275913, the AA genotype was found in 10 cases (50%) of group I, 10 cases (50%) of group II, and 5 cases (25%) of the control group. The AG genotype was found in 6 cases (30%) of group I, 6 cases (30%) of group II, and 2 cases (10%) of the control group. The GG genotype was found in 4 cases (20%) of group I, 4 cases (20%) of group II, and 13 cases (65%) of the control group (Table 2). There was a statistically significant difference between the three groups; the periodontitis groups (I and II) showed the highest prevalence of the AA and AG genotypes, while the control group showed the highest prevalence of the GG genotype.

As for gene rs763780, the CC genotype was found in 6 cases (30%) of group I, 2 cases (10%) of group II, and 5 cases (25%) of the

control group. The CT genotype was found in 6 cases (30%) of group I, 7 cases (35%) of group II, and 3 cases (15%) of the control group. The TT genotype was found in 8 cases (40%) of group I, 11 cases (55%) of group II, and 12 cases (60%) of the control group. There was no statistically significant difference between the three groups.

B. Comparison Between Stage II Periodontitis and Control Group

As regards to gene rs2275913, there was no statistically significant difference between the prevalence of the AA and AG genotypes in group I and the control group. As for the GG genotype, group I had a significantly lower prevalence of GG than the control group. The odds ratio was 0.135.

As for gene rs763780, there was no statistically significant difference between the prevalence of CC, CT, and TT genotypes in the group I and control groups (Table 3).

Table 2. The frequencies (N), percentages (%), and results of Fisher’s exact test comparing between genotype distributions in the three groups

Genotype	Gene	Stage II Grade B Periodontitis (N=20)		Stage III Grade C Periodontitis (N=20)		Control (N=20)		P Value
		N	%	N	%	N	%	
rs2275913	AA	10	50	11	55	5	25	0.008*
	AG	6	30	6	30	2	10	
	GG	4	20	3	15	13	65	
rs763780	CC	6	30	2	10	5	25	0.330
	CT	6	30	7	35	3	15	
	TT	8	40	11	55	12	60	

*Significant at P≤0.05

Table 3. The frequencies, percentages, and results of Chi-square test comparing between genotype distribution in stage II grade B periodontitis and control group

Genotype	Gene	Stage II Grade B Periodontitis (N=20)		Control (N=20)		P Value	Odds Ratio	95% CI
		N	%	N	%			
rs2275913	AA	10	50	5	25	0.102	3.000	0.786 – 11.445
	AG	6	30	2	10	0.114	3.857	0.673 – 22.109
	GG	4	20	13	65	0.004*	0.135	0.032 – 0.562
rs763780	CC	6	30	5	25	0.723	1.286	0.319 – 5.175
	CT	6	30	3	15	0.256	2.429	0.512 – 11.511
	TT	8	40	12	60	0.206	0.444	0.125 – 1.575

*Significant at P≤0.05

C. Comparison Between Stage III Periodontitis and Control Groups

As regards to gene rs2275913, there was no statistically significant difference between the prevalence of the AA and AG genotypes in group II and the control group, while the control group had a significantly higher prevalence of the GG genotype compared to group II. The odds ratio was 0.095.

As for gene rs763780, there was no statistically significant difference between

the prevalence of the CC, CT, and TT genotypes in group II and the control group (Table 4).

D. Hardy-Weinberg Equilibrium

The observed genotypes of groups I and II were consistent with the Hardy-Weinberg equilibrium because the calculations were non-statistically significant. Genotypes of the control group however, were not consistent with Hardy-Weinberg equilibrium (Table 5).

Table 4. The frequencies, percentages, and results of Chi-square test comparing between genotype distribution in stage III grade C periodontitis and control group

Genotype	Gene	Stage III Grade C Periodontitis (N=20)		Control (N=20)		P Value	Odds Ratio	95% CI
		N	%	N	%			
rs2275913	AA	11	55	5	25	0.053	3.667	0.958 – 14.028
	AG	6	30	2	10	0.114	3.857	0.673 – 22.109
	GG	3	15	13	65	0.001*	0.095	0.021 – 0.440
rs763780	CC	2	10	5	25	0.212	0.333	0.056 – 1.971
	CT	7	35	3	15	0.144	3.051	0.659 – 14.137
	TT	11	55	12	60	0.749	0.815	0.232 – 2.860

*Significant at P≤0.05

Table 5. Hardy-Weinberg equilibrium calculations

Genotype	Stage II Grade B Periodontitis (N=20)	Stage III Grade C Periodontitis (N=20)	Control (N=20)
rs2275913	x ² = 2.321 P Value = 0.128	x ² = 1.633 P Value = 0.201	x ² = 11.610 P Value = 0.001*
rs763780	x ² = 3.104 P Value = 0.078	x ² = 0.299 P Value = 0.585	x ² = 8.662 P Value = 0.003*

