



ASSOCIATION BETWEEN IL-10 GENE POLYMORPHISMS, TOBACCO SMOKING, AND THE RATE OF PERIODONTITIS PROGRESSION

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ABSTRACT:

Purpose: Periodontitis is a multifactorial disease with a significant impact on overall health and quality of life. While pathogenic anaerobic bacteria play a central etiologic role, other factors such as aging, tobacco smoking, stress, medications, and genetics also influence disease development and progression. According to the 2017 Classification of Periodontal and Peri-Implant Diseases and Conditions, grading helps predict the rate of progression, considering both primary criteria (clinical or radiographic evidence) and modifying factors (e.g., smoking, diabetes). Genetic predisposition further modifies the host response in periodontitis. This study examined the influence of tobacco smoking and Interleukin-10 (IL-10) single nucleotide polymorphisms (SNPs) on the rate of disease progression.

Materials and Methods: Seventy-two patients with generalized Stage III–IV periodontitis were examined clinically and radiographically. Buccal mucosa samples were collected for DNA extraction and IL-10 SNP analysis. Data were evaluated statistically.

Results: Distinct genotype distributions of IL-10 polymorphisms were identified. No significant association was found between these polymorphisms and the rate of progression determined by the BL/Age ratio. However, a statistically significant relationship was observed between tobacco smoking and BL/Age.

Conclusions: Tobacco smoking was confirmed as a major factor modifying the grade of periodontitis. Additionally, the absence of the A-allele was associated with a slower progression rate, suggesting that genotypes carrying the A-allele predispose to a more rapid progression of the disease.

Keywords: Interleukin – 10, periodontitis, risk factors, risk of progression, smoking,

INTRODUCTION

Periodontitis is a multifactorial disease that affects a substantial proportion of individuals across all populations. According to Eke PI, et al., at least half of the adult population in the United States is expected to develop periodontitis in recent decades [1]. When left untreated, periodontitis imposes significant psycho-emotional and financial burdens on both individuals and society, rendering it a condition of notable public health concern and economic impact [2,3]. While the pathogenic microbiota initiating periodontal disease is well characterised, the clinical manifestation of the disease is also influenced by genetic and epigenetic factors. The prevalence of periodontitis varies by geographic region, suggesting that certain racial or ethnic groups may possess a heightened genetic susceptibility, particularly to early-onset forms of the disease. At the individual level, the development and regulation of periodontitis involve a complex interaction between intrinsic factors, such as genetic background, and acquired influences, including environmental exposures and lifestyle choices. The disease is primarily driven by an inappropriate immune response to dysbiosis within the oral microbiome, leading to progressive destruction of periodontal tissues and the supporting alveolar bone. Elucidating the mechanisms by which gingivitis—a reversible inflammatory condition confined to the gingival tissues—progresses to periodontitis necessitates examination of both intrinsic determinants, such as genetic susceptibility and interindividual variability in immune competence, and extrinsic modulators, including environmental exposures and behavioral factors [4]. This comprehensive approach facilitates a deeper understanding of the molecular and cellular pathways governing disease progression and enables the development of precision-based therapeutic strategies. The initiation and progression of periodontitis are governed by a polygenic architecture, wherein

multiple genetic loci collectively modulate host immune responses to microbial challenge. This genetic heterogeneity contributes to population-level differences in the magnitude and regulation of inflammatory responses. Notably, these immunologic profiles may converge with those observed in other chronic inflammatory conditions—such as coronary artery disease, diabetes mellitus, metabolic syndrome, and obesity—suggesting the involvement of shared pathogenic pathways. Such associations underscore the broader systemic implications of immune dysregulation in the context of periodontitis [4].

Aim

The aim of the present manuscript is to investigate the impact of specific factors—namely interleukin-10 (IL-10) gene polymorphisms and tobacco smoking—on the progression rate of periodontitis.

Tasks

The study involves the selection of individuals diagnosed with periodontitis for the analysis of interleukin-10 (IL-10) single nucleotide polymorphisms (SNPs), with subsequent interpretation of the results in relation to the disease's rate of progression.

