

Smoking and Periodontal Disease – Current Perspective of the Possible Pathogenic Mechanisms

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Abstract: *Several developing and developed countries are experiencing an epidemic in diseases caused by cigarette smoking and tobacco use. Despite numerous smoke free initiatives and governmental tobacco-control policies, tobacco consumption still remains excessively prevalent. In addition to the damaging impact on general health, smoking also has an effect on oral health. Epidemiological studies have clearly demonstrated a strong association between tobacco use/ smoking habit and periodontal diseases in diverse populations. Smoking has been considered as the most important risk factor for periodontitis among all life style factors. The present review provides an overview of the various mechanisms by which smoking affects the periodontal tissues.*

Keywords: Pathogenic mechanisms, Periodontal disease, Risk factor, Smoking, Tooth loss

1. Introduction

It is well established that periodontal disease is predominantly a bacterial infection involving the dental biofilm or dental plaque. But the concept that the rate of progression, age of onset and severity of periodontal disease in an individual are often determined by systemic risk factors in the host is a relatively recent concept made possible by our understanding of the epidemiology of periodontal disease and the role of risk factors. As per the current evidence, tobacco smoking is the most important environmental risk factor for periodontitis¹.

In addition to the damaging impact on general health, smoking also has an effect on oral health, including dental implant failures, oral cancers and periodontal diseases². The finding that smoking is associated with periodontal disease suggests that it is probably a major risk factor for subsequent tooth loss³. The World Health Organization estimates that the number of smokers worldwide is more than 1 billion and is expected to increase to 1.7 billion by 2025⁴.

The possible etiopathogenic mechanisms as to how smoking contributes to periodontal destruction have been extensively reviewed. This review will provide an overview of the various mechanisms by which smoking affects the periodontal tissues.

2. Burden of Disease

Epidemiologic, clinical, behavioural and biologic evidence has equivocally implicated smoking in a substantial proportion of the global burdens of cancers and of cardiovascular and pulmonary diseases. Globally tobacco use has been related to more than 5 million deaths per year and this number is expected to increase to 8 million deaths in 2030⁵.

It is indeed surprising to see that global tobacco consumption is increasing despite the overwhelming scientific evidence gathered in the past few years and all the initiatives designed to curb tobacco use. It has been estimated that more than one billion people smoke daily worldwide, with China, India, Indonesia, Russia, USA, Japan, Brazil, Bangladesh, Germany and Turkey accounting for more than two-thirds of the smokers in the world⁵. The

burden of smoking on periodontal health has been assessed in few studies. In USA, population attributable fractions clearly indicate that approximately half of the cases of periodontitis may be attributable to smoking, depending on disease definition⁶. Thomson et al estimated that in a representative birth cohort of New Zealand subjects, two-thirds of new cases of periodontitis in subjects at 32 years could be attributable to smoking. These studies demonstrate that smoking clearly represents a major part of the burden of destructive periodontal disease⁷.

3. Clinical Findings Demonstrating the Relationship between Smoking and Periodontium

The relationship between smoking and periodontal tissues was first reported by Pindborg in 1940s when he demonstrated that necrotizing ulcerative gingivitis was associated with tobacco consumption^{8,9}. Subsequently several epidemiological studies clearly demonstrated a strong association between tobacco use/ smoking habit and periodontal diseases in diverse populations^{10,11,12}. Evidence indicates that smokers have more severe periodontal disease, increased bone, attachment and tooth loss, gingival recession and pocket formation than non-smokers^{13,14}.

Heitz Mayfield in 2005 reported that cigarette smoking is a strong dose-related predictor of periodontal disease progression¹⁵. There is a higher prevalence and higher probability of periodontal disease in current smokers than in non and former smokers¹⁶. The number of pack years of smoking has a positive dose response correlation with periodontitis progression¹⁷.

