PERIODONTITIS: A MULTIFACETED DISEASE OF TOOTH-SUPPORTING TISSUES

Abdullah Mana Alqahtani[1*], Mohammed Ali Alqahtani[2], Saeed Hussain Saeed Al Ojair[3], Mohammed Yahya Mofareh Asiri[4], Waleed Mohammed Abdullah Alhogban[5], Salem saeed jubran Alqahtani[6], Saad Mohammad H Alkhammash[6]

Abstract:

Background: Periodontitis is a prevalent infection-driven inflammatory disease affecting the tooth-supporting tissues. The disease's development and progression are influenced by genetics, environmental factors, and behaviors. The destruction of alveolar bone due to osteoclastogenesis activation is a hallmark of periodontitis, leading to tooth support loss. Various demographic characteristics and lifestyle factors such as smoking and diabetes significantly impact the prevalence and severity of periodontal disease. The immune response in the gingiva maintains a balance between oral biofilms and the host, with dysbiosis potentially leading to disease onset. **Objective**: This review aims to investigate the multifactorial nature of periodontitis, exploring genetic, environmental, and behavioral contributors. It also seeks to examine the relationship between periodontitis and systemic health conditions, assess its impact on quality of life, and explore potential biomarkers for early detection and novel therapeutic targets. **Conclusion**: Periodontitis is a complex inflammatory disease influenced by genetic, environmental, and behavioral factors, with the oral microbiota-host immune response interplay playing a critical role. The disease is linked to systemic health conditions, highlighting the importance of periodontal health for overall well-being. Understanding the pathophysiology and immunological aspects of periodontitis is crucial for effective early detection and treatment strategies. While periodontal therapy aims to reduce infection and inflammation, long-term success requires continuous maintenance and patient compliance. Further research into biomarkers and therapeutic interventions is essential for enhancing periodontal disease management outcomes.

Keywords: periodontal disease, alveolar bone loss, gingiva, bacteria, biofilm, immunity, inflammation, smoking.

1*General Dentist, Alsnaeyah PHCC, Khamis Mushait, Aseer Region ,Saudi Arabia
2Family Medicine Consultant, Addobat PHCC, Khamis Mushait, Asser Region ,Saudi Arabia
3General Dentist, Alzalal Health Center, Khamis Mushait, Asir Region, Saudi Arabia
4General Dentist ,Ballasmar PHCC, asir region , saudi arabia
5Resident in Endodontics,Ministry
of Health, Saudi Arabia
6General dentist, Aseer dental center, Health affairs in Abha, Ministry of health, Aseer, Saudi Arabia

***Corresponding Author:** Abdullah Mana Alqahtani
*General Dentist, Alsnaeyah PHCC, Khamis Mushait, Saudi Arabia

DOI: 10.53555/ecb/2022.11.10.133

Introduction:

Periodontitis, a condition characterized by infection-driven inflammation in the tissues supporting the teeth, known as the periodontium, is influenced by a combination of genetic, environmental, and behavioral factors [1]. The periodontium is a complex structure comprising the gingiva, connective tissue, root surface cement, alveolar bone, and periodontal ligament. Notably, the junctional epithelium located at the base of the gingival sulcus plays a crucial role in regulating bacterial presence in this area. Osteoclastogenesis activation and subsequent alveolar bone destruction are hallmark features of periodontitis, leading to irreversible loss of tooth support [2].

The prevalence of periodontal disease, particularly its milder forms, is high among adult populations worldwide, with rates around 50%. Severe periodontitis becomes more prevalent between the ages of 30 and 40, affecting approximately 10% of the global population. Various demographic factors such as age, gender, ethnicity, and socioeconomic status, as well as lifestyle factors like smoking, diabetes, metabolic syndrome, and obesity, contribute significantly to the development and progression of periodontitis [3]. Smoking and diabetes, in particular, can predispose individuals to advanced periodontal disease early in life, with smoking also being linked to tooth loss in young individuals. Severe periodontitis, a leading cause of tooth loss in adults, can result in tooth mobility and shifting, ultimately affecting an individual's ability to bite properly. Additionally, periodontal disease and tooth loss are associated with several chronic diseases and overall health conditions [4].

