

Smoking and periodontal tissues: a review*

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Abstract: The impact of smoking on general health has been widely studied and is directly related to several important medical problems including cancer, low birth weight, and pulmonary and cardiovascular disease. In the past 25 years, there has also been an increasing awareness of the role of cigarette consumption in oral health problems such as periodontal disease. Smoking is considered the major risk factor in the prevalence, extent and severity of periodontal diseases. This article will discuss the available evidence and provide the reader with an overview of the impact of smoking and its cessation on the pathogenesis and treatment of periodontal diseases.

Descriptors: Smoking Cessation; Smoking; Tobacco; Periodontitis; Periodontal Disease.

Introduction

It is estimated that tobacco use kills more than 5 million people per year. This means 1 in every 10 adult deaths worldwide. Smoking is a common risk factor in a number of chronic diseases, including cancer, lung diseases and cardiovascular diseases.¹

Smoking is the major risk factor in the prevalence, extent and severity of periodontal diseases.²⁻⁵ Cross-sectional studies have shown that smokers are two to seven times more likely to present periodontitis, compared to nonsmokers,^{2,6,7} and smoking has been associated with tooth loss during periodontal maintenance as well.^{7,8}

With respect to surgical or non-surgical periodontal therapy, several studies have shown that smokers have a worse response to treatment when compared to nonsmokers.^{9,10}

In southern Brazil,⁶ it has been estimated that smoking cessation programs could result in an approximate reduction of up to 12% in the number of cases of destructive periodontal disease (cases were defined as individuals with $\geq 30\%$ of teeth with periodontal attachment loss ≥ 5 mm). These statements draw attention to the extreme importance of implementing population-based smoking cessation programs both to increase general health (common risk factor approach)¹¹ and to decrease the prevalence of severe periodontal diseases in heavy smokers.

Owing to the significant impact of smoking on periodontal health, this study aimed at reviewing the literature regarding the negative effects of smoking on periodontal tissues, emphasizing the importance of smoking cessation to improve periodontal health and to benefit from the

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results of periodontal treatment.

Smoking and periodontal tissues Epidemiological studies

In the 1980s and 1990s several epidemiological studies established an association between smoking and destructive periodontal disease.¹²⁻¹⁵

Risk assessment based on an increasing body of investigations over the past few years suggests that tobacco-attributable risk odds ratios (OR) range between 2.5 and 6.0^{7,15,16} or are even over 6.0 in heavy smokers (e.g., > 20 cigarettes/day).¹⁵

The findings provided by Tomar and Asma,⁷ based on data from the NHANES III study, may be considered a strong body of evidence of smoking as a risk factor for periodontal diseases. In this study 12,329 subjects were evaluated, and the authors suggested that approximately half of the periodontitis cases in the USA could be attributed to smoking. In addition, they observed that current smokers were about 4 times more likely to be diagnosed with periodontitis than never-smokers, and that there was a dose-response relationship between the number of cigarettes smoked per day and the odds of periodontitis.

Clinical studies have demonstrated that smokers have more severe periodontal disease, with increased bone loss,^{17,18} greater periodontal attachment loss, more gingival recession and periodontal pocket formation.¹⁹ A patient's history of smoking has been associated with early attachment loss in adults.²⁰ In another study, cigarette smoking was considered a strong predictor of progressive periodontitis.²¹ Linden and Mullally²² found the odds ratio for periodontal disease to be as high as 14.1 for young smokers.

Brazilian epidemiological studies have also demonstrated this association. Susin *et al.*⁶ evaluated a representative sample of the Porto Alegre population (Rio Grande do Sul State, Brazil) and observed that smokers with moderate and strong dependence had 2.0 and 3.6 more risk, respectively, of having clinical attachment loss ≥ 5 mm than subjects who did not smoke. In another investigation, Lima *et al.*²³ concluded that smoking enhances bone loss resulting from periodontitis.