Corraini et al using multivariate analysis demonstrated that smoking is a risk indicator for clinical attachment level ≥ 5 mm (odds ratio = 2.4) and for clinical attachment level ≥ 7 mm (odds ratio = 8.2)¹⁸. A multivariate linear regression model in 2010 demonstrated that age, gender, plaque index and tobacco consumption were associated with the extent of gingival recession¹⁹. Cigarette smokers have a significantly higher frequency of probing depth ≥ 4 mm and a higher incidence of severe periodontitis compared with non-tobacco users, after adjusting for age, gender and socioeconomic variables²⁰.

Although smokers may present with increased plaque accumulation and exacerbated disease progression, they show significantly less gingival inflammation and lower gingival crevicular fluid volume compared to non-smokers. It is presumed that smoking decreases gingival bleeding and crevicular fluid volume as a result of changes in the proportion of blood vessels and vascular alterations in periodontal tissues²¹.

4. Mechanisms by Which Tobacco Smoke Exerts Adverse Effects on the Periodontium

The actual cellular and molecular mechanisms that could precisely explain the exacerbated severity and progression of periodontitis in tobacco/cigarette users have not been completely elucidated. The possible mechanism of action of smoking on periodontal tissues seems to be the suppression of some essential mediators for pathogen elimination, as well as the exacerbation of some mediators involved in tissue destruction which, together, may lead to an enhanced susceptibility to periodontitis.

Possible Mechanisms

1. Microbiota
2. Gingival blood flow
3. Neutrophil dysfunction
4. Effect on T cells & B cells
5. Altered cytokine production
6. Fibroblast, osteoblast & periodontal cell function
7. Tissue degrading enzymes
8. Oxidative stress
9. Up-regulation of RAGE
10. Osteoclast activation
11. Gene smoking interaction
12. Role of nicotine

Microbiota

Several studies have investigated the effects of tobacco smoking on the occurrence and composition of subgingival microflora with contradictory results. It was demonstrated that smoking select for specific periodontal pathogens like *P.gingivalis*, *Treponema denticola* and *T.forsythia*, and this was proposed to increase the risk for development and progression of periodontal disease²². These findings were confirmed by Kazor et al and Haffajee & Socransky^{23,24}. However other studies could not observe significant differences between the subgingival microbiota of smokers and non-smokers^{25,26}.

A large study compared the microbial profile of 124 non smokers, 98 former smokers and 50 current smokers in shallow (probing depth \leq 4mm) and deep (probing depth $>$ 4mm) periodontal pockets using checkerboard DNA-DNA hybridization. The results showed that current smokers had significantly higher prevalence of *T.forsythia*, *Eubacterium nodatum*, *F.nucleatum*, *P.intermedia*, *P.micra*, *Prevotella nigrescens*, *P.gingivalis* and *Treponema denticola* than did former smokers or non smokers in shallow sites, where as no significant differences could be observed in deep pockets among the groups. The authors suggested that the reasons

for the differences in colonization pattern was unclear but might be attributable to the disease distribution in the study sample.

The conflicting evidence regarding the impact of smoking on the periodontal microbiota might be explained by differences in study design, sample population characteristics, definition of periodontitis, smoking status, population sampling methods and microbiological analysis. It might be argued that influence of smoking on periodontitis is not extensively mediated by changes in the microflora and that immunological changes in the host play a critical role in disease occurrence.

Gingival Blood Flow

Smoking leads to peripheral vasoconstriction, probably associated with low doses of nicotine²⁷. Vasoconstriction leads to reduced gingival bleeding, hence the observation of less gingivitis and gingival bleeding in smokers compared to non-smokers. This also might be the reason for the compromised microvascular response, which in turn could lead to reduced oxygen tension in the periodontal pocket and thus favour the overgrowth of anaerobes, such as *P.gingivalis* and *T.denticola*.

Neutrophil Dysfunction

Another line of evidence linking smoking to etiopathogenesis of periodontal disease is that smoking alters neutrophil function, mainly through the effects of nicotine. Some investigations have reported no major differences in the neutrophil profile between smoking and non-smoking subjects with periodontitis²⁸. On the other hand, Guntch et al in 2006 demonstrated that heavy smokers presented with a lower number of neutrophils and that the viability of neutrophils and their ability to phagocytose were lower in light, moderate and heavy smokers compared to non-smokers²⁹.