*Significant at P≤0.05

Discussion

Although bacteria present in periodontal sites are the main cause of periodontal diseases, the host response also plays a decisive role in connective tissue and bone breakdown. Genetic factors are involved in the pathogenesis of periodontitis playing an important role in the initiation of the host immune response, and variations in genes associated with immunoregulatory molecules are considered crucial.^{27,28}

Interleukin-17 is a proinflammatory cytokine with gene polymorphisms that are associated with a risk of development of periodontitis. Infiltration of IL-17 producing cells was found to be related to the severity of inflammation in periodontal disease.²⁶ Several studies have aimed to evaluate the association between the rs2275913 polymorphism in IL-17A and the rs763780 polymorphism in IL-17F with stage II grade B and stage III grade C periodontitis in different populations.^{16,29,30}

In the present study we evaluated the rs2275913 polymorphism in IL-17A (G-197A) and the rs763780 polymorphism in IL-17F (7488T/C) in 3 groups: stage II grade B periodontitis, stage III grade C periodontitis, and a control group. Regarding gene rs2275913 (G-197A), our results showed a significantly higher prevalence of the AA and AG genotypes in the periodontitis groups compared to the control, while the control group showed the highest prevalence of the GG genotype indicating that the presence of the A allele could be considered a risk factor for periodontitis in the Egyptian population. The stage II grade B periodontitis group had a lower prevalence of the GG genotype compared to the control group, which was of statistical significance. The odds ratio was 0.135 indicating that the GG genotype may be protective against stage II grade B periodontitis. This was in accordance with Corrêa et al. who studied IL-17A polymorphisms in chronic periodontitis. They stated that “the polymorphism of IL-17A, especially the SNP involving the allele A are associated with the clinical and inflammatory parameters of the disease” with evidence of increased levels IL-17A in serum as well as IL-8 and myeloperoxidase activity in gingival tissues.²⁹

The stage II grade C periodontitis group had a significantly lower prevalence of GG compared to the control group. The odds ratio was 0.095 indicating that the GG genotype may be protective against stage III grade C periodontitis. These results were consistent with Chaudhari et al., who found that the carriage of the AA genotype of IL-17A G-197A was significantly associated with the occurrence of both chronic periodontitis and localized aggressive periodontitis, and that the genotype GG was associated with a healthy periodontium.³⁰ In contrast, a study done on the Brazilian population showed evidence that IL-17A expression and the A allele were found to be higher in healthy controls in comparison with the periodontitis groups.³¹

Regarding gene rs763780, genotype and allele frequencies of IL-17F 7488T/C polymorphisms were similar in both periodontitis groups and the healthy group with no statistically significant

difference. There was no statistically significant difference between the prevalence of CC, CT, and TT genotypes in group II versus the control group nor between group I versus the control group. These findings were in agreement with Corrêa et al. and Valentini Zacarias et al., who stated that IL-17F polymorphisms were not associated with chronic periodontitis.^{7,29} Saraiva et al. also found no association between IL-17F polymorphisms and different clinical presentations of periodontitis with the distribution of genotypes CT/TT and the alleles were similar between the periodontitis and the control groups suggesting a low frequency of polymorphic genotype of IL-17F.³¹ Thus, these results reinforce the idea that IL-17F has a weak proinflammatory role in the pathogenesis of periodontal diseases, although it has a high degree of similarity and shares many biological properties with IL-17A.³²

Several studies indicated that T helper 17 (Th17) cells (which predominantly secrete IL-17A and IL-17F) play a crucial role in the pathogenesis of autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases.^{33,34} IL-17 producing cells were also detected in high amounts in the gingival tissues of patients with periodontal disease especially in the apical portion of periodontal pockets where inflammation is higher, indicating a relation between IL-17 and periodontal diseases.²⁶ IL-17A promotes the expression of IL-8 through phosphorylation of nuclear factor kappa beta p65 subunit at serine 536-serine 468.³⁵

In 2014 Azman et al. conducted a study to determine the clinical association between the IL-17 family and periodontitis in non-smoking systemically healthy patients. They concluded that the IL-17 family has a role in periodontitis, with IL-17A demonstrating a major proinflammatory action and influence on other IL-17 proinflammatory members, while IL-17E was suggested to cease inflammation through its anti-inflammatory action by particularly inhibiting prostaglandin.³⁵

In a study done by Corrêa et al. in 2012, clinical parameters characteristic of

stage II grade B periodontitis were found to be associated with increased levels of IL-17A and IL-17F in gingival tissues, while only IL-17A concentration was found to be high in serum.²⁹

In conclusion, the present study showed that IL-17A polymorphisms are significantly associated with different clinical forms of periodontitis in the Egyptian population. The A allele may be a risk factor for periodontal diseases and thus may be used as a diagnostic risk predictor for stage II and III periodontitis. Our main limitation was the small sample size for genetic study although a sample size calculation was considered as previously mentioned.

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