Recent studies have also suggested that passive smoking may be associated with periodontal diseases.²⁴⁻²⁶ Erdemir *et al.*²⁵ evaluated 109 children (range 6–12 years), classified as either exposed to passive tobacco (n = 51) or as unexposed (n = 58). The authors showed higher cotinine levels and greater attachment loss in passive smokers, when compared to unexposed children. Nishida *et al.*²⁶ conducted a 2-year longitudinal study and observed that passive smoking increases the salivary levels of albumin, aspartate aminotransferase and lactoferrin. The authors suggested that passive smoking may affect inflammatory response and may be associated with a greater risk for periodontitis progression. Although additional studies are necessary, it seems that passive smoking also affects periodontal health negatively.

Biological effects and events

Although the association between smoking and periodontal disease has been extensively demonstrated through epidemiological studies, the mechanisms by which smoking contributes to the pathogenesis of periodontitis have not yet been totally understood.

It has been reported that smokers may present a significantly greater plaque index and that the average number of bleeding sites in smokers (27%) is smaller than in nonsmokers (40%).²⁷ Microbiological studies showed that smokers had a higher prevalence of bacterial species related to periodontal disease compared to nonsmokers, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Bacteroides forsythus*,²⁸ *Prevotella intermedia*, *Fusobacterium nucleatum*. However, some authors reported no differences between smokers and nonsmokers with respect to the detection of periodontal pathogens,^{29,30} both in terms of prevalence³¹ and amount of bacteria³² in the subgingival microbiota. Recent studies, using real time PCR, have demonstrated a positive relationship between degree of smoking and amount of bacteria/probing depth.^{33,34}

The influence of smoking on experimental gingivitis was evaluated in a group of dental students³⁵ (the volunteers were free of periodontitis and not

on any medication, and the group of smokers had been smoking for at least four years). This study revealed that the number of gingival bleeding sites, the amount of gingival exudate and the number of gingival sites with distinct redness were significantly lower in smokers than in nonsmokers with comparable levels of plaque indexes. Bergstrom *et al.*³⁶ found that the intensity of vascular reaction after 28 days of plaque-induced gingivitis in smokers was only 50% of that observed in nonsmokers.

The preponderance of evidence suggests that smoking may decrease gingival bleeding and that this may occur owing to changes in the proportion of blood vessels in the periodontal tissues.³⁷

As an attempt to determine the mechanisms involved in smoking modulation of the periodontal tissues, *in vitro* and *in vivo* studies have investigated the impact of cigarette compounds, including nicotine and cotinine, on the periodontal tissues. In general, nicotine has been reported to adversely affect proliferation, attachment and chemotaxis of periodontal ligament cells, and induce pro-inflammatory cytokine production by human gingival fibroblasts synergistically with lipopolysaccharide from *Escherichia coli* and *P. gingivalis*.³⁸⁻⁴⁰

In a rat model, the impact of cigarette compounds on the periodontal tissues showed a greater bone loss in the ligated teeth of the groups that received nicotine when compared to the control group.^{41,42} This evidence suggests that nicotine alone could affect periodontal bone loss resulting from periodontitis.^{41,42}

Nicotine is just one of the toxic compounds of cigarette smoke. A passive smoking model was devised with the objective of investigating the impact of cigarette smoke as a whole on periodontal tissues.⁴³ It was demonstrated that cigarette smoke inhalation (CSI) enhances periodontal bone destruction in ligature-induced periodontitis. An additional analysis of gingival tissue adjacent to periodontitis sites showed that matrix metalloproteinase (MMP)-2 levels were higher in the exposed versus non-exposed animals. This finding suggests that MMP-2 may be one of the molecules responsible for the increased tissue degradation observed in the periodontal tissues of smokers.⁴³ In general, these results

suggest that nicotine seems to be a key molecule for the intensified periodontal destruction observed in smokers and may contribute, at least partially, to the negative impact of cigarette smoke as a whole.

