Original Article

The Study of Genetic Predisposition on Periodontitis and Peri-Implantitis

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Abstract

Background: Peri-implant mucositis and peri-implantitis cases increase in number with the increase of implant applications. Peri-implant mucositis and peri-implantitis are defined as inflammatory diseases with inflammation and loss in soft and hard tissue, similar to the other periodontal diseases. As observed in many diseases, genetic predisposition factors also affect the progress of periodontitis and peri-implantitis. **Aim:** This study examines if there is any solid genetic predisposition causing periodontitis and peri-implantitis formation in Turkish patients. **Patients & Methods:** In order to evaluate single nucleotide polymorphism (SNP), Interleukin-8 (IL-8) and N-formyl-L-methionyl-L-leucyl-phenylalanine (fMLP), playing a role in the chemotaxis of neutrophils, and Fc Gamma Receptor IIA (FcγRIIA) and Fc Gamma Receptor IIIA (FcγRIIIA), playing a role in the antigen-antibody complexes and phagocytosis, were selected. Thirty-two Turkish non-smoking subjects, having periodontitis, thirty-three Turkish non-smoking subjects, having peri-implantitis and thirty-three Turkish non-smoking healthy subjects were selected. In total 98 adults participated in our study. Collected saliva samples from the participants were used for DNA isolation. SNPs were determined in these subgroups of the study by means of genotype-specific polymerase chain reactions. **Results:** When IL-8 A-251T, FcγRIIa -H131 and FcγRIIIa -V158 polymorphism were evaluated, no significant difference was found between periodontitis, peri-implantitis and healthy groups. However, this study observed that fMLP Receptor (FPR1) gene polymorphism creates a significant difference in individuals at higher risk of periodontitis or peri-implantitis. **Conclusion:** Results show that individuals with the G genotype have a higher risk of periodontitis, while individuals with G / C genotype have higher risk of peri-implantitis.

Keywords: *FcγRIIIa, fMLP receptor, IL-8, periimplantitis, periodontitis, polymorphism*

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Background

Peri-implant mucositis and peri-implantitis cases increase in number with the increase in implant applications. Peri-implant mucositis and peri-implantitis are defined as inflammatory diseases with inflammation and loss of soft and hard tissue, similar to other periodontal diseases. Peri-implantitis and periodontitis occur when the homeostasis between host response against microbial pathogens breakdowns.[1] The inflammatory signs which are modified by environmental and genetic factors are sometimes reversible but usually result in damage to periodontal and peri-implant tissues.[2] Periodontal status cannot be evaluated in terms of biofilm and bacteria levels only. All factors, affecting the disease, should be considered.[3] Peri-implant mucositis is the definition of the disease that occurs in the peri-implant tissues without any bone loss.[4,5]

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Inadequate treatment of peri-implant mucositis results in peri-implantitis.[6] Immunohistochemical studies show that peripheral tissues around implants and teeth have a comparable ratio of collagen, vascular, and plasma cells, but tissues surrounding implants have a lower proportion of lymphocytes, macrophages, and polymorphonuclear Leukocytes (PMNs). Peri-Implant tissues have to create a weaker barrier that prevents apical migration of inflammatory cells compared to natural teeth.[7]

Periodontitis and peri-implantitis have similar patterns. Host response has cutting-edge importance when the genetic origins of periodontitis and peri-implantitis patients are considered. To evaluate and understand the pathogenesis of periodontal and peri-implant diseases, cytokines, chemokines, growth factors, and their receptors that take part in the host response of periodontal and peri-implant tissues should be evaluated. As a result, treatments can be individually tailored to each patient.

Single-nucleotide polymorphisms (SNPs) in terms of diseases of periodontal and peri-implant tissues were examined in terms of the release of certain biomarkers and cytokines. Interleukin-8 (IL-8) and N-formyl-L-methionyl-L-leucyl-phenylalanine (fMLP), act as chemoattractant agents, and Fc Gamma Receptor IIA (FcγRIIA) and Fc Gamma Receptor IIIA (FcγRIIIA) take an active role at the infection site. The presence of these molecules affects the response of periodontal and peri-implant tissues and manages disease progression. This study aims to determine whether periodontal or peri-implant tissues are affected by the synthesis or release of these cytokines of individuals who are genetically evaluated as SNPs of IL-8 A-251T (rs4073), FcγRIIA (rs1801274), FcγRIIIA (rs396991) and fMLP receptor (FPR1) (rs2070745) and to understand their associations with periodontitis and peri-implantitis.

Materials and Methods

Study design

This study was conducted on patients, having periodontitis, peri-implantitis, and healthy subjects who were referred to the Department of Periodontology, Faculty of Dentistry, Istanbul University.

