REVIEW

10.2478/AMB-2026-0028

MOLECULAR MARKERS OF PERIODONTITIS AND POSSIBLE CLINICAL IMPLICATIONS

D. Nikolova[1,2]

[1]Department of Medical Genetics, Faculty of Medicine, Medical University – Sofia, Bulgaria
[2]Faculty of Public Health, Medical University – Sofia, Bulgaria

Abstract. *Periodontitis is an inflammatory condition of the gums. Without treatment, it would inevitably result in tooth loss and contribute to systemic health illnesses, such as diabetes, heart disease, stroke, and respiratory illnesses. Environmental and lifestyle factors greatly contribute to the onset of the disease. However, environmental factors and chronic diseases are not the only factors contributing to periodontitis. The importance of genetics in the etiology of this disorder is widely accepted, as each individual is at different risk of developing periodontal disease. As it is a mainly inflammatory condition, most of the genes involved are connected with the synthesis of inflammatory cytokines and are generally associated with the immune response of the host. It is important to reveal the genetic risk factors, as this knowledge can point out the individuals at risk, and will help the dentists to undertake preventive and treatment approaches based on the individual's specific genetic profile. In this review, we aim to summarize recent studies available so as to unveil the immune-associated molecular markers in the development of periodontal disease. In addition, we will mention some discussed trends for the future therapeutic approaches to the treatment of periodontitis.*

Key words: *periodontitis, genetic markers, susceptibility, therapy*

Corresponding author: *Dragomira Nikolova, Department of Medical Genetics, Faculty of Medicine, Medical University – Sofia, Bulgaria, email: dnikolova@medfac.mu-sofia.bg*

ORCID: *0000-0002-8929-8522*

Received: *12 March 2025;* ***Revised/Accepted:*** *12 May 2025*

HERITABILITY OF PERIODONTAL DISEASE

Periodontitis is an inflammatory condition of the gums. Without treatment, it inevitably results in tooth loss and contributes to systemic health illnesses, such as heart disease, respiratory illnesses, diabetes, and stroke. The importance of genetics in the etiology of this disorder is widely accepted, as each individual is at different risk of developing periodontal disease [1]. Heritability simply measures the share of genetic factors to the total variance of a given phenotype in the population [2].

A meta-analysis from 2019 summarized the data of 28 articles available online in order to calculate most precisely the heritability factor (H^2) of periodontitis [3]. The included data summarized the information of more than 50,000 subjects with the disease. The

analyzed articles presented data from twin studies, as well as from family studies reporting the level of heritability of periodontal outcomes, Genome-Wide Association Studies (GWAS) (case-control studies) or animal studies. Those analyses show that there is a substantial genetic predisposition to periodontitis which, as in every multifactorial disease, is due to several major genes and multiple genes of minor effect. Thus the H_2 factor of periodontitis was estimated at 0.38 in twin studies, 0.15 in family studies, and 0.29 when both studies were combined. The result was not influenced by race, population or by the disease stage [3]. Interestingly, smoking as a single factor increased the heritability parameter in the GWAS studies [4].

In recent years it has become important to clarify the individual's disease susceptibility in personalized treatments. It is also important to underline that genetics influences not only the susceptibility to periodontal diseases (gingivitis and periodontitis), but also the individual response to treatment procedures [5]. This will help to precise the therapeutic strategy as an increase of antibiotic and surgical regimens to those patients who generally show higher predisposition.

ROLE OF GENETIC FACTORS IN PERIODONTAL DISEASE

The carried genetic variants are not only connected with a higher/lower predisposition to periodontitis, but also determine other phenotypes, such as bad jaw shape, crooked teeth, overcrowded teeth, poor and easily damaged enamel, etc. [6]. Those conditions generally increase the risk of the disease by creating a favorable environment for different bacteria to grow (e.g., the periodontal pathogen Porphyromonas gingivalis). Sometimes conditions like hypodontia and oligodontia, which could be features of rare genetic conditions, also provoke the persistence of the disease.

