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Original Article

Association of IL-4 Polymorphism with Severe Periodontitis in a Sample of Iraqi Population

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Abstract

Introduction: Specific bacterial plaque and environmental factors cannot be considered the only cause of periodontitis. Still, several genetic factors affect the host response to the bacteria, like gene polymorphisms in anti-inflammatory cytokines. Several studies have reported that clones of T-helper 2 lymphocytes (TH2) are generated in response to dental plaque in periodontitis patients, while in healthy individuals, they are regulated by T-helper 1 (TH1) lymphocytes. Accordingly, such patients consistently produce more IL-4 (TH2) in response to bacterial stimulation, whereas healthy controls with intact periodontal tissues produce a significantly higher level of TH1.

Aim: The current work aimed to investigate the association between variations in IL-4 gene polymorphisms and susceptibility to periodontitis.

Materials and methods: The current study employed a case-control observational methodology involving 120 Iraqi participants. These participants were divided into two groups: the periodontitis group, consisting of 63 subjects, and the control group, consisting of 57 subjects. Clinical periodontal parameters were assessed for all participants, and subsequent genetic analysis of IL-4 was conducted using DNA sequencing. Venous blood samples were collected from each participant enrolled in the study. SPSS was used to conduct descriptive and inferential statistical analyses, including odds ratio, Hardy-Weinberg equilibrium, and Pearson correlation.

Results: The Hardy-Weinberg equilibrium for study groups regarding the rs1801275 and rs1805016 polymorphisms of IL-4 showed a non-significant difference between the observed and expected genotypes in both groups involved in the study and the overall sample. Moreover, there was no significant association between the IL-4 gene polymorphism and the clinical periodontal parameters.

Conclusion: The research conducted revealed a lack of correlation between IL-4 gene polymorphism and the susceptibility to periodontitis in individuals from Iraq. More research with a bigger sample size is required to validate these findings.

Keywords

gene polymorphisms, interleukin-4, periodontitis.

INTRODUCTION

Periodontitis is a complex multifactorial inflammatory disease of the teeth's supporting structures, characterized by progressive destruction of the alveolar bone and periodontal ligament, the formation of periodontal pockets, loss of clinical attachment, and tooth mobility.[1] Dental plaque, with its specific microorganisms, is responsible for initiating periodontitis. Still, the breakdown of the connective tissue and the bone is affected mainly by the host response influenced by risk factors like age[2], systemic diseases like diabetes mellitus, smoking, gender, patient's oral hygiene, and genetic factors.[3,4] Although bacterial dental plaque is the key to the development of periodontitis, each individual may have a dose-dependent response to the bacterial challenge that determines their susceptibility to periodontitis.[5]

Several genes with or without their polymorphisms could affect the severity and susceptibility to periodontitis. Polymorphisms in genes can cause changes in proteins or their expression, potentially influencing innate and adaptive immune responses and, ultimately, disease outcomes. On the other hand, specific genetic variants may have a protective function in the progression of diseases.[6] However, genes are accountable for about 50% of susceptibility to periodontitis.[7,8]

Pathogenic bacteria present in periodontal tissues elicit an immune response, which can gradually lead to the destruction of the periodontium through the inflammatory process.[9] Certain microorganisms present in dental plaque can induce the production of cytokines and other biologically active substances by cells in the periodontium, thereby modulating the immune response.[10] Periodontal diseases may be triggered and maintained by excessive production of pro-inflammatory cytokines or insufficient production of anti-inflammatory cytokines.[11]

IL-4 is one of the essential anti-inflammatory cytokines[12] that has a role in down-regulating the macrophage function[13] and suppressing the secretion of prostaglandin E2 (PG-E2)[14], tumor necrosis factor (TNF-α), and many pro-inflammatory interleukins, including IL-1 and IL-6[15]. The cytokine gene cluster located on the human chromosome 5q31-33 region is responsible for the genetic mapping of interleukin-4. It encompasses several polymorphisms[16], so genetic polymorphisms in the IL-4 gene may be responsible for the aggravation of periodontal disease by altering the level of IL-4[17] since the expressions of cytokines may be affected by gene polymorphisms, and this affects the progression and susceptibility to periodontitis[18].