Cigarette smoke up-regulates the expression of adhesion integrin (CD11/18 integrin) and down-regulates the surface expression of selectin (L-selectin) on neutrophils. Alterations in F-actin kinetics may affect neutrophil functions, which may impact on the pathogenesis of periodontal diseases in smokers³⁰.

Effect on T Cells & B Cells

T-lymphocyte (CD4⁺ and CD8⁺) levels are lower in the gingival tissues of smokers compared to non-smokers³¹. Current evidence suggests a destructive effect of cigarette smoke on the T-cells, including a reduction in T cell proliferation and function, smoking induced immunosuppression and alterations in the proportion of the sub populations of CD4⁺ and CD8⁺ cells³². Smoking leads to increased numbers of CD3, CD4 and CD8⁺ T cell subsets in the periodontal tissues which in turn leads to increased periodontal breakdown³³. The serum levels of IgG, especially of the IgG2 subclass and IgA are significantly lower in smokers compared to non-smokers and healthy controls suggesting a possible suppression of B-cell function and immunoglobulin production. The above findings suggest that cigarette smoking may be associated with the suppression of the number and function of several

immune cells from the innate and adaptive responses, which may be a potential mechanism by which smoking exacerbates periodontal breakdown.

Altered Cytokine Production

Smoking induced functional changes in the main immune cells (neutrophils, macrophages, natural killer cells, mast and dendritic cells, eosinophils and B and T lymphocytes) indicate multiple intracellular signaling pathways as possible mechanisms to explain the effects of smoking on cytokine production in periodontal tissues. Nicotine per se stimulates the production of interleukin-6 and interleukin-8 and the association of high doses of nicotine with lipopolysaccharide synergistically up-regulates the production of these mediators³⁴. Giannopoulou et al using multiple linear regression analysis demonstrated that smoking was associated with increased levels of interleukin-4, interleukin-6 and interleukin-8 in gingival crevicular fluid³⁵.

The salivary levels of biomarkers like prostaglandin E₂, lactoferrin, albumin, aspartate aminotransferase, lactate dehydrogenase and alkaline phosphatase are found to be significantly lower in current smokers compared to non-smokers suggesting a possible role of smoking in suppressing the host-defense system¹⁷. Smoking subjects with periodontitis exhibit decreased amounts of proinflammatory cytokines (interleukin 1 α , interleukin-6 and interleukin-12), chemokines (interleukin-8, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 and RANTES) and regulators of T-cells and natural killer cells (interleukin-7 and interleukin-15) than non-smokers, suggesting an immunosuppressive effect of smoking on periodontal tissues which may contribute to the high susceptibility to periodontitis³⁶. Also the levels of interleukin 1 β in the gingival crevicular fluid are reduced in periodontally diseased sites in smokers, but are enhanced in smokers who are periodontally healthy. This suggests the possibility of an imbalance in cytokine production that may affect the pathogenesis of periodontal disease in smokers.

The molecular intracellular signalling of cytokine production as a mechanism which might be related to the modulation of inflammation by smoking involves in addition to activation of nuclear factor kappa B, a number of transcription factors, including GATA, PAX5 and Smad 3/4, which also have been implicated in smoking related inflammation³⁷. Smoking induced cytokine expression thus seems to be a complex and multistep system with participation and cooperation of multiple signalling pathways.

