

Review Article

C-C Chemokine Ligand (CCL5), C-C Chemokine Receptor Type 5 (CCR5) and Tumor Necrosis Factor (TNF)- α Polymorphisms Detection in Patients with Periodontitis

Melgar-Rodríguez S¹, Reyes T¹, Tapia C¹, Martínez-Aguilar VM^{2*}, Díaz-Zúñiga J^{1,3*}

¹Conservative Dentistry Department, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

²Faculty of Dentistry, Universidad Autónoma de Yucatán, Mérida, México

³Department of Medicine, Faculty of Medicine, Universidad de Atacama, Copiapó, Chile

*Correspondence author: Víctor Martínez-Aguilar and Jaime Díaz-Zúñiga. Conservative Dentistry Department, Faculty of Dentistry, Universidad de Chile, Olivos 943, 8380492 Independencia, Santiago, Chile; Department of Medicine, Faculty of Medicine, Universidad de Atacama. Los Carrera 1579, Copiapó, Chile; E-mail: jdiaz@odontologia.uchile.cl; jaime.diaz@uda.cl

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Abstract

Periodontitis is a chronic non-communicable disease, caused by dysbiosis of the subgingival microbiota, resulting in inflammation and destruction of the periodontal tissues. Also, the inflammation could be aggravated by genetic factors, such as polymorphism of pro-inflammatory genes. In this context, the production levels of IL-1 β , IL-6 or TNF- α can determine the periodontal milieu and favor the progression of periodontitis. Thus, the aim of this research was to determine if there is an association between the polymorphic variants of the genes RANTES-403 G/A, CCR5 G59029A, TNF-308 G/A and the presence or absence of periodontitis.

Methods: For this purpose, 20 patients who attended the Faculty of Dentistry of the Autonomous University of Yucatán were clinically evaluated; saliva samples were taken to perform a quantification of pro-inflammatory mediators using ELISA. To determine the RANTES-403 G/A, CCR5 G59029A and TNF-308 G/A polymorphism, a real-time Polymerase Chain Reaction (qPCR) was performed using TaqMan® type probes (Thermo Fisher Scientific) and specific primers. The distribution was analyzed according to population parameters for the Hardy-Weinberg equilibrium.

Results: The periodontal evaluation resulted in 10 patients with periodontitis (cases) and 10 healthy people (controls). For the CCR5 G59029A polymorphism, a significant difference was found for allelic and genotypic frequency between healthy subjects and patients with periodontitis. The pro-inflammatory cytokines IL-1 β , IL-2, IL-6, IL-9, IL-13, IL-17A, IL-21, IL-22, IL-23 and IL-27 were increased in cases compared to controls, unlike the immuno-modulatory cytokines IL-4, IL-5, IL-10 or pro-inflammatory IL-12 and TNF- α where no differences were found between cases and controls. When analyzing the genotypic frequencies, the CCR5 homozygous mutated condition (AA) results in a protective factor of OR = 0.0296.

Conclusion: In patients with periodontitis the CCR5 G59029A OR polymorphism indicates a protective factor.

Keywords: Periodontitis; Dysbiosis; Pro-Inflammatory Cytokines; Protective Factor

Introduction

Periodontitis is a multifactorial, non-communicable, chronic inflammatory disease characterized by the inflammation of the periodontal tissues in response to the presence of bacteria present in a dysbiotic subgingival microbiota [1-3]. In periodontitis, some studies identified molecules present both in periodontal tissues and in oral fluids and determined the presence of higher levels of different cytokines and chemokines [4-10]. Among the molecules that increase in the presence of periodontitis we can recognize the Interleukin (IL)-1 β , IL-6, IL-12, IL-17A, IL-21, IL-22, IL-23, Tumor Necrosis Factor (TNF)- α , Interferon (IFN)- γ , Receptor Activator of Nuclear Factor κ B Ligand (RANKL) and C-C Chemokine Ligand (CCL)-3, CCL5, among others [8]. Of

them, TNF- α and CCL5 seem to play an important role in the immune response, as they are molecules linked to both neutrophils and macrophages, as well as TCD4+ lymphocytes [9].