AIM

Accordingly, it was hypothesized that there is no relationship between periodontitis and IL-4 gene polymorphism in Iraqi individuals; thus, the current study sought to investigate the association of IL-4 gene polymorphism with susceptibility to periodontitis in the Iraqi population.

MATERIALS AND METHODS

Subjects and study design

The study employed a case-control observational design and was conducted in the College of Dentistry, University of Baghdad. The data collection commenced in September 2019 and concluded in March 2020. The researchers acquired ethical approval for the current study from the Research Ethical Committees of the College of Dentistry, the University of Baghdad, in September 2019. Additionally, all participants voluntarily participated in the study and provided informed consent regarding the study's objectives and methodology.

Around 345 subjects were examined, and only 120 Iraqi subjects between the ages of 30 and 50 met the inclusion criteria. The participants were individuals of Arab Iraqi nationality who were categorized into two groups: the periodontitis group (cases) and the control group. The subjects involved in this study exhibited systemic health, did not engage in smoking, and provided informed consent to participate. Moreover, a physician examined all participants to ensure their fitness for inclusion criteria and excluded anyone with systemic disease. Furthermore, subjects with any form of oral disease/condition, subjects using medicaments, pregnant or lactating mothers and those who could not collaborate in the study were also excluded.

The periodontitis group had 63 subjects, all of whom were diagnosed with periodontitis according to the criteria outlined in Tonetti et al.[19], in which radiographical interdental bone loss was detectable at two or more non-adjacent teeth, or the patients had buccal clinical attachment loss more than 3 mm with probing pocket depth more than 3 mm detected at more than 2 teeth. Additionally, periodontitis patients should fully fit the following characteristics:

1. Generalized periodontitis, where over 30% of teeth show attachment loss.
2. Unstable periodontitis, when bleeding pockets were evident at a depth of 4 mm or when the pocket depth reached or exceeded 5 mm.
3. The percentage of interdental bone loss is more than 35%.

The remaining 57 subjects all had a clinically healthy gingiva with intact periodontium and were considered valid to be enrolled in the study according to the criteria given in Dietrich et al.[20], - probing pocket depths ≤3 mm and bleeding on probing less than 10% with no clinical attachment loss.

Clinical periodontal parameters

Calibration sessions were conducted between the initial examiner and a qualified periodontist on 10 patients who were not part of the study. These sessions continued until a consensus level of above 75% was achieved for all clinical periodontal parameters.

The process of obtaining blood samples and doing genotyping

Venous blood from the antecubital vein was collected using 2 ml vacutainer glass blood collection tubes. The collected blood was then transported into a buffered tube containing sodium citrate 3.2% and kept at −40°C for the genotyping of IL-4. The experimental procedures encompassed the extraction of DNA, wherein the genomic DNA was obtained from the blood sample using the QIAamp DNA Mini Kit, following the QIAGEN protocol. The process of PCR amplification was initiated by preparing and optimizing the primers. The primers regarding IL-4 were selected as shown in **Table 1**.

Table 1. Selection of IL-4 primers

IL-4 primers	The Forward Primer	5-GACACCTGGAGGAAGTAGAA-3
	The Reverse Primer	5-CAAGAGGACATGCACCTAAG-3

The primers utilized in this study were subjected to lyophilization and were obtained from Macrogen Company.

The primer template's optimal annealing temperature was investigated by amplifying it using the same primer pair described in **Table 1**. The annealing temperatures tested were 55°C, 58°C, 60°C, 63°C, and 65°C. Subsequently, the polymerase chain reaction (PCR) amplifications were conducted. The PCR cycling procedure was conducted using the PCR Express instrument (Thermal Cycler, BioRad, USA) with the subsequent temperature program: the denaturation process was carried out at a temperature of 94°C for 4 minutes, followed by a series of thirty cycles. Each cycle consisted of denaturation at 94°C for thirty seconds, annealing at temperatures of 55°C, 58°C, 60°C, 63°C, or 65°C for 30 seconds, and extension at 72°C for 30 seconds. The experimental protocol involved a concluding extended incubation period lasting 7 minutes at a temperature of 72°C, which was thereafter followed by a 10-minute incubation at a temperature of 4°C to halt the ongoing processes. Agarose gel electrophoresis was utilized to validate the presence of the amplified PCR product during the loading process. The PCR product was put into the well by immediately adding 5 µl. The electrical power supply was activated at a voltage of 100 volts and a current of 50 milliamperes for 90 minutes. The movement of DNA occurs from the cathode to the anode poles. The bands stained with ethidium bromide in the gel were observed utilizing gel imaging equipment. The PCR product underwent Sanger sequencing using ABI3730XL, an automated DNA sequencer, at Macrogen Corporation, Korea (http://dna.macrogen.com/eng). The data were gathered via electronic mail and subsequently examined by an expert in software analysis. Subsequently, the sequences of all samples were aligned with the source sequence and subjected to analysis utilizing the Basic Local Alignment Search Tool Program (BLAST) (http://blast.ncbi.nlm.nih.gov/Blast.cgi).