Fibroblast, Osteoblast & Periodontal Cell Function

Cigarette smoke condensate affects the proliferation of human gingival fibroblasts and increases the collagen degrading ability of these cells by changing the production and localization of matrix metalloproteinase and its inhibitors³⁸. Nicotine has been shown to negatively regulate the differentiation and mineralization of murine periodontal ligament cells, as the expression of extracellular matrix and osteoblastic transcription factor genes were reduced in these cells treated with nicotine³⁹. Periodontal ligament cells treated with various concentrations of cigarette smoke

extracts showed reduced survival and altered expression of molecules involved in the structural integrity of the ligament⁴⁰. Supplementation of osteoblast culture with nicotine and/or lipopolysaccharide increase the expression of matrix metalloproteinases 1,2 and 3 and tissue type plasminogen activator and decrease the expression of tissue inhibitor of matrix metalloproteinases 1,3 and 4⁴¹. Nicotine has also been shown to suppress the expression of bone sialoprotein in rat osteoblast like cells⁴². A lower serum concentration of osteoprotegerin and a higher ratio of receptor activator of RANKL/osteoprotegerin were observed in smokers than in non-smokers⁴³.

Tissue Degrading Enzymes

Increased release and diminished inhibition of tissue degrading enzymes such as collagenases and serine proteinases are essential for destruction of periodontal tissues. Smoking causes an elevation in the circulating levels of certain enzymes like myeloperoxidase, lysozyme, human neutrophil lipocalin and matrix metalloproteinases⁴⁴.

Studies have demonstrated that smokers with chronic periodontitis had significantly higher serum concentrations of myeloperoxidase and elastase and lower concentrations of tissue inhibitor of matrix metalloproteinases compared to non-smokers. However these differences were not seen in periodontally healthy individuals, regardless of smoking status. The matrix metalloproteinase 9/ tissue inhibitor of matrix metalloproteinase -1 ratio was also seen to be higher in smokers with periodontitis but not in periodontally healthy smokers. In addition to the elevated serum concentrations, tissue degrading enzymes have also been shown to be elevated in gingival crevicular fluid and in periodontal tissues.

In-vitro studies show that smoke and smoke components have an activating effect on leukocytes. Nicotine decreased chemotaxis and phagocytosis of neutrophils in a dose dependent manner while it increased degranulation and generation of eicosanoids on these cells. A decreased respiratory burst and increased degranulation in neutrophils are seen in smokers indicating a decreased ability to kill bacteria by the production of reactive oxygen species which contributes to increased release of tissue degrading enzymes and consequently tissue destruction⁴⁵.

Oxidative Stress

There is a relationship between oxidative stress, periodontitis and smoking related periodontitis. The possible mechanism may be an oxidant-anti oxidant imbalance which can cause progressive damage of the periodontal tissues. Polymorphonuclear cells in the infected sites produce reactive oxygen species (eg:- hydrogen peroxide and hydroxyl radical) when activated by inflammatory mediators and generate oxidative stress⁴⁶. In addition to this, neutrophils exposed to tobacco smoke display elevated destructive oxidative burst products, with the release of superoxide and hydrogen peroxide, which also may cause oxidative damage in several tissues⁴⁷. Systemic oxidative stress is associated with a decrease of total IgG and smoking is found to be an effect modifier of this association⁴⁸.

Up-regulation of RAGE

Another potential mechanism by which smoking may affect periodontal diseases is through the up-regulation of the receptor of advanced glycation end-products (RAGE). The biological function of RAGE is dependent on the presence of its various ligands (e.g. advanced glycation end products, S100-calcium binding protein, high-mobility group protein 1 etc)⁴⁹.

Smokers express a higher level of RAGE and the cells treated with normocotine present a time-dependent increase in RAGE expression, compared to non-smokers⁵⁰. These findings suggest that RAGE might be associated with periodontal disease related to smoking.

Osteoclast Activation

RANKL and osteoprotegerin are important modifiers of alveolar bone resorption. RANKL initiates osteoclast differentiation by activating the osteoclast progenitors and regulates the activity of mature osteoclasts. Osteoprotegerin inhibits osteoclast differentiation by binding to RANKL and blocking the RANK/RANKL interaction. Smokers have decreased levels of osteoprotegerin. Since there are contradictory reports on the levels of osteoprotegerin in the serum of smokers, this potential mechanism for the detrimental effect of smoking needs further investigation.