MATERIALS AND METHODS:

Participants in this study were diagnosed with periodontitis classified as Stage III and Stage IV and graded from B to C, in accordance with the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (5). Staging was determined by evaluating disease severity and complexity of case management using the following criteria:

- Stage III: Included patients with CAL ≥ 5 mm, RBL extending to the middle third of the root or beyond, and loss of up to four teeth due to periodontitis. Complexity features included probing depths ≥ 6 mm, vertical bone loss ≥ 3 mm, and Class II or III furcation involvement.
- Stage IV: Defined by severe periodontal destruction with loss of five or more teeth due to periodontitis, masticatory dysfunction, secondary occlusal trauma, bite collapse, or need for complex rehabilitation.

Grading was applied to reflect disease progression rate and risk factors.

- Grade B: BI/Age ratio 0,25 - 1; moderate progression rate, consistent with expected levels of destruction given biofilm deposits, and/or presence of risk factors such as smoking fewer than 10 cigarettes/day.
- Grade C: Rapid progression, with clinical attachment loss exceeding expectations for biofilm levels, radiographic evidence of rapid bone loss – BI/Age >1 , and/or presence of risk factors such as smoking ≥ 10 cigarettes/day.

None of the participants had received periodontal treatment within the preceding 6 months.

Exclusion criteria comprised the presence of systemic diseases known to influence the development or

progression of periodontitis (e.g., diabetes mellitus, hepatitis, immunodeficiency-related conditions), current immunosuppressive or anti-inflammatory therapy, as well as pregnancy or lactation. All subjects provided written informed consent, and the study protocol was approved by the KENIMUS Ethics Committee of the Medical University of Sofia, Bulgaria.

The clinical research methods include registration of hygiene status by FMPS (Full mouth plaque score) and gingival inflammation – FMBS (Full mouth bleeding score); Bleeding on probing (BOP) index; Probing Pocket Depth (PPD)*, Clinical Attachment Loss in mm (CAL)*;

*Measurements in mm were taken at 6 points for each tooth (mediobuccal, buccal, distobuccal, medio-lingual, lingual, distolingual), with a CP15 manual graduated periodontal probe (Hu Friedy). The data are registered in a periodontal chart.

The X-ray examination methods include orthopantomography and intraoral retroalveolar radiography in the posterior site with the most advanced bone loss for precise calculation of BLAge ratio.

Laboratory research methods:

Determination of the gene polymorphisms for Interleukin-10 (IL-10) at positions (-1087) and (-592) were performed by PCR amplification followed by restriction enzyme digestion.

Buccal mucosa samples were collected from all participants. DNA extraction was performed using a Nucleospin MACHEREY-NAGEL kit.

PCR Amplification

The amplification of the fragment containing the position -592 was performed in a 25 μ L reaction mixture with sense primer 52 gtttctctaggtcacagtga 32 and antisense primer 52 gtcattggtgagcactactctga 32. The amplification conditions were: denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 sec; annealing at 60°C for 30 sec; and extension at 72°C for 1 min. The final extension was at 72°C for 7 min.

The amplification of the fragment containing the position -1,082 was performed in a 25 μ L reaction mixture with sense primer 52 ctcgctgcaaccaactggc 32, antisense primer 52 tcttacgcaaccaactggc 32. The amplification conditions were: denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 sec; annealing at 62°C for 30 sec; and extension at 72°C for 30 sec. The final extension was at 72°C for 7 min.

Restriction Fragment Length Polymorphism (RFLP)

The two alleles of the polymorphic site at the position -592 was identified by incubating 15 μ L aliquot of the PCR product with restriction enzyme, followed by electrophoresis on agarose gels. The reaction was carried out in a thermostat for 16 h at 37°C. Restriction enzyme

RsaI cut the fragment at the position -592 when allele A was present, giving rise to 176 and 236 bp fragments.

The two alleles of the polymorphic site at position 1082 were determined using Mnl I restrictase. The enzyme was cut when allele G was present and generated 106 and 33 bp fragments. The conditions were the same as in previous assay.