Statistical analysis

Detailed statistical tests were performed using both descriptive and analytical statistics. For the analytical statistics, the Shapiro-Wilk test was done for normality of distribution to ensure whether the collected data followed a normal distribution. Chi-square and Fisher's exact test were employed for categorical variables. The odds ratio (OR) was used to measure the strength of the association of IL-4 SNP with health and periodontitis. The Hardy-Weinberg equation was used to compute the predictable homozygotes, heterozygotes, predictable rare homozygotes, and the frequency domain of the alleles from the detected genotypes. The statistical analysis was conducted using the SPSS software (version 21, IBM, USA).

RESULTS

The study included participants aged between 32 and 55 years. The mean age of the study group was 46.86±6.6, while the mean age of the control group was 38.86±4.4 **(Table 2)**. Moreover, the sex of patients was also illustrated in **Table 2**. In the periodontitis group, there were 57 male and 6 female participants, whereas the control group consisted of 36 male and 21 female participants. Concerning the documented clinical periodontal measures, it was observed that the group diagnosed with periodontitis exhibited significantly elevated values for plaque index (PI), gingival index (GI), bleeding on probing (BOP), and tooth loss in comparison to the control group (refer to **Table 2**).

Table 2. Demographic characteristics and clinical periodontal parameters of groups

	Periodontitis	**Control**	***P* value**
N	63	57	
Age range	32-55	32-55	
Age†	46.86±6.60	38.86±4.4	<0.001*S
Sex			
Male	57	36	0.035**
Female	6	21	
Clinical periodontal parameters†			
PI	2.66±0.38	0.52±0.04	<0.001*S
BOP	69.34±22.52	8±0.01	0.001**S
GI	1.83±0.32	0.49±0.03	<0.001*S
PPD	5.19±0.35		
CAL	6.47±0.52		
Missing teeth	6.39±2.15	0.59± .11	<0.001*S

PI: plaque index; BOP: bleeding on probing; GI: gingival index; PPD: probing pocket depth; CAL: clinical attachment loss; † Mean ± standard deviation; * The statistical significance level of $p<0.05$ was determined using the Mann-Whitney test. ** Significance at $p<0.05$ using chi-square test

The PCR loading showed the primer optimization for IL-4 according to primer design as illustrated in **Fig. 1**.

After Sanger sequencing, two polymorphisms were detected according to the primer design as demonstrated in **Figs 2, 3** at rs in rs1801275 and rs1805016.