Several genetic variants have been studied in relation to severe or chronic periodontitis. Usually most of them are connected with dysregulation of the immune response. The first report of an association of a specific gene polymorphism with chronic periodontitis was for interleukin-1 [7]. More efforts are focused on the identification of genetic factors contributing to aggressive periodontitis [8] and there was evidence that most of them are connected with deficiency of some factors of the innate immune response [9].

- Pro-inflammatory cytokines

IL-6 is produced by activated T cells and its role is connected with the process of bone destruction in periodontitis. A significant association was found between a variant in IL-6 gene (1363 G/T) and another one in IL-6R (+48,892 A/C) in Chinese patients with periodontitis [10]. At the same time, a meta-analysis comprising 53 different studies did not report any significant association of IL-6 polymorphisms with chronic periodontitis [11].

IL-10 is expressed by helper T cells. The results about this gene are contradictory. Berglundh et al. (2003, as cited in Kaarthikeyan and Meenakshi, 2019) found positive associations between IL-10 SNP and periodontitis in Swedish and Brazilian population [12], while Scarel-Caminaga et al. (2004, as cited in Kaarthikeyan and Meenakshi, 2019) did not find any significant association in the Caucasian population [12].

TNF-α is a proinflammatory cytokine produced by macrophages. The association between the TNF-α (G-308A) polymorphism and susceptibility to periodontitis (AP) has been investigated [13]. The results showed that A allele was associated with an increased risk of aggressive periodontitis in Asian population and of chronic periodontitis in both Asians and Caucasians. This significant association was neglected in Latin American population [13]. In a recent study the up-regulation of TNF-α and IL-1β created increased inflammation in the brain, thus contributing to the development of Alzheimer's disease (AD) and memory loss, proving the link between AD and periodontitis [14].

TGF-β has also a proinflammatory role and is a key factor in processes of cellular differentiation, apoptosis and angiogenesis. TGF-β2 shows a significantly higher expression in dental follicle stem cells (DFSC) under inflammatory conditions. This expression is inversely correlated with bone formation (osteogenesis). Authors showed that high levels of TGF-β2 inhibit bone formation [15].

IFN-γ is produced by NK cells. It plays an important role in the activation of inflammatory processes, which are the basis of periodontal disease. Polymorphism IFNγ +874A/T rs62559044 is connected with chronic periodontitis. Sheibak N. et al. (2022) studied the immunoexpression of IFNγ in human gingiva from CP patients with IFNγ +874A/T gene polymorphisms compared to a healthy group [16]. There was a noticeable increase in the IFNγ expression of gingival epithelium and fibroblasts in patients compared to the control group of individuals.

- Vitamin D

Primarily obtained from exposure to sunlight, vitamin D is connected with bone mineralization, including that of the jaw bone, and its deficiency logically leads to bone resorption. Additional intake of vitamin D de-

creases the risk of gingivitis and periodontitis and has preventive effect against teeth loss [17]. The level of vitamin D has been investigated in 2020 in a meta-analysis, which included sixteen studies. There was a positive association between lower levels of vitamin D and the presence of chronic periodontitis [18].

- Matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a famous family of enzymes, which destruct almost all types of extracellular matrix (ECM). MMP family contains 23 enzymes, collectively called matrixins. Their activity depends on the availability of Zn^{2+} and Ca^{2+} and most MMPs can degrade several substrates with different specificities. MMP-2 and MMP-9 are called gelatinases and they are specific to gelatin, while MMP-1 and MMP-3 are specific rather to collagen type IV (collagenases) [19].