DNA Electrophoresis and Genotype Determination

The digested product was electrophoretically separated on 3 % agarose gel (45 min at 95 V). The results of this restriction fragment length polymorphism assay were confirmed by Sanger sequencing of the promoter region of the IL-10 gene in the samples with different genotypes.

Statistical methods

Data was implemented by the statistical package PCA - IBM SPSS Statistics Version 21. $p < 0.05$ was chosen as the level of significance at which the null hypothesis is rejected. The following methods were applied:

1. Descriptive analysis – the frequency distribution of the considered signs, broken down by research groups, is presented in tabular form.
2. Pearson correlation analysis - to study the relationship between individual indicators.
3. Variation analysis – calculating estimates of central tendency and dispersion.
4. Principal component analysis (PCA) - to group indicators and patients
5. Student's t-test - for testing hypotheses about a difference between two independent samples.
6. Non-parametric Shapiro-Wilk test – to check the type of distribution.
7. Non-parametric Mann-Whitney test - for testing hypotheses of difference between two independent samples.

RESULTS:

A high bone loss-to-age (Bl/Age) ratio (>1) was observed among participants, to define the rapid rate of periodontitis progression/grading of periodontitis. Tobacco smoking, a well-established modifying factor in periodontal disease, was also associated with an accelerated progression rate. This aligns with existing evidence supporting its role in influencing the severity and grading of periodontitis. In the present study, we hypothesised that specific single nucleotide polymorphisms (SNPs) in the interleukin-10 (IL-10) gene may contribute to the rapid progression of periodontitis. To explore this hypothesis, we compared the potential impact of these genetic variants to that of tobacco smoking on disease progression.

All participants fulfilled the inclusion criteria, and written informed consent was obtained prior to study enrollment. The demographic characteristics, smoking status, and genotype distribution of the two investigated IL-10 SNPs are summarised in Table 1.

Regarding the genotype distribution of the IL-10

Table 1. Descriptive characteristics and genotype distribution.

Category	Count	Share	
Base (number of patients)	$N=72$		
Gender	Male	37	51.4%
	Female	35	48.6%
Age Group	up to 34	7	9.7%
	35-54	43	59.7%
	55 +	22	30.6%
Tobacco smoking	Smoker	40	55.6%
	Non-Smoker	32	44.4%
IL-10 - 592	AA	4	5.6%
	CA	29	40.3%
	CC	39	54.2%
IL-10 - 1082*	AA	27	42.2%
	AG	27	42.2%
	GG	10	15.6%
A-allele*	At least one A- allele	55	85.9%
	Absence of A-allele	9	14.1%
Bl/Age	>1	29	45.3%
	≤ 1	43	67.2%

*Data are available only for 64 patients

-592 SNP, an uneven distribution among the studied population was observed. Notably, the AA genotype was identified in only four participants, all of whom exhibited the highest levels of alveolar bone loss combined with younger age, suggestive of a rapid progression phenotype. In contrast, no such disparity was detected in the genotype distribution of the IL-10 -1082 SNP, where the genotypes appeared more evenly distributed across the cohort.

In addition, we examined the relationship between tobacco smoking and the bone loss-to-age (Bl/Age) ratio, independent of IL-10 genotype, as presented in Table 2. The analysis revealed a statistically significant association between smoking status and the Bl/Age ratio ($\alpha = 0.05$). Among smokers, 70% of patients exhibited a Bl/Age ratio ≤ 1 , a proportion considerably higher than that observed among non-smokers (47%). These findings further support the role of tobacco smoking as a critical modifying factor in the progression rate of periodontitis.

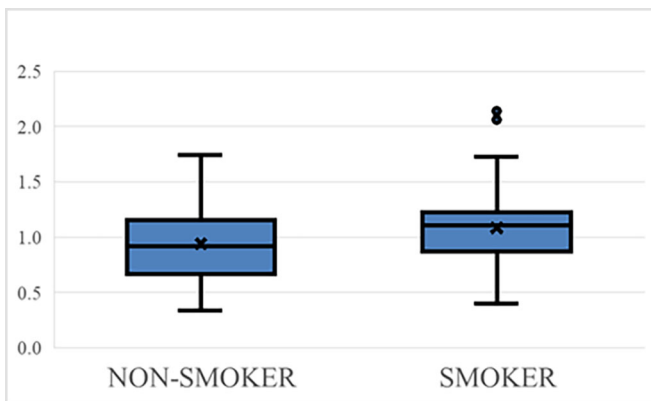
Table 2. Smoking and BI/Age.