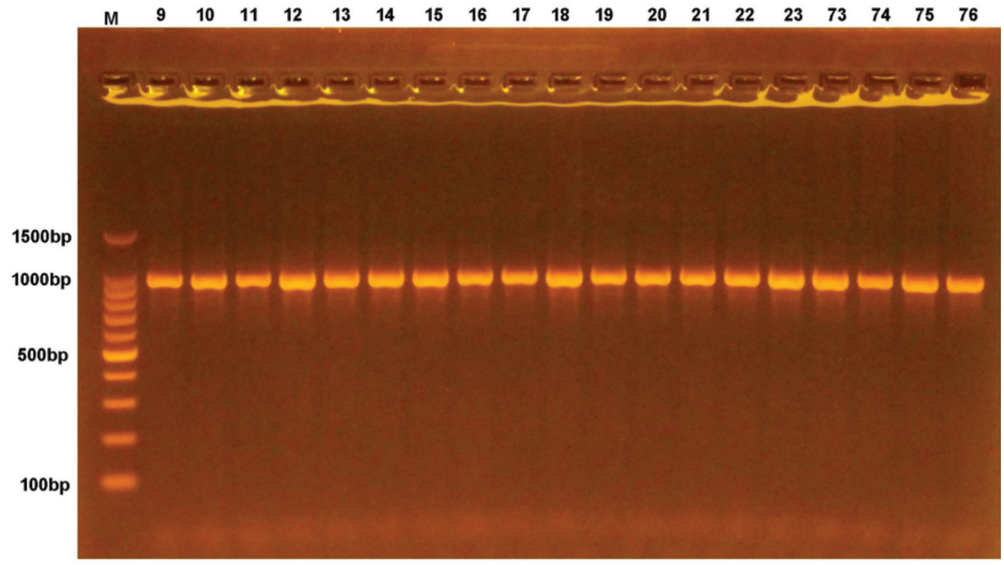

Figure 1. The amplification outcomes of rs1801275 were observed using fractionation on a 1% agarose gel electrophoresis, which was afterward stained with ethidium bromide. A 100 bp ladder marker was used as a reference for size determination.

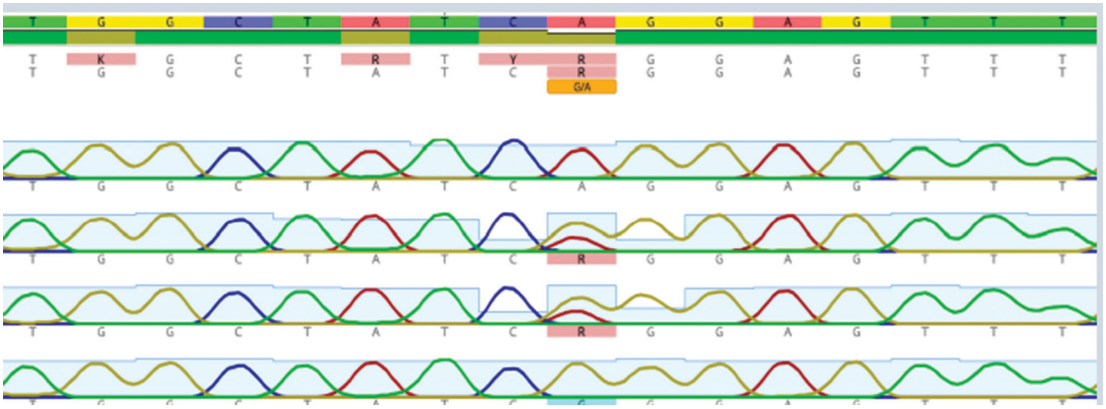

Figure 2. In this study, the rs1801275 SNP was analyzed using Sanger sequencing. The presence of a single peak denoted explicitly as 'A' is suggestive of an individual possessing a homozygous allele for the A gene. The presence of a single 'G' peak is indicative of a homozygous allele for the G variant. The presence of both the 'A' and 'G' peaks is indicative of the presence of an A/C heterozygous allele.