In periodontitis there is a proven increased expression of MMP proteins associated with the destruction of connective tissue components, like MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 [12]. Even so, a significant association of the MMP-1, -8, -9, -12, -2 or -13 polymorphisms with periodontitis was not detected [20]. The highest amount of MMP detected in chronic periodontitis was MMP-8 [19]. Because of its high levels in oral fluids, MMP-8 could be accepted as predictor and biomarker of the disease. On the other hand, the expression of MMP-9 is increased in periodontal inflammation during orthodontic treatment, and, therefore, could be used as a monitoring marker of such a treatment. Both MMP-8 and MMP-9 could potentially indicate the rate of dental implants' failure [21]. Some polymorphic variants in both genes were found to be protective and associated with a lower risk of chronic periodontitis (MMP-9-753 C/T variant), while others increase the risk and are considered predisposing (MMP-3-1171 5A/6A; MMP-8-799 C/T) [21]. Yet, there are controversial data about the role of MMP-9 in periodontitis and further studies are needed to illustrate its role in inflammation, bone formation and destruction [22].

- Human Leukocyte Antigens (HLAs)

Since it is highly polymorphic, Human Leukocyte Antigen (HLA) system has been discussed as responsible for individuals' response to treatment of different diseases, including periodontitis. Recognition of antigen peptides and their presentation to T cells is important for an immune response toward periodontal pathogens [23]. Research on HLA polymorphic variants associated with periodontitis is relatively old [24]. It was observed that patients with aggressive periodontitis had at least one of the alleles more often than healthy individuals: DRB1*0401, DRB1*0404, DRB1*0405 or DRB1*0408 [25]. In a meta-analysis, HLA-A9 and -B15 seemed to represent susceptibility factors for aggressive periodontitis, whereas HLA-A2 and -B5 were potential protective factors against periodontitis among Caucasians [26].

- Cathepsin C

Cathepsin C (CTSC) is a lysosomal cysteine protease, which activates a significant amount of immune cells [27]. In 2020, a study confirmed for the first time a significant increase in the expression of cathepsin C in periapical periodontitis. The expression started to increase one week after surgery and reached a peak 3 weeks after surgery. The study was conducted in knock-down mice. Correlation analysis also revealed a connection between the expression levels of cathepsin C and receptor activator of nuclear factor-κB ligand (RANKL). The authors' conclusion was that cathepsin C promoted the apical inflammation and bone destruction in mice [28]. Except in severe periodontitis, CTSC is implicated in syndromes associated with neurophil serine proteases as Papillon–Lefevre syndrome (PLS) and Haim–Munk syndrome (HMS). A characteristic feature of all these syndromes is the early-onset periodontitis.

There are many allelic variants in cathepsin C which have been reportedly associated with aggressive periodontitis or syndromes exhibiting periodontitis as a main symptom. The most prevalent mutations are missense variants, followed by nonsense and indels [27]. All variants have variable clinical phenotypes and severity of periodontal disease. As cathepsin C is connected with inflammation, its inhibition is a promising strategy to control periodontitis and there are currently inhibitors which are under clinical trials of different stages.

- CD14 and TLRs

The CD14 molecule is a glycoprotein receptor expressed on the surface of neutrophils, monocytes/macrophages and fibroblasts, which recognizes bacterial LPS. The LPS/LBP/CD14 complex then acts on the target cell via a toll-like receptor (TLR) [25]. Two polymorphisms of the CD14 encoding gene were studied, replacement of cytosine (C) with thymine (T) at position −159, described as −159 (C→T), and −1359 (G→T) [29]. For the − 1359 (G→T) polymorphism, the −1359*G allele was more frequently observed in patients with advanced disease than with moderate disease [30].

In a recent meta-analysis, authors confirmed a significant association between periodontitis and TLR-2 rs1898830 polymorphism [25].

- Other genes

Since 2009, it has been reported that certain genetic variations in *CDKN2B-AS1* are also consistently associated with periodontitis. The *CDKN2B-AS1* locus is a regulatory region and does not contain a protein-encoding gene. It is a long non-coding antisense RNA, also known as *ANRIL*. Importantly, it appears to be from a highly pleiotropic genetic region (chromosome 9, p21.3), as it is also associated with type 2 diabetes, ischemic stroke, and Alzheimer's disease. Since 2009, it has been reported that certain genetic variations in *CDKN2B-AS1* are also consistently associated with periodontitis [31].