Smoking Habits		BI/Age		Total
		>1	≤ 1	
Smoker	Count	12	28	40
	%	30.00%	70.00%	100.00%
Non-Smoker	Count	17	15	32
	%	53.10%	46.90%	100.00%

Significance=0.047 (Chi-square Test)

The graphical representation of BL/Age ratio regarding tobacco smoking more than 10 cigarettes daily is represented in Figure 1.

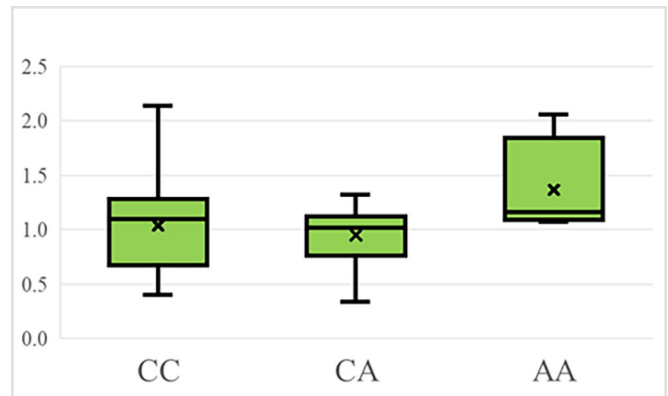
Fig. 1. Distribution of BI/Age regarding smoking.



The boxplot analysis revealed two markedly elevated outliers for the bone loss-to-age (BI/Age) ratio within the smoker subgroup, indicating cases of particularly rapid disease progression. The arithmetic mean BI/Age ratio among smokers was 1.08, which was significantly higher than the mean observed in the non-smoker group (0.94), with statistical significance established at $\alpha = 0.05$. These findings reinforce the association between tobacco use and an accelerated rate of periodontal tissue destruction.

To explore the potential association between IL-10 gene polymorphisms and the rapid rate of periodontitis progression, we analysed the relationship between specific genotypes and the bone loss-to-age (BI/Age) ratio. For the IL-10 SNP at position -592, the distribution of BI/Age values across genotypes was visualised using a boxplot, as presented in Figure 2.

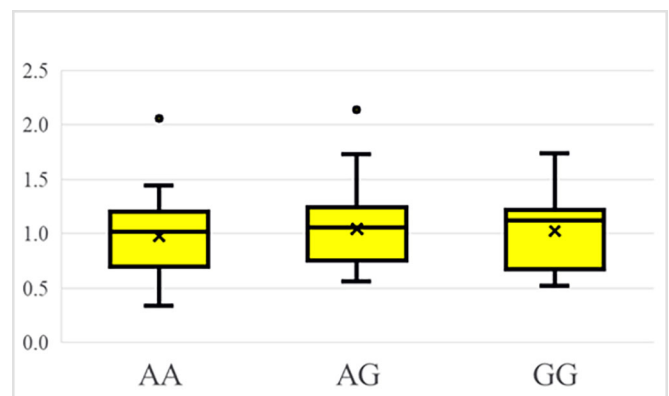
Fig. 2. Representation of the BI/Age regarding the SNP IL-10 -592 genotypes.



The highest BI/Age values were observed in individuals carrying the AA genotype, although this group comprised only four patients. A one-way ANOVA test was performed to evaluate the statistical significance of differences in BI/Age ratios among the three genotype groups (AA, AC, and CC). However, the analysis did not reveal any statistically significant differences between the groups.

When comparing the BI/Age ratio in relation to the IL-10 SNP at position -1082, certain trends were observed, although they did not reach statistical significance. These tendencies are illustrated in Figure 3, suggesting a possible, yet inconclusive, association between specific genotypes and the rate of periodontal disease progression.