Even in a state of periodontal health, immune cells are present in the gingiva, maintaining a balance between oral biofilms and the host. This ongoing communication sustains an active immune response, characterized by a dynamic interaction between the host and oral microbiota. The immune response in the periodontium mirrors that of other body tissues, with innate defenses acting against microbes initially and adaptive responses being activated in response to prolonged pathogenic challenges [5].

Accumulation of dental plaque at the gingival margin can trigger inflammation and an increase in anaerobic, proteolytic bacterial species. The presence of pathogenic periodontal bacteria in the gingival sulcus initiates an inflammatory response in the gingival tissue, which, if left unchecked, can lead to severe consequences in susceptible individuals. The interplay between oral microbiota components and host factors can either maintain a healthy balance (homeostasis) or disrupt it (dysbiosis), potentially leading to various degrees of periodontal tissue damage and disease onset [6,7]. Commensal bacteria associated with periodontal health play a crucial role in inhibiting the growth of disease-causing pathogens, highlighting the importance of a balanced oral microbiota in maintaining periodontal health.

Objectives:

The main objectives of this review are:

1. To investigate the various factors contributing to the development and progression of periodontitis, including genetic, environmental, and behavioral factors.
2. To examine the relationship between periodontitis and systemic health conditions, such as cardiovascular disease, diabetes, and respiratory diseases.
3. To assess the impact of periodontitis on quality of life, including oral health-related quality of life and overall well-being.
4. To explore potential biomarkers for early detection and monitoring of periodontitis, as well as potential targets for novel therapeutic interventions.

Epidemiology:

Periodontal diseases can be seen in up to 90% of the global population, making it the most common oral disease. In the United States alone, cross-sectional studies show that approximately 50% of adults currently have some form of gingivitis, and up to 80% have experienced some form of periodontal disease in their life. Certain groups have been shown to have an increased incidence of periodontal diseases. These groups include older individuals, males, and African-Americans. Lower-income and education levels were also associated with severe periodontitis [8].

Pathogenic Biofilms:

Multispecies biofilm formation and maturation on tooth surfaces involve intergeneric interactions leading to coaggregations between various bacterial taxa, resulting in the development of highly diverse bacterial communities at both supragingival (above the gumline) and subgingival (below the gumline) sites [9]. Fusobacterium nucleatum, a core anaerobic microbiota member in the oral cavity from early life onwards, plays a crucial role as a bridging organism in the maturation of dental biofilms, facilitating the colonization of late-arriving species with virulent properties. The gradual maturation and microbial composition shifts in biofilms influence the

pathogenicity of subgingival biofilms, where metabolically specialized microorganisms function in close proximity as interactive microbial communities. Merely focusing on its adherence capabilities may lead to underestimating other vital virulence characteristics of F. nucleatum, a significant bacterium in the initiation and progression of periodontal disease. Within a biofilm, this obligate anaerobe can thrive and proliferate in aerobic environments [10]. Recent findings suggest that F. nucleatum induces hypoxia, altering the environment to support the colonization of anaerobic pathogens in dental biofilms. The effects of F. nucleatum-induced hypoxia extend beyond biofilm composition shifts, influencing endothelial cells towards inflammation and activating angiogenesis [11].

In subgingival biofilms, anaerobic gram-negative species with biologically active lipopolysaccharide (LPS)-containing cell wall structures may play a crucial role in triggering inflammatory reactions in the gingiva, leading to periodontal destruction in susceptible individuals. Subgingival plaque samples from periodontitis patients and periodontitis-free individuals exhibit distinct differences. The so-called red complex, comprising Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, shows a strong association with periodontal disease [12]. In a study utilizing 454 pyrosequencing of 16S rRNA genes, P. gingivalis, T. denticola, and Filifactor alocis, a gram-positive anaerobe, emerged as the top three species [13]. P. gingivalis, considered the principal pathogen in periodontal disease, disrupts the interplay between subgingival biofilms and host responses, even in small quantities within the subgingival microbiota. It can significantly impact the numbers and organization of commensal bacteria at the site, as well as dysregulate innate immunity pathways. While P. gingivalis is uncommon in children and adolescents, its prevalence in saliva increases with age, being detected in the majority of the Finnish population over the age of 55 [15]. In contrast, the presence of Aggregatibacter actinomycetemcomitans, a gram-negative capnophilic coccobacillus associated with aggressive periodontal disease, is less age-dependent [16]. Besides these well-known pathogens, advanced molecular techniques have expanded the list of pathogenic species found in subgingival biofilms associated with periodontitis [17].