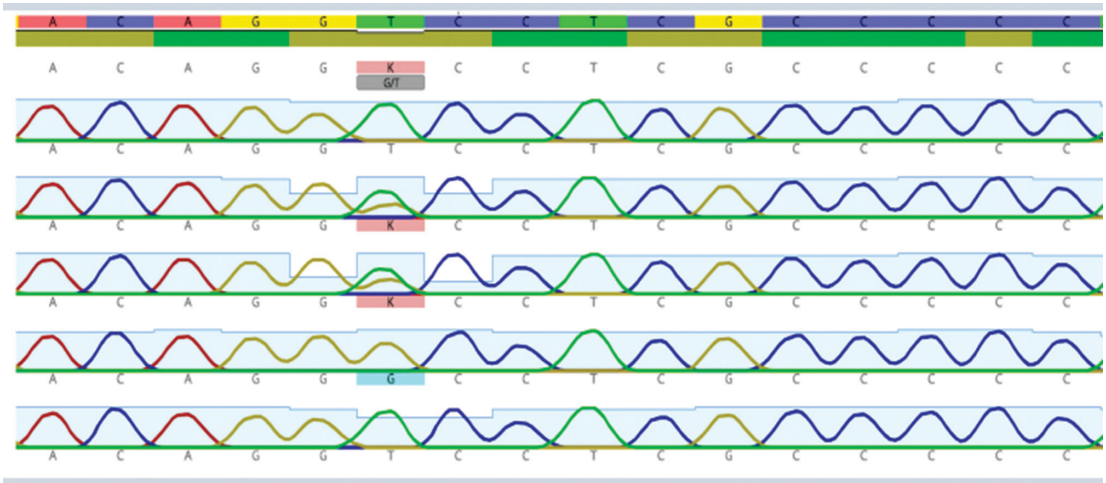

Figure 3. The rs1805016 SNP is analyzed via the Sanger sequencing method. A single peak denoted as 'A' is evidence of a homozygous allele, A solitary. The 'C' peak is suggestive of a homozygous C allele. The presence of the 'A' and 'T' peaks indicates the presence of an A/C heterozygous allele.

The two SNPs were analyzed by Hardy-Weinberg equilibrium. The results were non-significant in the periodontitis group, the control group, and in the total sample, as shown in **Table 3**.

Furthermore, concerning the rs1801275 polymorphism, twelve SNPs were observed in both the periodontitis and control groups, displaying no statistically significant variations. In contrast, the periodontitis group exhibited 6 SNPs, whereas the control group displayed 12 SNPs at rs1805016, with no statistically significant distinction observed between the two groups. The impact of IL-4 SNPs on the distribution of periodontitis was evaluated by calculating the odds ratio. The odds ratio was found to be 0.882 for rs1801275 and 0.3947 for rs1805016, as presented in **Table 4**.

Furthermore, **Table 5** described the Fisher exact test to find the genotype frequency of both SNPs in IL-4; it showed a non-significant difference in their distribution in both groups. The research demonstrated the impact of individual genotypes of IL-4 SNPs on the distribution and prevention of diseases. The study revealed that individuals with genotype A-G exhibited a more significant odds ratio (1.18) in relation to other genotypes for disease susceptibility in the rs1801275 locus, despite the lack of statistical significance in the p-value. The genotype T-G exhibits a higher susceptibility (0.53) to disease development in comparison to other genotypes present at the rs1805016 locus.

Regarding the correlation of IL-4 SNPs with clinical periodontal parameters, the current study illustrated a non-significant negative weak correlation between rs1801275 and all periodontal parameters in the periodontitis group while a non-significant positive weak correlation was found between rs1801275 and PlI, GI in the control group. For 1805016, a non-significant negative weak correlation was found between 1805016 and all periodontal parameters in the periodontitis group except for the PPD, which showed a non-significant weak positive correlation. In the control group, a non-significant positive weak correlation was found between rs1805016 and PlI, GI **(Table 6)**.

Table 3. Hardy-Weinberg equilibrium for groups in rs1801275 and rs1805016 polymorphisms

rs1801275 polymorphism	Periodontitis N=63		Control N=57		Total N=120	
	Observed in	**Expected in**	**Observed in**	**Expected in**	**Observed in**	**Expected in**
AA	51	51.6	45	42.9	96	94.5
AG	12	10.8	9	12.9	21	24
GG	0	0.6	3	0.9	3	1.5
Hardy-Weinberg equilibrium	0.232		1.815		0.611	
P value	0.629		0.17		0.43	
rs1805016 polymorphism	**Periodontitis N=63**		**Control N=57**		**Total N=120**	
	Observed in	**Expected in**	**Observed in**	**Expected in**	**Observed in**	**Expected in**
TT	57	57	45	42.9	102	99.9
TG	6	5.7	9	12.9	15	19.2
GG	0	0.0	3	0.9	3	0.9
Hardy-Weinberg equilibrium	0.0525		1.82		1.89	
P value	0.818769		0.177		0.17	

Table 4. The quantity of SNPs observed in the IL-4 gene among individuals in the periodontitis and control groups

	Periodontitis		Control		Fisher exact	*P* value	Odds ratio	CI
	n	**%**	**n**	**%**				
rs1801275	12	19.05%	12	21.05%	1	0.8743	0.882	0.1873 to 4.1577
rs1805016	6	9.52%	12	21.05%	0.39	0.3188	0.3947	0.0635 to 2.4544

CI: confidence interval.