All participants, included, were systemically healthy and away from regular drug use and smoking. The subjects who were involved in this study were between 18 and 60 years old and did not receive any periodontal treatment within the prior six months. Periodontal index, bleeding in probing and radiological evaluations were done for each subject.

The study was conducted in conformity with the Declaration of Helsinki and the approval for the study was granted by the Istanbul University Faculty of Dentistry Ethical Council of Clinical Trials with number 27.02.2019/389. First, all patients were informed both verbally and in writing about the study then written consent from participants were obtained before proceeding.

Subjects inclusion criteria

Inclusion criteria of subjects having periodontitis:

- There are at least 4 incisors, 6 premolars or molars in each jaw
- At least 30% of existing teeth have 5 mm or deeper periodontal pockets
- Bone loss of more than 3 mm in at least 30% of existing teeth
- The presence of bleeding and pus in probing at least 30% of existing teeth

Inclusion criteria of subjects having peri-implantitis:

- More than 6 mm of pocket depth in at least 1 peri-implant region
- Bone loss of 3 mm or more in at least 1 peri-implant region
- The presence of bleeding and pus in probing at least 1 peri-implant region

Inclusion criteria of the control group:

- Periodontally healthy individuals, without the above disease criteria, and without any history of peri-implant and periodontal diseases, were considered in the study.

Sample collection and laboratory works

After individuals in the study were divided into groups, saliva samples were taken 5 ml (minimum) from each participant. Each sample, taken, was colorless, odorless, and not dense and was stored in appropriate storage conditions.

Everyone, included in the study, was asked to give saliva samples to individual containers in a clinical setting. Saliva samples were taken from the patients who came on an empty stomach in the early hours of the day, first by spitting 5 milliliters of 10-milliliter tubes with a spit of water and then centrifuged at 1000 rpm by removing the particulate parts of these samples. Until the completion of the individual numbers of the experimental groups and the realization of DNA extraction, the samples were collected in sterile Cryo.S tubes (Greiner Bio-one, GmbH, Germany) and stored at a temperature of −80°C in the freezer (New Brunswick Scientific, U410, USA). The saliva samples collected for use in the study were kept in hot water until a temperature of 37°C and DNA extraction was provided by using the saliva sample QIAamp DNA Mini Kit (Qiagen 51306; Hilden, North Rhine-Westphalia, Germany). The purified DNA,

obtained, was analyzed with LightCycler 480 software to examine SNP.

Statistical analyses

The data collected in the study were analyzed with the SPSS 23.0 (Statistical Packages of Social Sciences) program. The normality of the distribution was tested by using the Kolmogorov-Smirnov test. Descriptive statistics were shown as mean ± standard deviation for continuous variables yet as frequency and percentage for categorical variables. Two independent samples t-test was used for the comparison of continuous data, conforming to the normal distribution of the groups, and the Mann-Whitney U test was used for the comparison of continuous data, not conforming to normal distribution. The Chi-square test and Fisher's exact test were used to analyze the difference between polymorphism and other common categorical variables between the groups. Logistic regression analysis was applied to the independent variables whose univariate analysis results were found to be statistically significant and it was determined whether they constituted a risk factor for the disease. Conformity to the logistic regression model was determined by the Hosmer-Lemeshow test. The Odds Ratio and 95% confidence intervals for these ratios were calculated for the appropriate model. If the values obtained were $P < 0.05$, the difference was considered significant.

Results

The study included a total of 98 subjects who were referred to the Department of Periodontology, Faculty of Dentistry, Istanbul University. Of the participants, 32 subjects were suffering from periodontitis, 33 subjects were suffering from peri-implantitis, and 33 subjects were healthy [Table 1]. The sample size of the study was calculated by using PASS 15 Power Analysis and Sample Size Software (2017-NCSS, LLC.). During the consideration of appropriate sample size, the results of the previously done study[8] were benchmarked and in our study, and each group sample size was calculated as n = 31 by two-tailed alternative hypothesis, 90% Power, 5% Type I Error and 5% dropout ratio for each group.

Periodontitis, peri-implantitis, and healthy groups were evaluated in terms of IL-8 A-251T polymorphism. AA genotype was found in 12.5% of individuals with periodontitis, 27.2% of individuals with peri-implantitis, and 21.2% of healthy individuals. TT genotype was found in 28.1% of individuals with periodontitis, 33.3% of individuals with peri-implantitis, and 30.3% of healthy individuals. AT genotype was seen in 59.4% of individuals with periodontitis, 39.5% of individuals with peri-implantitis, and 48.5% of healthy individuals. Genotype differences between groups were evaluated by the Chi-Square test. When IL-8 A-251T polymorphism was evaluated, no significant difference was found between periodontitis, peri-implantitis, and healthy groups.