Another gene with a reported association to periodontitis is *VAMP3*. It is a membrane protein connected with vesicles' transportation and a secretion of inflammatory factors by the platelets. It is connected with a development of periodontal pathogens [32].

ROLE OF SALIVA IN ORAL HEALTH

Saliva is a complex, slightly acidic secretory biological fluid, whose amount in different individuals ranges from to 0.7 mL of saliva per minute to a total of 1–1.5 liters of serous and mucinous saliva [33]. Its normal pH (range 6.7-7.6) maintains the microflora of the oral cavity and helps the re-mineralization of the enamel. However, genetic variations can influence saliva composition, thereby impacting its protective capabilities. Saliva is important for oral health, as it has several functions: 1) it dilutes and eliminates sugar, 2) buffers acids to avoid tooth decay, 3) moisturizes oral tissues, 4) helps the re-mineralization of the tooth enamel, and 5) has antimicrobial properties to fight against oral bacteria.

A lot of research is put on investigating saliva as a source of markers for diagnosis and monitoring of periodontic diseases, most of all because its collection is easy and non-invasive. There are attempts to use it also for different systemic diseases. The markers which have been proposed with a higher level of reliability are MIP-1α, IL-1ß, IL-6, MMP-8, or hemoglobin. Many additional factors could have effect of salivary quality during collection: smoking, stress, gender, blood contamination, flow rate, and even circadian rhythms. Systemic diseases are also connected with periodontitis as diabetes or cardiovascular diseases. In metabolic syndrome, dietary changes had a positive influence on inflammatory variables of periodontal disease in saliva [34].

Table 1. Immune-associated molecular markers with a role in the development of periodontitis

Molecular markers	Connection to periodontitis	References
Proinflammatory cytokines		
• IL-6	Connected with bone destruction in periodontitis	[10]
• IL-10	Contradictory findings in periodontitis	[12]
• TNFα	Imposes susceptibility to chronic and aggressive periodontitis	[13]
• TGFβ	Inversely correlated with bone formation	[15]
• IFNγ	Increases in human gingiva in the condition of inflammation, associated with chronic periodontitis	[16]
Vitamin D	Connected with bone mineralization, its deficiency linked to bone resorption	[18]
Matrix metalloproteinases	Family of enzymes that destruct almost all types of extracellular matrix (ECM)	
• MMP-1		
• MMP-2	– MMP-8 is acknowledged as predictor and biomarker of the disease	[19, 21, 22]
• MMP-3		
• MMP-8		
• MMP-9	– MMP-9 is highly elevated during inflammation in periodontal treatment	
HLA antigens		
DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408	Important for an immune response toward periodontal pathogens	[24, 25]
HLA-A9 and -B15	Susceptibility factors for aggressive periodontitis	[26]
Cathepsin C	Promotes apical inflammation and bone destruction	[27, 28]
CD14, TLR2	Recognize bacterial LPS, single-nucleotide variants in both genes are associated with periodontitis	[25, 30]
Other markers	CDKN2B-AS1	[31]

A study of 2022 discusses the usage of uric acid and arginase in saliva as discriminating agents between healthy individuals and patients with periodontitis. The level of arginase increased while the level of uric acid decreased with the development of periodontal disease in time. The authors concluded that arginase can be considered a marker of inflammation, while, on the contrary, uric acid is an anti-inflammatory marker of periodontal therapy [35]. A more recent study divides the saliva markers of periodontitis as: 1) osteogenic markers (associated with alveolar bone loss, for example osteocalcin, RANKL and OPG; collagenases (as MMP-8, -13); gelatinases (MMP-2, -9)); 2) hormones (cortisol); 3) inflammatory markers (IL-1α, IL-1β, IL-6, TNF-α, PGE2, TGF-β, and MIP-1α/CCL3); 4) oxidative stress markers (8-hydroxydeoxyguanosine (8-OHdG)), 5) systemic markers (CRP); 6) microbial markers (*Actinobacillus actinomycetemcomitans and others*) [33]. Salivary biomarkers are promising and reliable source for diagnosis of oral diseases in the future.