Numerous periodontitis-associated species, including A. actinomycetemcomitans, P. gingivalis, and F. nucleatum, as well as polymicrobial aggregates, possess the ability to invade periodontal tissues, evading host defense mechanisms. This evasion contributes to the persistence of inflammation and the progression of periodontal tissue destruction [18].

Pathophysiology:

Periodontal disease does not arise solely from the presence of a single periodontal pathogen; rather, it is the result of a complex interplay between the composition of the subgingival biofilm and the host response, where host factors and specific niches play crucial roles. Dysbiotic biofilms, characterized by an abundance of immunostimulatory pathobionts and their virulence factors, along with a reduced inhibitory effect of commensal bacteria, lead to an increased inflammatory response [19]. The interaction of polymicrobial biofilms with gingival epithelia triggers cellular responses that pave the way for initial pocket formation and attachment loss, primarily due to the metabolic and virulence synergisms among the bacteria [19]. The deepening of periodontal pockets creates an anaerobic environment with inflammatory conditions and abundant substrates from tissue destruction, favoring the growth of inflammophilic periodontal pathogens and pathobionts [20]. Furthermore, smoking exacerbates disturbances in the subgingival microbiota, promoting the abundance of periodontal pathogens while reducing beneficial commensals, thereby increasing the risk of periodontal disease [21].

Immunologic Players of the Periodontium:

The periodontium is constantly engaged in interactions with bacteria, with immune cells such as neutrophils, macrophages, and lymphocytes playing vital roles in maintaining a healthy equilibrium. Neutrophils, for instance, continuously migrate through the junctional epithelium to the gingival sulcus, releasing antimicrobial peptides like α-defensins to combat invading bacteria and promoting the adhesion and spread of keratinocytes on the tooth surface [22]. Resident cells in the periodontium, including keratinocytes, fibroblasts, dendritic cells, and osteoblasts, are not passive barriers against bacterial invasion; rather, they play active roles in initiating innate immune responses and regulating adaptive immune responses. The complement pathway, a key component of the immune response, serves to opsonize and kill bacteria, as well as activate various immune cells in the periodontium [23].

Keratinocytes, the predominant cells in the gingival epithelium, are capable of producing and secreting

a variety of immune response mediators, including human β-defensins, cathelicidins, proinflammatory cytokines, chemokines, and angiogenetic proteins [24]. In the healthy gingiva, innate response is mainly regulated by keratinocytes and neutrophils; keratinocytes secrete hBDs to protect the oral and sulcular epithelium, whereas neutrophils secrete α-defensins to protect the junctional epithelium. Gingival keratinocytes recognize pathogen-associated molecular patterns (PAMPs) by their pattern recognition receptors, such as toll-like receptors (TLRs). mRNA expressions of TLR 1–9 are detected in connective tissue and epithelial layers of the gingiva [25]. In addition, bacterial signaling molecules (cyclic dinucleotides and quorum signaling molecules) activate cytokine response in gingival keratinocytes. There is also a reciprocal interaction between innate-immune proteins and keratinocytes. For example, proinflammatory interleukins (IL-1α, IL-1β, IL-6) activate the protein expression and secretion of hBDs from keratinocytes, while keratinocytes can suppress the inflammatory response by secreting monocyte chemotactic protein-induced protein-1 [26].

The gingival connective tissue, periodontal ligament, and bone's organic component are predominantly composed of collagen, with fibroblasts responsible for synthesizing new collagen bundles and removing old collagen through the secretion of matrix metalloproteinases (MMPs). Overexpression of MMPs by gingival fibroblasts can induce the release of cytokines and chemokines or cleave cytokines, disrupting immune response signaling cascades. The interaction between neutrophils and gingival fibroblasts exemplifies the bidirectional communication between resident and immune cells [27].