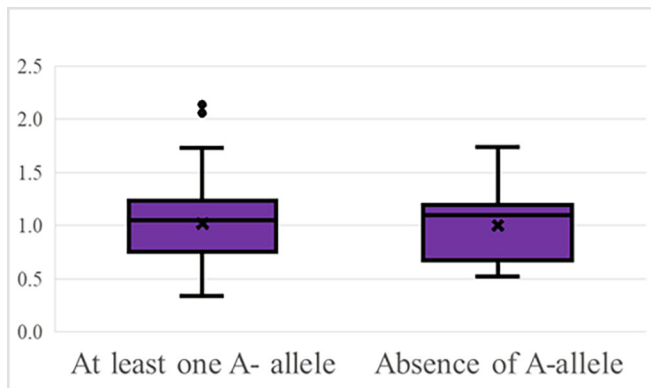
Fig. 3. Representation of the BI/Age regarding the SNP of IL10-1082 genotypes.



The genotype distribution for the IL-10 -1082 SNP appeared relatively balanced across the study population. However, the highest BI/Age values were predominantly observed in individuals carrying at least one A allele, which is consistent with our initial hypothesis regarding its potential role in accelerating disease progression. Despite this observed pattern, statistical analysis revealed

no significant differences in BI/Age ratios among the three genotype groups. To further evaluate our hypothesis on the potential influence of IL-10 genotypes and alleles on the rapid progression of periodontitis, additional comparative analyses were conducted. The results of these analyses are summarised in Figure 4.

Fig. 4. Representation of BI/Age regarding the A-allele.



DISCUSSION:

Periodontal disease—particularly when poorly controlled—remains a leading cause of tooth loss and edentulism worldwide. The rapid progression of periodontitis is influenced by a complex interplay of factors, including pathogenic microorganisms, as well as genetic and epigenetic determinants. According to the 2017 Classification of Periodontal and Peri-Implant Diseases and Conditions, the rate of progression—reflected in the grading system—is significantly impacted by modifying factors, among which tobacco smoking plays a critical role in accelerating disease progression [5]. The bone loss-to-age (BI/Age) ratio is a key parameter with considerable diagnostic and prognostic value. It contributes not only to the accurate staging and grading of periodontitis but also informs decisions regarding the frequency of periodontal maintenance and recall intervals [5, 6].

Cigarette smoking is a major environmental risk factor that markedly contributes to the initiation, progression, and increased severity of periodontal disease. Epidemiological and clinical studies consistently demonstrate that smokers exhibit significantly greater clinical attachment loss, deeper periodontal pockets, and higher rates of tooth loss compared to non-smokers. These adverse outcomes are primarily linked to smoking-induced alterations in host immune function, including impaired neutrophil activity, diminished antibody production, and compromised fibroblast function—factors that collectively impair tissue repair and host defense mechanisms against microbial insult. Moreover, smoking negatively affects the

clinical outcomes of both non-surgical and surgical periodontal interventions. Smokers frequently show a reduced therapeutic response to scaling and root planing, as well as lower success rates in regenerative procedures and dental implant therapy. This impaired healing potential is partially attributed to the local effects of nicotine, which include vasoconstriction, reduced gingival perfusion, and inhibition of collagen synthesis and angiogenesis—processes that are essential for periodontal tissue regeneration. Notably, smoking cessation has been shown to improve periodontal health. Former smokers generally demonstrate better treatment responses and slower disease progression compared to current smokers; however, a full restoration of risk levels equivalent to never-smokers may require extended periods of abstinence [7].

Tobacco smoking is associated with a wide range of adverse health outcomes, including an increased risk and severity of periodontitis. It exerts detrimental effects on both the initiation and progression of periodontal disease. Meta-analyses have consistently demonstrated that individuals who smoke tobacco cigarettes exhibit a higher incidence of periodontitis and a more rapid rate of disease progression, particularly at a younger age, compared to non-smokers [8]. The findings of the present study align with this evidence, as a significantly elevated BI/Age ratio was observed among smokers, supporting the association between tobacco use and accelerated periodontal breakdown.