CLINICAL IMPLICATIONS

Early diagnosis of periodontitis

The discussed set of biomarkers may provide effective reproducibility, sensitivity and specificity which enables to set patient diagnostic criteria in periodontology. Many different technologies have been used in the identification of those markers as microarray technology, microfluidic technology, and chip technology [33]. Those technologies are applied to detect periodontal markers in unstimulated saliva or during immune response. Probably a combination of several technologies will help in identifying a set of molecular markers to assess the periodontal health caused by oral and systemic effects.

The first genetic test that was invented to analyze the susceptibility to periodontitis was the periodontal susceptibility test (PST). However, it is not exhaustive and takes into account only the levels of two inflammatory markers: IL-1α and IL-1. Therefore, it rather determines the level of inflammation in oral cavity and estimates the risk to develop periodontitis in the near future. A retrospective study of 2018 reports that 67% of periodontitis-positive patients have been diagnosed positive with the PST. On the other hand, IL-1 is not the only cytokine involved in the host's inflammatory response and the environmental factors play also an undeniable role [36]. As this test measures the scale of the inflammatory reaction of the organism, it can indicate the risk for severe periodontal infections, exaggerated immune response or a possible acceptance/rejection of tooth implants or prolonged disease activity. However, there is a space for the invention of genetic susceptibility test that will comprise more genetic markers with higher sensitivity and reproducibility.

Treatment strategies based on genetic approach

Dental care and oral health outcomes can be improved using personalized prevention and treatment strategies based on genetic information. Analyzing an individual's genetic profile helps to identify genetic factors that may influence dental health.

- TNFRSF1A inhibition

The strategy of inhibiting some up-regulated genes and factors with a significant role in periodontitis is gaining popularity. A study investigated the effect of tumor necrosis factor receptor 1 (TNFRSF1A) inhibition on the risk for the disease. Unfortunately, the observed effect did not meet the expectations and the authors did not find a potential efficacy of TNFR1 inhibition on periodontitis risk [37].

- MMPs inhibitors

The MMP inhibitors adopted in periodontal therapy are modified tetracyclines whose main function is to inhibit the connective tissue degradation [38]. Indeed, serum levels of MMPs can be lowered by antibiotics such as doxycycline or tetracycline as they exhibit an effect over the activity of MMP-8 and -9. They are applied in doses lower than other antimicrobial agents used for therapy [39]. Various MMPs (MMP-2, MMP-8, and MMP-9) are inhibited also by chlorhexidine (CHX). Usually, it is used to control plaque and reduce gingival inflammation. Most probably, their mechanism of action is through chelation.

- Antioxidant therapy

A study from 2020 discusses the nature of periodontitis as emerging from oxidative stress [38]. Therefore, different epigenetic factors leading to oxidative stress, such as smoking or diabetes, may increase the predisposition to periodontitis. As a result, therapies, such as resveratrol and other antioxidants, which provide increased antioxidant activity and potentially provoke reversal of periodontitis, are used.

- Nanoparticles

Nanotechnology creates products by manipulating atoms and molecules at nanoscale [40]. This technology is already in use for the treatment of periodontitis by different products, such as hydrogels with antibacterial properties, whose advantage is their ability to decrease the growth of bacterial pathogens and biofilm formation. On the other hand, they reduce the production of reactive oxygen species (ROS), thus exhibiting anti-inflammatory activities [41]. Several

studies demonstrated the usage of nanoparticles in systemic administration of antibiotics – triclosan, tetracycline, minocycline, tinidazole, doxycycline, etc., [42]. Nanoparticles provide stability and sustained release at a local site. This local availability is important, as systemic administration of antibiotics is associated with increased hepatic and renal toxicity due to ineffective penetration and uptake [42].