Dendritic cells differ from keratinocytes and fibroblasts by acting as phagocytes and antigen-presenting cells. In a healthy environment, dendritic cells are in their immature forms and have high phagocytic capacity against invading microorganisms, but during infection they initiate a maturation process that involves their migration to lymph nodes to activate $CD4^+$ T cells [28] and promote the polarization of T-helper (Th)1, Th2, Th17, and B cells. Uncontrolled upregulation of Th1 and Th17 cell pathways enhances alveolar bone loss via the induction of osteoclastogenesis. There is also evidence that dendritic cells can differentiate to osteoclasts; however, it is unknown how much of the bone resorption seen in periodontitis is actually induced by dendritic cell-derived osteoclasts.

Neutrophils serve as the primary defense system in periodontal tissues, continuously migrating through the junctional epithelium into the gingival sulcus. While parainflammatory neutrophil populations are typical in the healthy oral cavity, proinflammatory neutrophil phenotypes are prevalent in periodontal disease. Severe forms of periodontitis may be linked to neutrophil function defects, such as leukocyte adhesion deficiency 1 (LAD-1), where the lack of effective neutrophil surveillance against bacterial infection contributes to excessive periodontal degradation [29].

Inflammatory Process and Periodontal Tissue Destruction:

The junctional epithelium serves as a crucial barrier between the root surface and the gingiva, offering protection against oral microbes and their by-products by employing various molecular mechanisms such as adhesion, cell-cell interactions, chemotaxis, proinflammatory cytokines, epithelial growth, MMP activation, and antimicrobial peptide production [30]. If this defense system is compromised by bacterial virulence factors like P. gingivalis gingipains and prolonged inflammation, characterized by symptoms such as gingival bleeding and changes in soft tissue appearance, the junctional epithelium may migrate towards the root surface, triggering collagen degradation and ultimately leading to the formation of periodontal pockets. It is important to note that while gingival inflammation precedes periodontitis and is a significant risk factor for disease progression, not all cases of gingivitis progress to periodontitis [31].

During the development of periodontal pockets, the production of new tissue by resident cells such as keratinocytes, fibroblasts, and osteoblasts is inhibited, while the degradation of tissue by neutrophils, macrophages, and osteoclasts is enhanced, disrupting the balance between tissue regeneration and removal [32]. Proinflammatory cytokines (IL-1β, IL-6, IL-23, TNF-α), chemokines (IL-8), and antimicrobial peptides generated by keratinocytes, fibroblasts, and dendritic cells act as chemoattractants for neutrophils, which migrate to inflamed areas and promote the chemotaxis of nonresident cells like macrophages, lymphocytes, plasma cells, and mast cells [33]. Phagocytic cells work to eliminate pathogens by releasing antimicrobial agents, reactive oxygen species, and enzymes. However, high levels of collagenolytic MMPs and elastase can trigger the breakdown of type I collagen in the connective tissue and periodontal ligament, with MMP-8 playing a key role as the primary collagenase in periodontal

tissues. In cases of severe periodontal disease, the inflammatory cell infiltrate, primarily composed of plasma cells, can extend deep into the connective tissue, causing damage to the periodontal ligament and alveolar bone [34].

Periodontal Therapy—Impact on Oral and General Health:

The main objective of periodontal therapy is to diminish the infectious and inflammatory burden while halting the progression of tissue destruction [35]. The eradication of pathogenic biofilms and the control of inflammation are crucial in halting the degradation of periodontal tissues; however, the extent of tissue regeneration is limited and varies based on factors such as the type of tissue defects, overall health status, and age. In cases of advanced periodontal disease, the active anti-infective treatment phase is often supplemented with surgical interventions to eliminate residual pockets, thereby enhancing the microbial environment at periodontal sites, or in some instances, with systemic antimicrobials to reduce pathogen load. Notably, in individuals who smoke, the efficacy of treatment is compromised, underscoring the importance of smoking cessation as an integral component of their periodontal therapy. Quitting smoking can have a positive impact, potentially by reducing pathogen levels and promoting the growth of beneficial commensal bacteria within subgingival biofilms [36].