Clinical studies have shown that smokers exhibit a two- to eight-fold increased risk of periodontal attachment loss and alveolar bone resorption. Furthermore, they demonstrate significantly poorer responses to both non-surgical and surgical periodontal treatments, with clinical outcomes markedly inferior to those of non-smokers. These observations are consistent with our findings and further reinforce the role of smoking as a strong predictor of higher periodontitis grading and poorer prognosis. Collectively, this evidence supports the classification of tobacco smoking as a modifiable risk factor of major relevance in the prevention and management of periodontal disease [9]. In addition, smoking is implicated not only in the progression but also in the onset of periodontitis, as evidenced by the advanced bone loss observed in relation to patients' age—a relationship further highlighted by the elevated BI/Age ratio in smokers [10]. The present study reinforces previous findings by demonstrating a significantly higher BI/Age ratio among smokers, consistent with earlier reports indicating that tobacco use accelerates alveolar bone loss and attachment destruction.

Numerous studies have investigated the association

between genetic polymorphisms of various immune-regulatory molecules and individual susceptibility to periodontitis. Among the most extensively studied are cytokine gene polymorphisms, particularly those involving interleukins. Interleukin-10 (IL-10), a key anti-inflammatory cytokine, has been the subject of considerable research due to its potential immunomodulatory role in periodontal disease. However, the relationship between IL-10 gene polymorphisms and periodontitis remains inconclusive [11]. Some studies have reported no significant association between IL-10 single nucleotide polymorphisms (SNPs) and susceptibility to periodontitis, which is consistent with the findings of the present investigation [12]. Conversely, other research has suggested that IL-10 polymorphisms, particularly at the -592 position, may be associated with increased susceptibility to periodontitis in an ethnicity-dependent manner [13]. In our study, we observed that the AA genotype at the -592 SNP position was associated with the highest BI/Age ratios, suggesting a possible link to more severe or rapidly progressing forms of periodontitis. However, due to the limited number of individuals with this genotype, the association did not reach statistical significance. These results highlight the complexity of gene–environment interactions in periodontal disease and underscore the need for larger, ethnically stratified studies to clarify the role of IL-10 polymorphisms in disease progression. Moreover, the interplay between genetic background and environmental factors such as tobacco smoking may further influence the clinical expression of periodontitis, as reflected in the trends observed in our data.

Several studies have proposed the potential use of IL-10 as a biomarker for assessing the severity and progression of periodontal disease. As a key anti-inflammatory cytokine, IL-10 has been found at elevated levels in patients with advanced periodontitis (Stage III/IV), which is likely indicative of a compensatory host response aimed at mitigating ongoing inflammation. However, IL-10 levels have not shown a consistent correlation with clinical parameters of disease severity or progression grade, suggesting that its role may be more regulatory than diagnostic. These findings are in agreement with the results of our study, where no significant association was observed between IL-10 genotypes and disease progression markers such as the BI/Age ratio [14].

Nonetheless, other studies have suggested that polymorphisms in the IL-10 gene - particularly at the -592 position—may be associated with increased susceptibility to periodontitis, supporting its potential utility as a genetic biomarker for disease risk. This interpretation

aligns with our working hypothesis and the overarching aim of the present study [15]. A notable example is the 3-year prospective study conducted by Chatzopoulos GS, et al. (2022), which evaluated whether specific genetic variants, including IL-6 -572 G/C and IL-10 -592 C/A, influenced the long-term progression of chronic periodontitis following non-surgical therapy. The study included 37 patients monitored over three years after receiving standard periodontal treatment. While clinical improvements were observed in all participants, the investigated polymorphisms did not significantly predict disease recurrence or progression. Interestingly, the study did report a higher risk of disease progression among male patients, particularly when bleeding on probing was considered a diagnostic criterion [16]. These findings highlight the multifactorial nature of periodontitis progression and suggest that while IL-10 polymorphisms may contribute to disease susceptibility, they may not independently determine long-term treatment outcomes. In line with these observations, our study did not identify a statistically significant association between IL-10 -592 or -1082 polymorphisms and the BI/Age ratio, despite some suggestive trends—particularly among individuals carrying the AA genotype at -592. These findings support the notion that while IL-10 genetic variants may modulate host immune responses, their role in predicting the rate of periodontitis progression remains limited and may be influenced by additional host and environmental factors. Our results further emphasise the need for integrative models that consider gene–environment interactions, such as tobacco smoking, in assessing disease susceptibility and progression risk. Taken together, the evidence suggests that IL-10 polymorphisms may serve as contributory—but not definitive—markers in the multifactorial landscape of periodontal disease.