Periodontitis, peri-implantitis, and healthy groups in our study were evaluated in terms of FcγRIIa-H131 polymorphism. When the individuals included in the study were examined, the GG genotype was found in 18.7% of individuals with periodontitis, 12.1% of individuals with peri-implantitis, and 18.1% of healthy individuals. AA genotype was found In 37.5% of individuals with periodontitis, 30.3% of individuals with peri-implantitis, and 42.4% of healthy individuals. GA genotype was observed in 43.8% of individuals with periodontitis, 57.6% of individuals with peri-implantitis, and 39.5% of healthy individuals. Genotype differences between groups were evaluated by the Chi-Square test. As a result of statistical analysis, no significant difference was found between periodontitis, peri-implantitis, and the healthy group in terms of FcγRIIa-H131 polymorphism.

Our study, it was investigated whether the FcγRIIIa-158V gene polymorphism yielded a genetic predisposition when compared with periodontitis and peri-implantitis patients and healthy individuals. When the individuals included in the study, were examined, the GG genotype was found in 25% of individuals with periodontitis, 15.1% of individuals with peri-implantitis, and 15.1% of healthy individuals. TT genotype was observed in 18.7% of individuals with periodontitis, 36.3% of individuals with peri-implantitis, and 27.2% of healthy individuals. GT genotype was seen in 56.3% of individuals with periodontitis, 46.6% of individuals with peri-implantitis, and 57.7% of healthy individuals. Genotype differences between groups were evaluated by the Chi-Square test. There was no significant difference between the groups. This demonstrated that the FcγRIIIa gene polymorphism does not affect periodontitis or peri-implantitis.

Our study investigated whether fMLP Receptor (FPR1) gene polymorphism showed a genetic predisposition when compared with periodontitis and peri-implantitis patients and healthy individuals. When the individuals included in the study were examined, the GG genotype was found in 71.8% of individuals with periodontitis, 45.4% of individuals with peri-implantitis, and 57.5% of healthy individuals. CC genotype was found in 6.2% of individuals with periodontitis, 12.1% of individuals with peri-implantitis, and 9% of healthy individuals. GC genotype was observed in 22% of individuals with periodontitis, 42.5% of individuals with peri-implantitis, and 33.5% of healthy individuals. Genotype differences

Table 1: Genotype distributions in groups

Biomolecules	Genotype	Peri-implantitis	Periodontitis	Healthy
IL-8	A genotype	9	4	7
	T genotype	11	9	10
	A-T genotype	13	19	16
FCGAMMAIIA	A genotype	10	12	14
	G genotype	4	6	6
	A-G genotype	19	14	13
FCGAMMAIIIA	T genotype	12	6	9
	G genotype	5	8	5
	T-G genotype	16	18	19
FMLP	G genotype	15	23	19
	C genotype	4	2	3
	G-C genotype	14	7	11

between groups were evaluated by the Chi-Square test. Among the groups evaluated in our study, the G genotype was observed more in the periodontitis group and the G/C genotype was observed more in the peri-implantitis group, and the statistically significant difference was determined in terms of genotype distribution ($p < 0.05$). As a result, the study allowed us to conclude that individuals with the G genotype have a higher risk of periodontitis, while individuals with a G/C genotype have a higher risk of peri-implantitis.

Discussion

Any associations between single or multi-gene polymorphisms to evaluate host response against periodontitis and peri-implantitis might open a path to prevent and intercept the inflammatory host response against microorganisms, therefore an individualized approach can be tailored for each patient. Although there have been some studies in this field to determine the relevancy, results are varying.

IL-8 has a role in the induction and enhancement of acute and chronic inflammatory processes. The high release of IL-8 facilitates the migration of neutrophils to the gingival groove.[9,10] Neutrophils have a crucial role in the pathogenesis of periodontal and peri-implant diseases. Previous papers show that none of the IL-8 SNP's are individually correlated with aggressive or chronic periodontitis.[11,12] There is also no relevance between IL-8 rs4073 (-251A/T), rs2234671, rs2230054, rs1126579, rs2227306, rs2227307, rs2227532, and T-738A polymorphisms, and the susceptibility to periodontitis.[13] The variations of genetic markers between ethnically-diverse groups and the differences between the occurrence of -251A/T genotype frequency may lead to an association with periodontitis in Asians and mixed populations but not Caucasians.[13-17] IL-8 − 251A/T polymorphism is related to a decreased risk of periodontitis in the Brazilian population[16] however the polymorphism is related to an increased risk of periodontitis in the Asian population.[15] According to the findings of our study, we observed that polymorphisms, encoding IL-8, may not lead to a significant change in IL-8 synthesis in patients with periodontitis and peri-implantitis.