During periodontitis, TNF- α induces the recruitment of circulating leukocytes and stimulates the production of other mediators, such as IL-1, IL-6 and Matrix Metalloproteinases (MMPs), amplifying or maintaining the inflammatory response [11]. For the TNF gene, various polymorphisms are described where the allele at position -308 denoted as TNF2 is the most studied and is associated with a high transcription of the TNF- α mRNA [12-14]. Otherwise, is secreted by macrophages, eosinophils, fibroblasts, endothelial cells, epithelial and endometrial cells and its presence induces the migration of CD4+ T cells, dendritic cells, among other immune cells [15]. CCL5 has affinity with various receptors, showing more importance of the CCR1, CCR3 and CCR5 receptors. CCL5-CCR5 binding trigger an increase in cell survival and the production of pro-inflammatory cytokines and chemokines [16]. Thus, CCL5 and CCR5 are associated with diseases such as arthritis, atopic dermatitis, nephritis, colitis, among other [16].

Polymorphisms are considered variants in the sequence of a gene, present in at least 1% of the population. Polymorphisms can significantly influence traits, disease risk or drug responses. These variations can provide a survival or reproductive advantage, leading to adaptations in a population or they may have neutral effects. Some polymorphisms can also be harmful, increasing susceptibility to diseases, while others can be protective against certain conditions or influence how an individual responds to medications [17-19]. The most common polymorphisms are Single Nucleotide Polymorphism (SNP), which is the change of a nitrogenous base [20]. Different studies demonstrate that the rs1800629, rs1800630 and rs1799964 polymorphisms related to TNF- α are predisposing to periodontitis, particularly in the Asian population [21]. The most frequent polymorphism that affect TNF- α gene is the change of A by G. On the other hand, in a study carried out in the Saudi population, no relationship was found between the presence of TNF-308 G/A and periodontitis [22]. The CCL5-403 polymorphism, which is a SNP located in the promoter region of the human CCL gene where a G is changed for an A at locus 403, increased transcription of CCL5 [23,24]. The CCL5-403 polymorphism was detected in higher frequency in Taiwanese population affected by aggressive periodontitis compared to patients with chronic periodontitis or healthy controls. This suggests that the CCL5-403 G/A polymorphism may play a central role in the development of the most aggressive forms of periodontitis [25]. The A/G polymorphism located at bp 59029 in the CCR5 promoter doubles the expression of CCR5 [26,27]. The CCR5 G59029A polymorphism causes up to a two-fold increase in CCR5 expression, as well as an increase in CCR5 expression in peripheral blood mononuclear cells [28,29]. The evidence does show a need to determine the presence of genetic polymorphisms linked to periodontitis within affected populations to understand the disease's genetic basis and host susceptibility. Thus, the population with polymorphisms associated with TNF- α , CCL5 or CCR5 can increase the risk of periodontitis by altering inflammation and immune responses, making these molecules potential therapeutic targets. Targeting these molecules or their receptors could help prevent or reduce the severity of periodontitis and its systemic effects.

Methodology

Patients Selection

30 patients who attended the Faculty of Dentistry of the Autonomous University of Yucatán, Mérida, Mexico, between May 2020 and April 2023 were included. All patients underwent a complete dental examination, recording personal data, number of teeth present, absent and restored, periodontal examination and imaging. As an inclusion criterion, individuals between 19 and 80 years of age were selected, who did not have uncontrolled chronic non-communicable diseases such as diabetes mellitus II, hypertension, dyslipidemia, smoking, alcoholism, sedentary lifestyle or chronic stress, who had not received antibiotic treatment, NSAIDs, antifungals or periodontal therapy in the last six months and who did not present active caries lesions. All patients signed the informed consent which was duly approved by the ethics committee (FODO-2019-002).

Periodontal Screening and Examination

The complete protocol was explained to each patient with the aim of accepting or rejecting the participation in the study, accessing it by signing the informed consent. A general clinical history and periodontal probing were performed on each patient with a calibrated periodontal probe (UNC-15, Hu-Friedy, Chicago, IL, USA) by a single properly calibrated operator, which will be recorded in the free access program Periodontal Chart. Patients were classified according to the new classification of periodontal and peri-implant diseases and conditions [30].