- Gene therapy

Gene therapy has always been discussed as a tool for modification of stem cells, in the case of periodontal diseases – stem cells in dental tissues. By introducing specific lacking genetic factors, it can supply the missing characteristics and recover the bone formation in severe periodontal cases. The process begins with selecting the most proper therapeutic genes and their incorporation into a carrier (vector). Usually inactivated viruses are used as vectors – retroviruses, adenoviruses, adeno-associated viruses, and herpes viruses. Non-viral vectors are used to a lesser extent and they include lipid vectors, calcium vectors, protein complexes, etc. [43]. The first approved gene therapy was the gamma-retroviral vector-based therapy for the treatment of adenosine deaminase deficiency (ADA). Another gene editing technology that promises a further potential to be largely usable is the CRISPR-Cas9.

Gene therapy has the potential to be used largely in dentistry for gene delivery, bone repair, tooth repair, orthodontic tooth movement and different malignancies of the oral cavity. For periodontitis, bone repair and its ability to regenerate are a primary aim. There were attempts for bone regeneration by introducing an adenoviral vector bearing bone morphogenetic proteins (BMP) [44]. According to the results, produced biologically active BMP-7 is effective in stimulating bone regeneration. Attempts have been made to insert a mitogen activator of osteoblasts (Platelet-Derived Growth Factor, PDGF) into gingival fibroblasts using adenoviral vector with the aim to restore tissue regeneration [42]. A new approach is the usage of bacteriophages to destroy or limit periodontal pathogens, which participate in plaque formation [45]. The challenges of this approach are connected with the number of effectively transformed cells, the ways of integration into tissues, and with maintaining a subsequent level of the gene expression.

CONCLUSION

According to the World Health Organization (WHO), dental diseases affect more than 3.5 million people worldwide. As one of them, periodontitis affects almost 10% of the population. There is a subsequent genetic predisposition to periodontal diseases, which has been broadly studied and confirmed. Nevertheless, environmental factors could also impact the severity of the diseases, its onset and therapy outcomes. The first periodontitis susceptibility test is a good attempt to predict the degree of inflammation and, therefore, the therapy success. However, more genetic factors need to be implemented in future tests to assess the level of predisposition to the disease.

Acknowledgements: *This manuscript is a part of a project with a contract No. D-125/29 May 2024 of the Council of Medical Sciences (CMH) of Medical University – Sofia, Bulgaria.*

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

REFERENCES

1. The Role of Genetics in Periodontal Disease: Understanding Your Risk and Prevention Strategies, Highlands Ranch Periodontics, 2023, August 24 https://inhighlandsranchperio.com/blog/the-role-of-genetics-in-periodontal-disease-understanding-your-risk-and-prevention-strategies/.
2. Visscher PM, Hill WG Wray NR. Heritability in the genomics era – concepts and misconceptions. Nat Rev Genet, 2008, 9(4):255-66.
3. Nibali L, Bayliss-Chapman J, Almofareh SA, et al. What Is the Heritability of Periodontitis? A Systematic Review. J Dent Res. 2019, 98(6):632-641.
4. Teumer A, Holtfreter B, Volker U, et al. Genome-wide association study of chronic periodontitis in a general German population. J Clin Periodontol, 2013, 40(11):977-85
5. Nibali L, Di Iorio A, Tu YK, Vieira AR. Host genetics role in the pathogenesis of periodontal disease and caries. J Clin Periodontol, 2017, 44 Suppl 18:S52-S78
6. Silman A. Genetic Bad Teeth: Understanding the Influence of Genetics on Dental Health, in Smile Spa. 2023, October 17 https://www.drsilmansmilespa.com/genetic-bad-teeth-understanding-the-influence-of-genetics-on-dental-health
7. Kornman KS, Crane A, Wang HY, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol, 1997, 24(1):72-7
8. Stabholz A, Soskolne WA, Shapira L. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. Periodontol 2000, 2010, 53:138-53
9. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. Periodontol 2000, 2010, 53:124-37
10. Zhang HY, Feng L, Wu H, Xie XD. The association of IL-6 and IL-6R gene polymorphisms with chronic periodontitis in a Chinese population. Oral Dis, 2014, 20(1):69-75
11. Nikolopoulos GK, Dimou NL, Hamodrakas SJ, et al. Cytokine gene polymorphisms in periodontal disease: a meta-analysis