FcγR's have significant roles in an acute inflammatory response in periodontal tissues. During the establishment of periodontal disease, FcγR's not only increase NK cells, macrophages, and subgroups of T lymphocytes but also increase the efficiency of phagocytosis, cell-induced cytotoxicity, and a variety of cytokines in the inflamed tissue due to the progression of inflammation.[18,19] This shows that there is a relationship between FcγR polymorphisms and various inflammatory and infectious diseases such as periodontitis.[20-23] The SNP of FcγRIIa, either as histidine (H) or arginine (R) at position 131, affects the affinity of the receptor for IgG.[24] Neutrophils with the HH131 genotype of FcγRIIa can bind efficiently to IgG2 with a higher phagocytosis rate and higher bactericidal activity than the RR131 genotype.[24] The polymorphism of FcγRIIIa might change phenylalanine (F) to valine (V) at position 158 of Immunoglobulin-like domain 2. The F158 isoform can bind IgG1 and IgG3 with lower affinity than the V158 isoform; moreover, the F158 genotype binds fewer immune complexes and reduces inflammatory reactions.[25,26] According to the changes in the polymorphism of FcγRIIa, and FcγRIIIa in acute inflammations, they are also expected to show similar results in periodontal diseases. The FcγRIIIa-158V and FcγRIIa-H131 polymorphisms change not only the severity but also the recurrence of chronic periodontitis in the Japanese population.[22] FcγRIIa-H131 and FcγRIIIa-158V polymorphisms are associated with susceptibility to periodontitis in Caucasians.[20] It is mentioned that there might be differences among populations.[27-29] significant differences are observed

in studies conducted in Caucasian populations, but no significant differences between the relevant polymorphisms and periodontitis are observed in African and East Asian populations.[29-32] The similarities in infection progress in periodontitis and peri-implantitis cases might address those polymorphisms of FcγRIIa and FcγRIIIa effects might also be similar in both diseases. We have not seen any studies on the relationship between these polymorphisms and peri-implantitis. In our study, we investigated both diseases and observed no relationship between the FcγRIIa-H131 and FcγRIIIa-158V polymorphisms and periodontitis and peri-implantitis.

fMLP receptors, having three subgroups (FPR1, FPR2, FPR3), which bind to G-protein, have significant roles in chemotaxism.[33-35] In cases of aggressive periodontitis, the ability of chemotaxis and phagocytosis of neutrophils are negatively affected by the decreased number of receptors on the cell surface or lack of chemotaxis response against fMLP.[36,37] Polymorphisms of the fMLP receptor (FPR1) gene are effective in cases of aggressive periodontitis.[38] A positive correlation with the FPR1 gene polymorphism is observed in individuals who are clinically evaluated for aggressive periodontitis in a study conducted on African Americans.[39] Our study with Turkish people showed that there is a relationship between fMLP receptor (FPR1) gene polymorphism and the risk of periodontitis or peri-implantitis. The association of the G genotype with a higher risk of periodontitis, and the association of the G/C genotype with a higher risk of peri-implantitis might address that fMLP's attitude might vary in periodontitis and peri-implantitis.

Conclusion

In conclusion, our study addresses that when IL-8 A-251T, FcγRIIa-H131 and FcγRIIIa-V158 polymorphism were evaluated, no significant difference was found between periodontitis, peri-implantitis, and healthy groups. However, it was observed that fMLP Receptor (FPR1) gene polymorphism creates a significant difference in individuals at higher risk of periodontitis or peri-implantitis. Results show that individuals with the G genotype have a higher risk of periodontitis, while individuals with G/C genotype have a higher risk of peri-implantitis. Even though our study with Turkish people shows similarities and differences with other studies done with various populations, as stated above, to understand SNP's and periodontitis, peri-implantitis associations clearly, further investigations with larger observational groups with various populations are needed to be done.

List of abbreviations

IL = Interleukin
SNP = Single Nucleotide Polymorphism
FcγR = Fc Gamma Receptor
fMLP = N-Formyl-L-Methionyl-L-Leucyl-Phenylalanine
DNA = Deoxyribonucleic Acid
PMN = Polymorphonuclear Leukocyte
IgG = Immunoglobulin G
FPR = Formyl Peptide Receptor
NK = Natural Killer
H = Histidine
F = Phenylalanine
V = Valine
R = Arginine
A = Adenine
T = Thymine
G = Guanine
C = Cytosine
Rs (Rsid) = Reference SNP ID.

Ethics approval and consent to participate

The study was conducted in conformity with the Declaration of Helsinki and the approval for the study was granted by the Istanbul University Faculty of Dentistry Ethical Council of Clinical Trials with number 27.02.2019/389. All patients were informed verbally and in writing about the study and written consents were obtained.

Consent for publication

Not applicable.

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Conflicts of interest

There are no conflicts of interest.

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