While anti-infective therapy leads to a reduction in overall bacterial counts, the proportions of periodontal pathogens and the prevalence of sites colonized by these pathogens may rebound over time. Consequently, consistent daily oral hygiene practices by the patient and regular professional supportive periodontal care are essential to sustain treatment outcomes and bolster the long-term success of the therapy [37]. Additionally, individuals with advanced periodontal disease and issues like masticatory dysfunction and bite collapse resulting from extensive tooth loss require comprehensive rehabilitation to restore bite function and address aesthetic concerns. Despite undergoing treatment, patients with periodontitis who receive prosthodontic reconstructions still face an elevated risk of tooth loss post-treatment. Various patient-related factors, including age, socioeconomic status, compliance with treatment recommendations, and the presence of conditions like diabetes, are associated with the potential loss of abutment teeth [38].

Conclusion:

In conclusion, periodontitis is a complex inflammatory disease influenced by a combination of genetic, environmental, and behavioral factors. The interplay between the oral microbiota and the host immune response plays a crucial role in the development and progression of the disease. Periodontal health is essential for overall well-being, as periodontitis has been linked to various systemic health conditions. Understanding the pathophysiology and immunologic players of the periodontium is key to developing effective strategies for early detection and treatment. Periodontal therapy aims to reduce infection and inflammation, but long-term success requires ongoing maintenance and patient compliance. Further research into biomarkers and therapeutic interventions is crucial for improving outcomes in periodontal disease management.

References:

1. Eke P.I., Dye B.A., Wei L., Thornton-Evans G.O., Genco R.J. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J. Dent. Res. 2012;91:914–920. doi: 10.1177/0022034512457373. [PubMed] [CrossRef] [Google Scholar]
2. Kassebaum N.J., Bernabé E., Dahiya M., Bhandari B., Murray C.J., Marcenes W. Global burden of severe periodontitis in 1990–2010: A systematic review and meta-regression. J. Dent. Res. 2014;93:1045–1053. doi: 10.1177/0022034514552491. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. Genco R.J., Borgnakke W.S. Risk factors for periodontal disease. Periodontol. 2000. 2013;62:59–94. doi: 10.1111/j.1600-0757.2012.00457.x. [PubMed] [CrossRef] [Google Scholar]
4. Kosaka T., Ono T., Yoshimuta Y., Kida M., Kikui M., Nokubi T., Maeda Y., Kokubo Y., Watanabe M., Miyamoto Y. The effect of periodontal status and occlusal support on masticatory performance: The Suita study. J. Clin. Periodontol. 2014;41:497–503. doi: 10.1111/jcpe.12241. [PubMed] [CrossRef] [Google Scholar]
5. Darveau R.P. Periodontitis: A polymicrobial disruption of host homeostasis. Nat. Rev. Microbiol. 2010;8:481–490. doi: 10.1038/nrmicro2337. [PubMed] [CrossRef] [Google Scholar]
6. Sanz M., Beighton D., Curtis M.A., Cury J.A., Dige I., Dommisch H., Ellwood R., Giacaman R.A., Herrera D., Herzberg M.C., et al. Role of microbial biofilms in the maintenance of oral health and in the development of dental caries