Sample Collection

All patients were instructed to obtain a stimulated saliva sample. To do this, each patient was given a cotton swab, which they chewed for 45 seconds without swallowing, depositing the accumulated saliva and the swab into a 50 mL tube free of RNase. The saliva samples were centrifuged to separate the cellular phase from the liquid phase. The pellet was resuspended in buffer (in detail below) and purification of the total genomic DNA proceeded. Also, a Gingival Crevicular Fluid (GCF) was taken according previous published protocol in the deepest sites [5]. The concentration of total proteins was quantified from the supernatant using a SynergyTM device (Bio-Tek, Winooski, VT, USA), measuring the absorbance at 480 nm, aliquoted into 2 mL tubes and stored at -80°C until analysis.

Pro-inflammatory Mediators Quantification

From 100 µL of the saliva supernatant, the secretion levels of the molecules IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-17A, IL-21, IL-22, IL-23, IL-27 and TNF- α were quantified using Multiplex, following the manufacturer's instructions (R&D Biosystems) and evaluated absorbance at 480 nm using a spectrophotometer (SynergyTM).

Total Genomic DNA Extraction

The saliva samples obtained were centrifuged at 14,000 xg for 5 min at room temperature. From the pellet, the genomic DNA was purified for the quantification of the polymorphisms, using an extraction kit and following the manufacturer's instructions (FavorPrepTM Tissue Genomic DNA extraction Mini Kit, Favorgen Biotech Corp.). Briefly, the pellet was resuspended in 200 µL of FATG1 buffer and 20 µL of proteinase K and incubated at 60°C for 30 min. After elution, the sample was incubated for 2 min with 4 µL of RNAase A, followed by 200 µL of FATG1 buffer at 70°C for 1 h and subsequently 200 µL of 100% ethanol was added. The column with the sample was inserted into a collection tube and centrifuged for 1 min at 18,000 xg and then the column was washed with 400 µL of FATG buffer. Next, 2 column washes were performed: 400 µL of W1 buffer and 1 min of centrifugation at 18,000 xg and 750 µL of wash buffer followed by 1 min of centrifugation at 18,000 xg. Finally, the column was incubated with 200 µL of elution buffer (pH 7.5-9.0) for 3 min and centrifuged at maximum speed for 2 min to elute total DNA. Samples were quantified using a spectrophotometer (SinergyTM) and stored at -80°C until quantification by qPCR.

Polymorphisms Detection

To determine the CCL5 -403 G/A, CCR5 G59029A and TNF-308 G/A polymorphism, a real-time Polymerase Chain Reaction (qPCR) was performed using TaqMan[®] type probes (Thermo Fisher Scientific) and specific primers (Table 1). Genomic DNA was obtained from patients' saliva samples using the FavorPrepTM kit. This procedure was carried out in the Basic Dental Science laboratory of the Faculty of Dentistry of the Autonomous University of Yucatán. From 1 µL of DNA at a concentration of 1 µg/µL, the target genes were amplified by qPCR using the Type-it Fast SNP probe PCR Master Mix 2x kit (Qiagen) and according to the following amplification conditions: 95°C for 2 min followed by 40 cycles each of 95°C for 15 s and 60°C for 30 s. The genotypic and allelic frequencies of the CCR5 G59029A, CCL -5403 G/A and TNF- α -308 G/A polymorphisms were determined by simple counting in all patients studied, both for cases and controls and the distribution was analyzed according to population parameters for Hardy-Weinberg equilibrium.

Results

Epidemiological Data

Between may 2020 and April 2023, a total of 30 patients were included. Based on periodontal screening we determined the periodontal diagnosis were 10 patients were diagnosed with health and 20 were diagnosed with periodontitis stage III or IV. The age average, female percentage and periodontal clinical parameters are summarized on Table 1.

	Healthy (n=10)	Periodontitis (n=20)
Age	69.0 $\pm$ 0.5	71.0 $\pm$ 4.8
Gender (Female)	50% (5)	60% (12)
CAL (mm)	-0.67 $\pm$ 0.89	-6.8 $\pm$ 1.96
BoP (%)	5.30 $\pm$ 2.90	41.90 $\pm$ 10.23
PI (%)	12.70 $\pm$ 2.49	45.50 $\pm$ 7.09

Table 1: Clinical information.