Although a number of studies have considered smoking as a true risk factor for periodontitis, the mechanisms involved are still not clear. In an *in vitro* study, nicotine, both in and not in association with lipopolysaccharide (LPS) from periodontopathogenic bacteria, was shown to increase IL-6 and IL-8 protein production by human gingival fibroblasts.⁴⁰ A microarray analysis demonstrated that peripheral blood mononuclear cells exposed for 5 minutes to tobacco smoke presented an elevated expression of 20 genes previously reported to be associated with periodontal pathogenesis.⁴⁴

Higher levels of TNF- α and IL-8 were observed in the gingival crevicular fluid of smokers compared to nonsmokers.⁴⁵ In contrast, pro- and anti-inflammatory cytokines have been reported to be lower in association with smoking and its compounds. It seems that cigarette smoke contains potent inhibitors of both gene expression and protein production, at least for IL-1 β , IL-8, IL-2 and TNF- α .⁴⁶

Although significant, these studies do not provide an accurate description of the underlying mechanisms by which smoking affects the periodontium. In order to investigate possible mechanisms involved in the smoking modulation of periodontal attachment loss, César-Neto *et al.* investigated the profile of a number of pro- and anti-inflammatory cytokines plus pro- and anti-resorptive agents in the gingival tissues of smokers versus nonsmokers with moderate to severe chronic periodontitis. The following molecules were evaluated:

- IL-1 β ,
- IL-1ra,
- IL-6,
- IL-8,
- IL-10,
- interferon (INF)- γ ,
- TNF- α ,
- MMP-2 and -8,
- receptor activator of NF- κ B ligand (RANKL) and
- osteoprotegerin (OPG).^{47,48}

With respect to smoking modulation on gene expression, it was found that IL-1 β , IL-8, IL-10, TNF- α , MMP-8 and OPG were lower in smokers than nonsmokers, whereas IL-6, IL-1ra⁴⁷ and INF- γ ⁴⁸ were higher. Increased RANKL:OPG and IL-6:IL-10 ratios were found in sites with periodontitis in smokers versus nonsmokers, whereas the 1 β :IL-1ra ratio in smokers was similar to that observed in the healthy group⁴⁷ It was then concluded that smoking modulation of bone destruction in periodontal disease may involve reduced levels of anti-inflammatory and anti-resorptive factors such as IL-10 and OPG, respectively, and may also involve high levels of pro-inflammatory cytokines such as IL-6 and INF- γ .⁴⁷

Periodontal treatment in smokers

It has been demonstrated that smoking has an adverse influence on all forms of periodontal therapy, and that up to 90% of refractory periodontitis patients are smokers.⁴⁹

In the periodontal field, a number of clinical studies have compared the response of smokers and nonsmokers to various types of periodontal therapy, including both non-surgical and surgical therapies.⁵⁰ Most of the studies show significantly greater reductions in probing depths and bleeding on probing, and a significantly greater gain of clinical attachment after non-surgical and surgical treatments in nonsmokers, compared to smokers.⁵¹ A similar scenario is observed in the treatment of furcation regions⁵² and after regenerative procedures.⁵³

Recent studies have suggested that the adjunct use of local and systemic antimicrobial therapy may improve the clinical results obtained with scaling/root planing⁵⁴ and guided tissue regeneration in smokers.⁵⁵ Machion *et al.*^{56,57} showed that the association of scaling and root planing to local 10% doxycycline in the treatment of smokers with chronic periodontitis may lead to better clinical results than mechanical therapy alone.

Microbiological examination of these patients revealed that the adjunct use of locally delivered doxycycline after scaling and root planing may favor the elimination of *T. forsythensis* and *P. gingivalis* in a greater proportion of sites than conventional me-

chanical therapy.⁵⁸ These studies provide valuable information for dealing with the limitations of periodontal therapy in smokers.