and periodontal diseases. Consensus report of group 1 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal disease. J. Clin. Periodontol. 2017;44(Suppl. 18):5–11. doi: 10.1111/jcpe.12682. [PubMed] [CrossRef] [Google Scholar]
7. Thomson W.M., Shearer D.M., Broadbent J.M., Foster Page L.A., Poulton R. The natural history of periodontal attachment loss during the third and fourth decades of life. J. Clin. Periodontol. 2013;40:672–680. doi: 10.1111/jcpe.12108. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005 Nov 19;366(9499):1809-20. [PubMed] [Reference list]
9. Kolenbrander P.E., Palmer R.J., Jr., Periasamy S., Jakubovics N.S. Oral multispecies biofilm development and the key role of cell-cell distance. Nat. Rev. Microbiol. 2010;8:471–480. doi: 10.1038/nrmicro2381. [PubMed] [CrossRef] [Google Scholar]
10. Gursoy U.K., Pöllänen M., Könönen E., Uitto V.J. Biofilm formation enhances the oxygen tolerance and invasiveness of Fusobacterium nucleatum in an oral mucosa culture model. J. Periodontol. 2010;81:1084–1091. doi: 10.1902/jop.2010.090664. [PubMed] [CrossRef] [Google Scholar]
11. Mendes R.T., Nguyen D., Stephens D., Pamuk F., Fernandes D., Hasturk H., Van Dyke T.E., Kantarci A. Hypoxia-induced endothelial cell responses - possible roles during periodontal disease. Clin. Exp. Dent. Res. 2018;4:241–248. doi: 10.1002/cre2.135. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Socransky S.S., Haffajee A.D., Cugini M.A., Smith C., Kent R.L., Jr. Microbial complexes in subgingival plaque. J. Clin. Periodontol. 1998;25:134–144. doi: 10.1111/j.1600-051X.1998.tb02419.x. [PubMed] [CrossRef] [Google Scholar]
13. Griffen A.L., Beall C.J., Campbell J.H., Firestone N.D., Kumar P.S., Yang Z.K., Podar M., Leys E.J. Distinct and complex bacterial profiles in human periodontitis and health revealed by 16S pyrosequencing. ISME J. 2012;6:1176–1185. doi: 10.1038/ismej.2011.191. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Hajishengallis G. The inflammophilic character of the periodontitis-associated microbiota. Mol. Oral Microbiol. 2014;29:248–257. doi: 10.1111/omi.12065. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Könönen E., Paju S., Pussinen P.J., Hyvönen M., Di Tella P., Suominen-Taipale L., Knuuttila M. Population-based study of salivary carriage of periodontal pathogens in adults. J. Clin. Microbiol. 2007;45:2446–2451. doi: 10.1128/JCM.02560-06. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Könönen E., Müller H.P. Microbiology of aggressive periodontitis. Periodontol. 2000. 2014;65:46–78. doi: 10.1111/prd.12016. [PubMed] [CrossRef] [Google Scholar]
17. Curtis M.A. Periodontal microbiology - the lid's off the box again. J. Dent. Res. 2014;93:840–842. doi: 10.1177/0022034514542469. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Saglie F.R., Marfany A., Camargo P. Intragingival occurrence of Actinobacillus actinomycetemcomitans and Bacteroides gingivalis in active destructive periodontal lesions. J. Periodontol. 1988;59:259–265. doi: 10.1902/jop.1988.59.4.259. [PubMed] [CrossRef] [Google Scholar]
19. Jiao Y., Hasegawa M., Inohara N. The role of oral pathobionts in dysbiosis during periodontitis development. J. Dent. Res. 2014;93:539–546. doi: 10.1177/0022034514528212. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Herrero E.R., Fernandes S., Verspecht T., Ugarte-Berzal E., Boon N., Proost P., Bernaerts K., Quirynen M., Teughels W. Dysbiotic biofilms deregulate the periodontal inflammatory response. J. Dent. Res. 2018;97:547–555. doi: 10.1177/0022034517752675. [PubMed] [CrossRef] [Google Scholar]
21. Mason M.R., Preshaw P.M., Nagaraja H.N., Dabdoub S.M., Rahman A., Kumar P.S. The subgingival microbiome of clinically healthy current and never smokers. ISME J. 2015;9:268–272. doi: 10.1038/ismej.2014.114. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Gursoy U.K., Könönen E., Luukkonen N., Uitto V.J. Human neutrophil defensins and their effect on epithelial cells. J. Periodontol. 2013;84:126–133. doi: 10.1902/jop.2012.120017. [PubMed] [CrossRef] [Google Scholar]
23. Damgaard C., Holmstrup P., Van Dyke T.E., Nielsen C.H. The complement system and its role in the pathogenesis of periodontitis: Current concepts. J. Periodontal Res. 2015;50:283–293. doi: 10.1111/jre.12209. [PubMed] [CrossRef] [Google Scholar]