The Table 1 represent the mean $\pm$ standard deviation of each group. CAL: Clinical Attachment Loss, BoP: Bleeding on Probing, PI: Plaque Index.

Patients with Periodontitis Stage III-IV have More Pro-Inflammatory Cytokines

From the GCF samples of all patients, the secretion levels of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-17A, IL-21, IL-22, IL-23, IL-27 and TNF- α were quantified using Multiplex (Fig. 1). For the pro-inflammatory cytokines IL-1 β , IL-2, IL-6, IL-9, IL-13, IL-17A, IL-21, IL-22, IL-23 and IL-27, an increase was detected in people with periodontitis compared to those with periodontal health.

Polymorphisms Identification

For the quantification of the polymorphisms, DNA samples derived from saliva from 10 healthy people and 10 patients affected by stage IV periodontitis were used. Regarding the -403 G/A polymorphism of the CCL5 gene, a frequency of 60% (n=6) of the Wild Genotype (WG)(GG), 10% of the mutated Heterozygous (HT)(n=1) and 30% of the Mutated Homozygous (MT)(AA) was observed in the cases (Table 2). In controls, a frequency of 40% (n=4) of the WT (GG), 40% (n=4) of the HT (GA) and 20% of the MT (AA) was observed. No statistically significant differences were found between the genotypes and alleles of the cases and controls for this polymorphism.

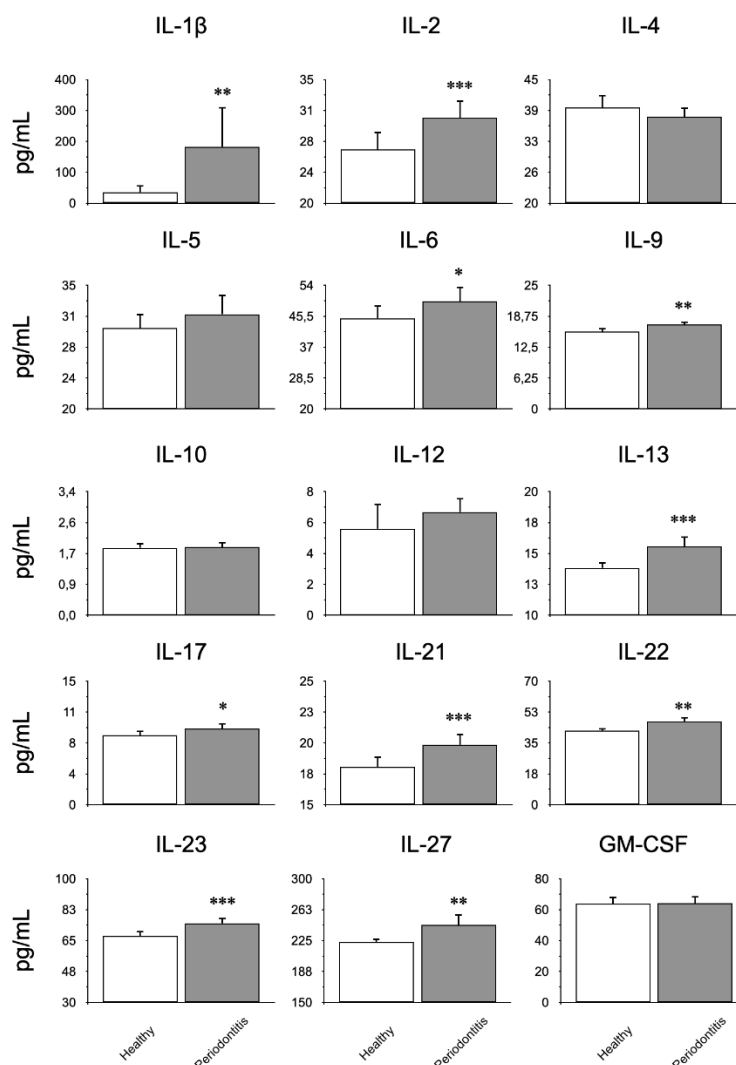


Figure 1: Quantification of pro-inflammatory mediators in GCF of patients with or without periodontitis. From FCG samples from healthy subjects and patients with periodontitis. The levels of IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-17A, IL-21, IL-22, IL-23, IL-27 and TNF- α were quantified using Multiplex. Analysis from 30 patients in total. ANOVA-Tukey analysis, *p<0.05, **p<0.01, ***p<0.001.