Reactive Oxygen Species

Another possible mechanism by which smoking affects periodontal tissues is by the generation of reactive oxygen species. It is suggested that one puff of cigarette contains up to 10^{17} oxidant molecules. These molecules are important for intracellular bacterial killing but may also cause destruction of extracellular tissues. The tissue destruction can be direct ie via increased oxidative stress or indirect, by inducing a pro inflammatory state⁵¹.

The literature regarding the effect of smoking on the generation of reactive oxygen species is inconclusive. Most studies investigating the effects of smoking have shown that smoking causes a reduction in the generation of reactive oxygen species⁴⁵. However, some recent animal and clinical studies have shown an increased generation of reactive oxygen species^{52,53}. Moreover, several studies have shown a systemic imbalance between oxidant-antioxidant levels as a result of decreased plasma levels of circulating antioxidants. Such reduction in antioxidants combined with increased numbers of activated leukocytes could contribute to periodontal tissue destruction.

Gene Smoking Interaction

It has been suggested that susceptibility to periodontal disease has a strong genetic component⁵⁴. However, the possibility of a gene-environment interaction between a specific genotype and smoking has not been explored for periodontitis. Some studies have shown an additive effect of a specific genotype and smoking. These studies investigated

a possible composite effect of interleukin 1 β C (3953/4) T polymorphism and smoking. The original study on this polymorphism indicated that smoking attenuated the effect of the genotype, while later studies showed an additive effect^{55,56}. A recent meta-analysis showed a significant association between the same polymorphism and chronic periodontitis⁵⁷. It has been shown that the combined effect of being genotype positive and smoking increased the risk of tooth loss by 7.7 fold⁵⁸ and the likelihood of having periodontitis from 2.4 to 4.5⁵⁹. However there was no increase in risk among non-smokers who were genotype positive. Another study showed that smokers positive for the high ligand - binding genotype of the Fc γ -receptor (Fc γ RIIa-H/H131) have more periodontitis than smokers not positive for this genotype and non-smokers positive for the genotype⁶⁰.

Role of Nicotine

The exact role of nicotine on periodontal inflammation is still unclear. Some in-vitro studies have shown that application of nicotine to various types of cultured cells induced an inflammatory response that could be of importance for the initiation and progression of periodontitis⁶¹. Animal studies have shown that systemic administration of nicotine increased alveolar bone loss in rats with ligature induced periodontal inflammation⁶². Another study showed that smoke extract increased the respiratory burst in neutrophils, where as nicotine and cotinine alone had no effect⁵³.

5. Effect of Passive Smoking

The effect of passive smoking on periodontal health has not been extensively studied. A study using the data from NHANES III reported that the odds of having periodontitis was 1.6 higher among individuals exposed to passive smoking after adjusting for sociodemographic factors, diabetes and dental care. Another study showed that passive and active smoking increased the likelihood of having periodontitis by 2.9- fold and 4.9- fold respectively after adjusting for other lifestyle factors. Exposure to passive smoke was associated with elevation of interleukin 1- β , albumin and aspartate aminotransferase levels in saliva⁶³. Taken together, the literature seems to indicate a relationship between passive smoking and destructive periodontal diseases. Further longitudinal studies are necessary to find out the role of passive smoking on immunological changes in the periodontium.

6. Conclusion

Although there are several possible mechanisms which could clearly explain the higher prevalence of periodontal disease and reduced healing seen in smokers, there is no clear evidence that points to one particular mechanism as being of greater importance. The response to smoking is likely to be mediated through a number of pathways, including a shift towards a more pathogenic subgingival flora, reduced microcirculation, dysfunction of neutrophils, production of proinflammatory cytokines and increased levels of pathogenic T-cells. Evidence indicates that smoking is an important risk factor for periodontal disease as well as for many other chronic diseases and events in

humans, including heart disease, stroke and cancer. Hence it is imperative for dentists to actively encourage their patients to engage in smoking cessation activities, which is a major key in improving their oral health as well as their overall health.

Conflict of Interest

There are no conflicts of interest or source of funding for this article.

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