24. Liu J., Du X., Chen J., Hu L., Chen L. The induction expression of human β-defensins in gingival epithelial cells and fibroblasts. Arch. Oral Biol. 2013;58:1415–1421. doi: 10.1016/j.archoralbio.2013.04.013. [PubMed] [CrossRef] [Google Scholar]
25. Song B., Zhang Y.L., Chen L.J., Zhou T., Huang W.K., Zhou X., Shao L.Q. The role of Toll-like receptors in periodontitis. Oral Dis. 2017;23:168–180. doi: 10.1111/odi.12468. [PubMed] [CrossRef] [Google Scholar]
26. Jura J., Skalniak L., Koj A. Monocyte chemotactic protein-1-induced protein-1 (MCPIP1) is a novel multifunctional modulator of inflammatory reactions. Biochim. Biophys. Acta. 2012;1823:1905–1913. doi: 10.1016/j.bbamcr.2012.06.029. [PubMed] [CrossRef] [Google Scholar]
27. Cavalla F., Hernández-Rios P., Sorsa T., Biguetti C., Hernández M. Matrix metalloproteinases as regulators of periodontal inflammation. Int. J. Mol. Sci. 2017;18:440. [PMC free article] [PubMed] [Google Scholar]
28. Wilensky A., Segev H., Mizraji G., Shaul Y., Capucha T., Shacham M., Hovav A.H. Dendritic cells and their role in periodontal disease. Oral Dis. 2014;20:119–126. doi: 10.1111/odi.12122. [PubMed] [CrossRef] [Google Scholar]
29. Fine N., Hassanpour S., Borenstein A., Sima C., Oveisi M., Scholey J., Cherney D., Glogauer M. Distinct oral neutrophil subsets define health and periodontal disease states. J. Dent. Res. 2016;95:931–938. doi: 10.1177/0022034516645564. [PubMed] [CrossRef] [Google Scholar]
30. Bosshardt D.D., Lang N.P. The junctional epithelium: From health to disease. J Dent. Res. 2005;84:9–20. doi: 10.1177/154405910508400102. [PubMed] [CrossRef] [Google Scholar]
31. Lang N.P., Schätzle M.A., Löe H. Gingivitis as a risk factor in periodontal disease. J. Clin. Periodontol. 2009;36(Suppl. 10):3–8. doi: 10.1111/j.1600-051X.2009.01415.x. [PubMed] [CrossRef] [Google Scholar]
32. Henderson B., Kaiser F. Bacterial modulators of bone remodeling in the periodontal pocket. Periodontol. 2000. 2018;76:97–108. doi: 10.1111/prd.12160. [PubMed] [CrossRef] [Google Scholar]
33. Sorsa T., Tjäderhane L., Konttinen Y.T., Lauhio A., Salo T., Lee H.M., Golub L.M., Brown D.L., Mäntylä P. Matrix metalloproteinases: Contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. Ann. Med. 2006;38:306–321. doi: 10.1080/07853890600800103. [PubMed] [CrossRef] [Google Scholar]
34. Kurgan S., Kantarci A. Molecular basis for immunohistochemical and inflammatory changes during progression of gingivitis to periodontitis. Periodontol. 2000. 2018;76:51–67. doi: 10.1111/prd.12146. [PubMed] [CrossRef] [Google Scholar]
35. Reynolds M.A., Kao R.T., Camargo P.M., Caton J.G., Clem D.S., Fiorellini J.P., Geisinger M.L., Mills M.P., Nares S., Nevins M.L. Periodontal regeneration - intrabony defects: A consensus report from the AAP regeneration workshop. J. Periodontol. 2015;86(Suppl. 2):105–107. doi: 10.1902/jop.2015.140378. [PubMed] [CrossRef] [Google Scholar]
36. Delima S.L., McBride R.K., Preshaw P.M., Heasman P.A., Kumar P.S. Response of subgingival bacteria to smoking cessation. J. Clin. Microbiol. 2010;48:2344–2449. doi: 10.1128/JCM.01821-09. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Axelsson P., Nyström B., Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. J. Clin. Periodontol. 2004;31:749–757. doi: 10.1111/j.1600-051X.2004.00563.x. [PubMed] [CrossRef] [Google Scholar]
38. Müller S., Eickholz P., Reitmeir P., Eger T. Long-term tooth loss in periodontally compromised but treated patients according to the type of prosthodontic treatment. A retrospective study. J. Oral Rehabil. 2013;40:358–367. doi: 10.1111/joor.12035. [PubMed] [CrossRef] [Google Scholar]