Smoking cessation and periodontal tissues

There is clinical and histological evidence demonstrating that the negative effect of smoking on periodontal tissues may be reverted after quitting smoking. A histological study in rats showed that the interruption of smoke exposure would reverse the negative impact of cigarette smoke inhalation (CSI) on periodontitis-related bone loss.⁵⁹ Additionally, this study radiographically investigated the effect of CSI on mandibular bone quality.⁵⁹ The results revealed similar levels of bone loss for both the control and cessation groups, while the group continuously exposed to CSI presented significantly increased periodontal destruction.

Moreover, the radiographic findings regarding bone quality may be of particular relevance in the field of clinical implantology, since bone quality and smoking are well recognized factors associated with clinical implant failures. A complementary study was performed to confirm the radiographic findings and to investigate whether the figure observed for the basal mandibular bone would also occur in the tooth supporting alveolar bone.⁶⁰ Data analysis showed that animals continuously exposed to cigarette smoke inhalation presented a decreased proportion of mineralized tissue, when compared to the control and cessation groups, while both control and cessation groups presented similar results. These findings confirm the previous data regarding the mandibular basal bone showing a beneficial effect of smoking cessation on mandibular bone quality.

It is unclear how long after smoking interruption the body recovers its normal inflammatory conditions. Domagala-Kulawik⁶¹ reported that even after smoking cessation, many changes in the immune system (caused by tobacco) are still present. On the other hand, Bouloukaki *et al.*⁶² suggested that, there is an increase of CD8⁺ T-cells and a decrease of the CD4⁺/CD8⁺ within 6 months after smoking cessation. Morozumi *et al.*⁴⁶ state that it takes more than 8 weeks for levels of IL-1 β , IL-8, TNF- α and VEGF

to return to their normal values, and that the role (or function) of neutrophils is still not completely recovered after this period.

Morozumi *et al.*⁶³ and Nair *et al.*⁶⁴ reported an increase in gingival blood flow after smoking cessation, as observed with Laser Doppler flowmetry.

Fullmer *et al.*⁶⁵ conducted a 12-month longitudinal study that revealed the crucial role of smoking cessation in changing the subgingival biofilm and, consequently, the response to periodontal treatment. In this study, the authors concluded that smoking cessation promoted changes in the subgingival ecosystem, featured by changes in the levels of microbial species.

With respect to mechanical periodontal treatment, there are just two interventional clinical studies evaluating the benefits of quitting smoking on periodontal conditions after treatment.^{66,67} Both studies (one performed in the United Kingdom⁶⁶ and the other performed in Brazil)⁶⁷ conducted a 12-month prospective evaluation that assessed the adjunctive effect of smoking cessation on the non-surgical periodontal therapy of subjects with severe chronic periodontitis. Preshaw *et al.*⁶⁶ evaluated 49 smokers intending to quit smoking. All participants received non-surgical periodontal treatment and

smoking cessation therapy according to their individual needs. The authors concluded that smoking cessation promoted an additional benefit in reducing probing depth after non-surgical periodontal treatment. Rosa *et al.*⁶⁷ observed similar findings in a similar experimental design and with a sample (n = 93 subjects) larger than that used by Preshaw *et al.*⁶⁶ (n = 49). Rosa *et al.*⁶⁷ concluded that smoking cessation promoted clinical attachment gain after a one-year follow-up, in the quitters' group only. In addition, the magnitude of clinical attachment gains of sites initially > 4 mm was significantly greater in the quitters' group.

Conclusion

In light of the existing evidence, it can be concluded that smoking is a strong risk factor for periodontal diseases. The mechanisms by which tobacco use favors periodontal destruction still need complementary investigation to be better understood. It seems that a down-regulation of anti-inflammatory factors associated with an up-regulation of pro-inflammatory cytokines is involved. In addition, smoking cessation is the main option to revert the harmful effects of tobacco on periodontal risk and therapy.

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