Table 5. Genotype frequency of IL-4 SNPs

Genotype Frequency		Periodontitis		Control		Fisher exact test	*P* value	Odd ratio	CI 95%	Population penetrance
		%	**Frequency**	**%**	**Frequency**					
rs1801275	AG	12	19.05%	9	15.79%	1	0.847	1.18	0.23–6.13	0.24%
	GG	0	0%	3	5.26%	0.484	0.465	0.295	0.0112 to 7.790	0%
rs1805016	TG	6	9.52%	9	15.79%	0.64	0.51	0.530	0.08–3.56	0.12%
	GG	0	0%	3	5.26%	0.457	0.425	0.26	0.0101 to 6.967	0%

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Table 6. The rs1801275 and rs1805016 correlation with clinical periodontal parameters

Sperman correlation			PlI	GI	BOP	PPD	CAL
1801275	Periodontitis	*r*	−0.321	−0.37	−0.302	−0.360	−0.350
		p	0.155	0.100	0.183	0.108	0.119
	Control	*r*	0.120	0.190			
		p	0.624	0.434			
1805016	Periodontitis	*r*	−0.040	−0.150	−0.188	0.026	−0.121
		p	0.86	0.515	0.412	0.91	0.602
	Control	*r*	0.120	0.190			
		p	0.624	0.434			

DISCUSSION

In addition to environmental factors, genetics is a significant factor that decisively affects the host's susceptibility to periodontitis.[21,22] In 1990, the first argument emerged by Schafer et al. in that genetics had a fundamental part in the initiation and advancement of periodontal diseases as they assumed that the primary key to whether individuals are susceptible to developing periodontitis or not is mainly dependent on the way their bodies responded to the microbial attack.[23] In this regard, the association between the SNP of the inflammatory immune response and periodontitis has gained important attention in recent studies as a possible contributor to periodontal disease[24,25] affording a more detailed understanding of the development and progression of periodontal disease and contributing to the advancement of novel diagnosis, treatment, and preventive approaches. Based on the idea proposed by Seymour et al.[26] concerning the role of TH1 and TH2 lymphocytes in periodontal disease progression, they proposed that in patients with progressing periodontitis, clones of TH2 are generated upon activation with bacteria. Accordingly, such patients constantly revealed amplified secretion of IL-4 upon stimulation of T-helper 2 lymphocytes by pathogenic dental plaque bacteria, while the non-progressing disease is regulated by TH1 clones, suggesting that periodontally healthy individuals with intact periodontal tissues produced a significantly increased level of IFNγ (TH1).[10] For the above-mentioned information, the current study was conducted investigating the association of IL-4 polymorphisms with susceptibility to periodontitis. Yet, the present work demonstrated no significant association between IL-4 polymorphism and periodontitis in the Iraqi human population. This finding was supported by the non-significant results of Hardy-Weinberg equilibrium for rs1801275 and rs1805016 polymorphisms between the observed and expected genotypes in the periodontitis and control groups and the total sample. Furthermore, there were non-significant associations between the IL-4 gene polymorphism and the clinical periodontal parameters, which was in agreement with several other populations, such as Czech[27], Macedonian[28], Iranian[29], Brazilian[30,31], and Japanese[32], as their studies showed no association between polymorphisms in the IL-4 gene and periodontitis, as well as consistent with the longitudinal study done by Walther et al., as they reported IL-4 polymorphisms were unpredictable for further CAL loss[33].