of 53 studies including 4178 cases and 4590 controls. J Clin Periodontol, 2008, 35(9):754-67
12. Kaarthikeyan G, Meenakshi S. Genetic Biomarkers in Periodontal Disease Diagnosis. In: Periodontal Disease – Diagnostic and Adjunctive Non-surgical Considerations, N.M.A. Yussif (Ed.) Rijeka, IntechOpen, 2019. https://www.intechopen.com/chapters/67970
13. Zhang X, Zhu X, Sun W. Association Between Tumor Necrosis Factor-α (G-308A) Polymorphism and Chronic Periodontitis, Aggressive Periodontitis, and Peri-implantitis: A Meta-analysis. Journal of Evidence Based Dental Practice, 2021, 21(3):101528.
14. Wang RP-H, Huang J, Chan KWY, et al. IL-1β and TNF-α play an important role in modulating the risk of periodontitis and Alzheimer's disease. Journal of Neuroinflammation, 2023, 20(1):71.
15. Um S, Lee J-H, Seo B-M. TGF-β2 downregulates osteogenesis under inflammatory conditions in dental follicle stem cells. International Journal of Oral Science, 2018, 10(3):29.
16. Sheibak N, Heidari Z, Mahmoudzadeh-Sagheb H. Immunoexpression of interferon-gamma in the interdental gingiva of chronic periodontitis patients with interferon-gamma (+874A/T) rs62559044 polymorphism. Journal of Oral Biology and Craniofacial Research, 2022; 12(5):727-732.
17. Jagelavičienė E, Vaitkevičienė I, Šilingaitė D, et al. The Relationship between Vitamin D and Periodontal Pathology. Medicina (Kaunas), 2018, 54(3):45.
18. Machado V, Lobo S. Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. Nutrients, 2020, 12(8):2177
19. Checchi V, Maravic T, Bellini P. The Role of Matrix Metalloproteinases in Periodontal Disease. Int J Environ Res Public Health, 2020, 17(14):4923.
20. Li W, Zhu Y, Singh P, et al. Association of Common Variants in MMPs with Periodontitis Risk. Dis Markers, 2016, 2016:1545974
21. Luchian I, Goriuc A, Sandu D, et al. The Role of Matrix Metalloproteinases (MMP-8, MMP-9, MMP-13) in Periodontal and Peri-Implant Pathological Processes. Int J Mol Sci, 2022, 23(3):1806.
22. Wan C-Y, Yin Y, Li X, et al. MMP-9 deficiency accelerates the progress of periodontitis. Genes & Diseases, 2024, 11(5):101231.
23. Durge K, Baliga V, Dhadse P, et al. Human Leukocyte Antigen and Periodontal Diseases. Journal of Datta Meghe Institute of Medical Sciences University, 2021; 16(2):401-3
24. Reichert S, Altermann W, Stein JM, et al. Individual composition of human leukocyte antigens and periodontopathogens in the background of periodontitis. J Periodontol, 2013; 84(1):100-9.
25. Brodzikowska A, Górski B. Polymorphisms in Genes Involved in Inflammation and Periodontitis: A Narrative Review. Biomolecules, 2022, 12 12(4):552.
26. Stein JM, Machulla HK, Smeets R, et al. Human leukocyte antigen polymorphism in chronic and aggressive periodontitis among Caucasians: a meta-analysis. J Clin Periodontol, 2008, 35(3):183-92.
27. Chitsamankhun C, Siritongtaworn N, Fournier BPJ, et al. Cathepsin C in health and disease: from structural insights to therapeutic prospects. Journal of Translational Medicine, 2024, 22(1):777.