CCL5-408 G/A					
	Genotypic Frequency			Allelic Frequency	
	GG	GA	AA	G	A
Cases	6	1	3	13	7
	-60%	-10%	-30%	-65%	-35%
Controls	4	4	2	12	8
	-40%	-40%	-2%	-60%	-40%
OR		0.1667	1		0.8077
95% CI		0.0133 - 2.0930	0.1118 - 8.9473		0.2240 - 2.9121
GG: Wild Genotype; GA: Heterozygous Genotype; AA: Homozygous Mutated, OR: Odds Ratio, CI: Confidence Interval. *p<0.05, **p<0.01.					

Table 2: Genotypic and allelic frequencies analysis of CCL5-403/G/A in patients with gingival health and periodontitis.

In the G59029A polymorphism of the CCR5 gene, a frequency of 60% (n=6) of (WT) (GG), 40% of HT(GA) and 0% (n=0) of MT (AA) was observed in the cases. On the other hand, in the controls a frequency of 20% (n=2) of the WT (GG), 20% (n=2) of the HT (GA) and 60% of the MT (AA) was observed. When analyzing the genotypic frequencies, it is detected that presenting the homozygous mutated condition (AA) results in a protective factor of 0.0296 times (CI= 0.0250 - 0.4588). Furthermore, the allele frequencies were 80% (n=16) for the G allele and 20% (n=4) for the A allele in the cases and 30% (n=6) for the G allele and 70% (n=14) for the A allele in the controls. A statistically significant difference of one (p<0.05) was found (Table 3). In the -308 G/A polymorphism of the TNF gene, a frequency of 80% (n=8) of WT (GG), 20% (n=2) of HT (GA) and 0% (n=0) of MT (AA) was observed in the cases. On the other hand, in the controls, a frequency of 90% (n=9) of the WT (GG), 10% (n=1) of the HT (GA) and 0% of the MT (AA) was observed. No statistically significant differences were found between the genotypes and alleles of the cases and controls for this polymorphism (Table 4).

TNF-308 G/A					
	Genotypic Frequency			Allelic Frequency	
	GG	GA	AA	G	A
Cases	8	2	0	18	2
	-80%	-20%	0%	-90%	-10%
Controls	9	1	0	19	1
	-90%	-10%	0%	-95%	-5%
OR		2.25	--		2.1111
		0.1701 - 29.7687	--		0.1758 - 25.3499
GG: Wild Genotype; GA: Heterozygous Genotype; AA: Homozygous Mutated, OR: Odds Ratio, CI: Confidence Interval. *p<0.05, **p<0.01.					

Table 3: Analysis of genotypic and allelic frequencies of CCR5 G59029A from patients with gingival health and periodontitis.

CCR5 G59029A					
	Genotypic Frequency			Allelic Frequency	
	GG	GA	AA*	G	A*
Cases	6	4	0	16	4
	-60%	-40%	0%	-80%	-20%
Controls	2	2	6	6	14
	-20%	-20%	-60%	-30%	-70%
OR		0.6667	0.0296		0.1071
95% CI		0.0647 - 6.8716	0.0012 - 0.7443		0.0250 - 0.4588
GG: Wild Genotype; GA: Heterozygous Genotype; AA: Homozygous Mutated, OR: Odds Ratio, CI: Confidence Interval. *p<0.05, **p<0.01.					

Table 4: Analysis of genotypic and allelic frequencies of TNF-308 G/A of patients with gingival health and periodontitis.