A study by Stolf CS, et al. (2022) investigated the IL-10 promoter polymorphism rs6667202 and its influence on IL-10 concentrations in gingival crevicular fluid. Among healthy individuals, the AA genotype was associated with significantly lower IL-10 levels compared to AC and CC genotypes, suggesting a functional role of this polymorphism in modulating anti-inflammatory responses under baseline conditions. However, in patients with Grade C periodontitis, this genotype-dependent effect was not observed, indicating that the heightened inflammatory milieu may override the polymorphism's regulatory influence. These findings imply that while rs6667202 may have functional relevance in health, it does not appear to modulate IL-10 expression or disease progression in the context of severe periodontal inflammation [17].

Several additional studies have linked IL-10 gene polymorphisms to disease severity and progression, primarily through their effects on immune regulation and clinical outcomes. Meta-analysis on IL-10 polymorphisms refers to the association of the IL-10 -592 A allele with BOP $\geq 30\%$ and higher risk of further periodontal breakdown. Supporting this, Pashova-Tasseva ZP, et al. (2024) demonstrated a significant association between the IL-10 -592 A allele and severe periodontitis in a Bulgarian population, further implicating this genotype in more aggressive forms of the disease. Additionally, Li X, et al. (2018) found that individuals with the low-producing IL-10 ATA haplotype (-1082A/-819T/-592A) exhibited increased subgingival colonisation by periodontopathogens such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. This microbial dysbiosis may enhance the inflammatory burden and promote rapid tissue destruction, especially in genetically susceptible hosts [18-20].

Our findings are in alignment with these reports, as the highest BI/Age values were observed in patients carrying the AA genotype at the -592 position, despite the lack of statistical significance due to the small subgroup size. This trend suggests a potential link between low-producing IL-10 genotypes and more rapid periodontal destruction. However, consistent with the study by Stolf et al., our data also indicate that in the context of severe inflammation, genetic influence may be modulated or masked by dominant environmental factors such as tobacco smoking. These results underscore the importance of evaluating gene-environment interactions when interpreting the role of IL-10 polymorphisms in the progression of periodontitis.

CONCLUSION/S/:

This study contributes to the growing body of evi-

dence on the multifactorial nature of periodontitis progression by exploring the interplay between interleukin-10 (IL-10) gene polymorphisms and tobacco smoking. While no statistically significant associations were found between IL-10 -592 and -1082 polymorphisms and the BI/Age ratio, notable trends were observed—particularly among carriers of the AA genotype at the -592 position—suggesting a potential influence on disease severity. In contrast, tobacco smoking emerged as a significant modifying factor, with smokers exhibiting a markedly higher BI/Age ratio and thus a more rapid rate of periodontal destruction.

These findings emphasise the importance of considering both genetic and environmental risk factors when assessing periodontitis progression. Although IL-10 polymorphisms alone may not serve as definitive biomarkers for grading, their potential contributory role—especially when interacting with environmental factors like smoking—warrants further investigation in larger, ethnically diverse cohorts. Integrating genetic screening with behavioral risk assessment may ultimately enhance personalised prevention and treatment strategies in periodontal care.

Abbreviations:

IL-10 - Interleukin-10
 SNPs - Single nucleotide polymorphisms
 CAL - Clinical Attachment Loss
 FMPS - Full mouth plaque score
 FMBS - Full mouth bleeding score
 BOP - Bleeding on probing
 PPD - Probing Pocket Depth

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