28. Yin W, Dong M, Ye D, et al. Cathepsin C promotes the progression of periapical periodontitis. Science Bulletin, 2020, 65(11):951-957.
29. Holla LI, Buckova D, Fassmann A, et al. Promoter polymorphisms in the CD14 receptor gene and their potential association with the severity of chronic periodontitis. J Med Genet, 2002, 39(11):844-8.
30. Behm C, Blufstein A, Gahn J, et al. Soluble CD14 Enhances the Response of Periodontal Ligament Stem Cells to Toll-Like Receptor 2 Agonists. Mediators Inflamm, 2019; 2019:8127301.
31. Loos BG, Van Dyke TE. The role of inflammation and genetics in periodontal disease. Periodontol 2000, 2020, 83(1):26-39.
32. Munz M, Richter GM, Loos BG, et al. Genome-wide association meta-analysis of coronary artery disease and periodontitis reveals a novel shared risk locus. Sci Rep. 2018, 8(1):13678..
33. Shi F, Liu W, Yao Y, et al. Predictive salivary biomarkers for early diagnosis of periodontal diseases – current and future developments. Turkish Journal of Biochemistry, 2023; 48(4):335-344.
34. Haririan HAO, Laky M., Xiaohui R. Saliva as a Source of Biomarkers for Periodontitis and Periimplantitis. Sec. Periodontics, 2021; 2.
35. Priya KL, Mahendra J, Mahendra L, et al. Salivary Biomarkers in Periodontitis Post Scaling and Root Planing. J Clin Med, . 2022, 11(23):7142.
36. Laurencin-Dalicieux S, Cazajus C, Barthet P, et al. Periodontal susceptibility test (PST) and periodontal risk assessment how strong is the link?. Journal of Clinical Periodontology, 2018, 45(S19):190-190.
37. Alayash Z, Baumeister SE, Holtfreter B, et al. Inhibition of tumor necrosis factor receptor 1 and the risk of periodontitis. Front Immunol, 2023; 14:1094175.
38. Sczepanik FSC, Grossi ML, Casati M, et al. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. Periodontol 2000. 2020, 84(1):45-68.
39. Lahdentausta LSJ, Paju S, Mantyla P, et al. Saliva and serum biomarkers in periodontitis and coronary artery disease. J Clin Periodontol, 2018, 45(9):1045-1055.
40. European Union. Nanotechnologies, 2007 https://ec.europa.eu/health/scientific_committees/opinions_layman/en/nanotechnologies/l-2/1-introduction.htm.
41. Johnson A, Kong F, Miao S, et al. Therapeutic effects of antibiotics loaded cellulose nanofiber and kappa-carrageenan oligosaccharide composite hydrogels for periodontitis treatment. Sci Rep, 2020, 10(1):18037.
42. Yadalam PK, Kalaivani V, Fageeh HI, et al. Future Drug Targets in Periodontal Personalised Medicine – A Narrative Review. Journal of Personalized Medicine, 2022. 12(3):371.
43. Barhate A, Bajaj P, Shirbhate U, et al. Implications of Gene Therapy in Dentistry and Periodontics: A Narrative Review. Cureus, 2023, 15(11):e49437.
44. Franceschi RT, Wang D, Krebsbach PH, Rutherford RB. Gene therapy for bone formation: in vitro and in vivo osteogenic activity of an adenovirus expressing BMP7. J Cell Biochem, 2000, 78(3):476-86.
45. Łusiak-Szelachowska M, Weber-Dąbrowska B. Bacteriophages and Lysins in Biofilm Control. 2020; 35(2):125-133.