Discussion

In the present research we evaluated whether or not people affected by periodontitis present polymorphisms associated with the CCL5, CCR5 and TNF genes and whether or not their presence is linked to a possible higher risk of developing the disease. In the period included, 30 patients were evaluated, resulting in 10 healthy people and 20 patients with periodontitis stage III-IV. Further, we determined both the allelic and genotypic frequency of the CCL5 -403 G/A, CCR5 G59029A and TNF-308 G/A polymorphisms in their saliva samples. For the CCR5 G59029A polymorphism, a significant difference was found when analyzing both the allelic and genotypic frequencies. Furthermore, when analyzing the odds ratio, it was detected that this polymorphism could be a protective factor given that the OR was 0.0296 (CI= 0.0250 - 0.4588). Among allelic or genotypic frequencies, no significant differences were observed between case and control patients for CCL5 -403 G/A and TNF-308G/A polymorphisms. For the pro-inflammatory cytokines —IL-1 β , IL-2, IL-6, IL-9, IL-13, IL-17A, IL-21, IL-22, IL-23 and IL-27— an increase was detected in people with periodontitis compared to those with periodontal health, unlike the immuno-modulatory cytokines —IL-4, IL-5, IL-10— or pro-inflammatory cytokines —IL-12 and TNF- α — which did not differ between the groups.

In the quantification of the cytokines IL-1 β , IL-2, IL-6, IL-9, IL-13, IL-17A, IL-21, IL-22, IL-23 and IL-27, an increase was observed in patients with periodontitis. These cytokines are identified as essential for the immune response of neutrophils, macrophages, dendritic cells or T helper lymphocytes during periodontitis and play the role of activating immune cells and inducing the destruction of periodontal tissues [4-9]. Indeed, in patients affected by gingivitis or periodontitis these cytokines are found in high concentrations in the gingival crevicular fluid [31]. The cytokine IL-2 is associated with B cell activation, stimulation of macrophages and natural killer cells, T cell proliferation and osteoclast activation [32]. IL-13 is an immuno-regulatory cytokine that suppresses the production of pro-inflammatory cytokines in monocytes and macrophages and similarly to our results, the IL-13 cytokine have been found in periodontal lesions but not in healthy tissue [33-35]. Otherwise, IL-17A, IL-21 and IL-22 were detected in the GCF of patients affected by periodontitis [4,36,37]. Furthermore, IL-27 induced the expression of the anti-inflammatory cytokine IL-10 in Th1, Th2 and Th17 cells and induce the inhibition of Th17 lymphocytes [8]. In general terms, cytokine levels are related to the presence of periodontitis, with the exception of IL-27, which has a different role in the literature. The cytokines role in the periodontal milieu can change due to cellular plasticity and the ability of immune cells to differentiate and dedifferentiate toward different effector phenotypes [38]. Our results correlate with the evidence, where pro-inflammatory mediators can be detected to a higher or lesser extent depending on the state of disease activity [39,40].

CCR5, it is a receptor found in monocytes, eosinophils, basophils, leukocytes and activated T cells [28,41]. The most frequent genotypes of CCR5 G59029A polymorphism detected in patients with periodontitis were G/A (47.4%) and A/A (47.4%), with an OR=1.147, which was contrary to our results where it was considered a protective factor with an OR=0.029 [27]. The AA genotype of the CCR5 G59029A polymorphism is capable of increasing the expression of CCR5, as well as inducing alterations in the binding capacity to its ligand (CCR5/CCL5) [42]. Furthermore, the risk allele A of this polymorphism is associated with periodontitis, since the CCR5 receptor is related to the differentiation of osteoclasts that act directly on the bone tissue that supports the tooth [43]. However, in the population of the present study the prevalence of allele A was only 20%. The CCR5 G59029A polymorphism is associated with a protective effect against periodontitis. This is because has been found to be present only in individuals with healthy gums but completely absent in those with periodontitis. Our findings contradict those of a previous study on a similar population, where the polymorphism was identified as a risk factor for periodontitis [27]. This discrepancy suggests that more research is necessary to understand the true impact of this polymorphism on the development and progression of the periodontal disease.

There are studies that claim that the binding of the ligand to CCR5 may provide an important signal for the induction of IL-12 synthesis by the CD8 α ⁺ subset of dendritic cells [44]. Our study indicates a significant increase in the levels of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α in individuals with periodontitis compared to healthy individuals, suggesting that this increase could be associated with the presence of the G59029A polymorphism in CCR5 gene.