Inversely, a study on the population in Germany showed a borderline association between IL-4 and periodontitis.[34] In another Brazilian study, the results showed that IL-4 gene was associated with periodontitis.[35] The small sample size, number, and sites of investigated polymorphisms, other ethnicities, and the effect of various environmental factors on susceptibility to periodontitis could explain the conflicting results reported in other literature sources. It is conceivable that a deduction reached in one population or racial group may be completely different in another population.[36]

The impact of IL-4 single nucleotide polymorphisms on the vulnerability to periodontal disease throughout the Iraqi population was shown to be negligible. On the contrary, another study reported that stimulation with dental plaque bacteria, for instance, *T. forsythia* and *P. intermedia,* would bring about meaningfully increased levels of the inflammatory response, leading to high production of different cytokines, and the IL-4 gene polymorphisms in periodontitis patients would not only affect the production of cytokines such as IL-4, IL-10, IFNγ, IL-1β, IL-6, and TNF-α, which in turn can affect periodontal disease. Polymorphisms in genes encoding some cytokines or their receptors can affect the production of not only their own but also other mediators. However, one of the major limitations of the current study is the lack of quantitative measurement of important cytokines that had a role in the development and progression of periodontal disease.[10] Furthermore, the small sample size of the people studied was due to financial considerations, which suggests the need for a future study with more patients. However, to mitigate the influence of confounding variables, this study did not include diabetes and smoking as risk factors for periodontal disease. This decision was made due to the potential for these diseases to exacerbate susceptibility to periodontitis in the presence of SNP. Another limitation of this study is the genetic heterogenicity of periodontal disease, which restricted the generalizability of the results. However, this study represents a limited number of investigations that have examined the role of IL-4 polymorphisms in periodontal disease within a sample of the Iraqi population.

CONCLUSION

Considering the limitations, it is possible to conclude that there is no evident association between polymorphisms in IL-4 and the susceptibility to periodontitis. Moreover, it was observed that there was a lack of association between clinical periodontal measures and the IL-4 single nucleotide polymorphism, indicating that the SNP has a minimal impact on the advancement and intensity of the illness. It is crucial to acknowledge that this study was constrained by its modest sample size and the fact that it was conducted at a single institution. Additional research with bigger sample size and multicenter methods is necessary to validate these findings.

Ethical Clearance

This study was approved by the Ethical Committee, College of Dentistry University of Baghdad.

Conflict of Interest

None.

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Ассоциация полиморфизма IL-4 с тяжёлым периодонтитом в выборке населения Ирака

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Резюме

Введение: Специфический бактериальный налёт и факторы окружающей среды не могут считаться единственной причиной пародонтита. Тем не менее, несколько генетических факторов влияют на реакцию организма-хозяина на бактерии, например полиморфизм генов противовоспалительных цитокинов. В нескольких исследованиях сообщалось, что клоны Т-хелперов 2 (TH2) генерируются в ответ на зубной налёт у пациентов с пародонтитом, тогда как у здоровых людей они регулируются Т-хелперами 1 (TH1) лимфоцитами. Соответственно, такие пациенты последовательно производят больше IL-4 (TH2) в ответ на бактериальную стимуляцию, тогда как здоровые люди с интактными тканями пародонта производят значительно более высокий уровень TH1.

Цель: Целью настоящей работы было изучение связи между вариациями полиморфизма гена IL-4 и предрасположенностью к пародонтиту.

Материалы и методы: В настоящем исследовании использовалась методология наблюдения „случай-контроль“ с участием 120 иракских участников. Эти участники были разделены на две группы: группа пародонтита, состоящая из 63 человек, и контрольная группа, состоящая из 57 человек. Клинические параметры пародонта были оценены у всех участников, а последующий генетический анализ IL-4 был проведён с использованием секвенирования ДНК. Образцы венозной крови были взяты у каждого участника, включенного в исследование. SPSS использовался для проведения описательного и статистического анализа, включая отношение шансов, равновесие Харди-Вайнберга и корреляцию Пирсона.

Результаты: Равновесие Харди-Вайнберга для исследуемых групп относительно полиморфизмов rs1801275 и rs1805016 IL-4 показало незначимую разницу между наблюдаемыми и ожидаемыми генотипами в обеих группах, участвовавших в исследовании, и в общей выборке. Более того, не было выявлено значимой связи между полиморфизмом гена IL-4 и клиническими параметрами пародонта.

Заключение: Проведённое исследование выявило отсутствие корреляции между полиморфизмом гена IL-4 и предрасположенностью к пародонтиту у лиц из Ирака. Для подтверждения этих выводов необходимы дополнительные исследования с большей выборкой.

Ключевые слова

полиморфизмы генов, интерлейкин– 4, пародонтит