The CCL5 concentrations in the GCF are generally higher in patients with periodontitis than in healthy subjects [45]. CCL5 has affinity for various receptors including CCR1, CCR3, CCR4 and CCR5. This interaction triggers cell migration, contributing to inflammatory and immune responses. The specific cells that CCL5 attracts include monocytes, mast cells, dendritic cells, NK cells, eosinophils, basophils, CD4⁺ T cells, CD8⁺ T cells and B cells [41,46,47]. CCL5 secretion by gingival fibroblasts is often triggered by inflammatory responses, particularly those mediated by pro-inflammatory cytokines like as TNF- α and IL-1 β [45].

However, in our study, we found that a specific CCL5 polymorphism, rather than being a risk factor, appeared to be a protective factor. This conclusion is based on the observation that the OR for the polymorphism was close to zero, while allele frequencies were close to one. This suggests that the genotype frequencies of the CCL5 polymorphism might be protective against periodontitis, while the allele frequencies are not significantly associated.

TNF- α is a pro-inflammatory cytokine secreted by monocytes and macrophages, plays a significant role in inflammation by inducing the production of adhesion molecules, stimulating Matrix Metalloproteinases (MMPs) and activating pre-osteoclasts [48-51]. These actions contribute to various inflammatory processes and bone remodeling. The study by Azab and Elfasakhany found that the TNF- α -308 G/A polymorphism is not correlated with susceptibility to periodontitis in a Saudi population [22]. This means that the presence of either the G or A allele at this specific location in the TNF- α gene does not appear to influence whether an individual is more or less likely to develop periodontitis. It is important to acknowledge that cytokine genes have various polymorphisms and further research is needed to determine if specific polymorphisms are associated with periodontitis risk [52-54]. Conversely, in our study we found a significant association between a specific TNF genotype and allele frequency with increased susceptibility to periodontitis. That individuals with a particular TNF genotype or the G allele of that gene have a 2.2-fold increased risk of developing periodontitis, implying a genetic predisposition within the studied population.

Periodontitis is a chronic non-communicable disease affecting the supporting structures of the teeth and has been linked to an increased risk of other chronic non-communicable diseases [30]. Periodontitis is indeed linked to a wide range of other chronic non-communicable diseases. This connection is thought to be partly due to the systemic spread of pro-inflammatory mediators and pathogens from the oral cavity into the bloodstream, as observed in cases of severe periodontitis [3,7,55-62]. The CCL5 -403 G/A, CCR5 G59029A and TNF-308 G/A polymorphisms are associated with other diseases linked to the host's inflammatory response, for example, in patients with Type 2 Diabetes Mellitus (T2DM) [47]. Also, in Ethiopian subjects with T2DM, a higher frequency of the TNF- α GG genotype at the -308 G/A position was observed, potentially indicating a role for this polymorphism in impairing insulin-sensitive glucosa uptake [63]. This suggests that individuals with the GG genotype might develop diabetes more rapidly than those with other genotypes [63]. The CCR5 G59029A gene mutation is associated with an increased risk of chronic kidney failure in diabetic patients, potentially due to the mutation's impact on CCR5 expression and subsequent macrophage infiltration into the kidneys. This mutation may lead to higher CCR5 levels and increased activation by CCL5, prompting macrophages to migrate into the glomerulus and renal interstitium, contributing to kidney damage [64,65]. Finally, the CCL5 -403G/A gene polymorphism is linked to increased susceptibility to childhood asthma in Caucasian individuals due to its influence on CCL5 expression, which contributes to airway inflammation by attracting eosinophils. Specifically, the -403 G/A allele is associated with higher CCL5 levels, leading to higher eosinophil recruitment and, consequently, amplified allergic airway inflammation [66].

Conclusion

Identifying the genetic marker CCR5 G59029A polymorphism can help identify patients at higher risk of periodontitis allowing for personalized care plans that include more frequent preventive checkups and treatments like prophylaxis, polishing and root planing to improve therapeutic success. This genetic information, along with other known risk factors, helps explain why some individuals are more susceptible to severe form of periodontitis even with good oral hygiene.

Conflict of Interest

The authors declare no conflict of interest.

Financial Disclosure

None.

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