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SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

Smoking and Periodontal Health

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Abstract

Purpose of Review Smoking is a strong and modifiable risk factor for periodontitis. The adverse effects of smoking on oral health are at the center of long-term studies. The aim of this review is to assess these effects with new findings.

Recent Findings Studies in different populations have demonstrated strong associations between smoking and severity of periodontitis. Additionally, researchers have observed similar effects in various types of smoking such as water pipe smoking and smokeless tobacco. Microbiological analyses recently have shown increased early colonization of periodontal pathogens in smokers. Lower levels of immunoglobulins and impaired fibroblast attachment to matrix proteins are new observations. Smoking markedly influences response to treatment, and smokers are resistant to conventional periodontal therapy. Implant failure and risk of peri-implantitis are higher among smokers.

Summary Latest data supports that severity of periodontitis is higher in smokers. Smoking cessation is beneficial for improving periodontal status and periodontal therapy outcomes.

Keywords Periodontal disease · Smoking · Risk factor · Immune response · Periodontal therapy

Introduction

It is known that smoking causes unfavorable effects in the body. The World Health Organization (WHO) reported that cigarette smoking is the leading cause of disease development, death, and poverty. The tobacco epidemic is one of the biggest public health problems in the world and causes more than 7 million deaths per year. More than 6 million deaths related to smoking are associated with direct tobacco use, while the remaining roughly one million deaths are second-hand smoke exposure. Although awareness of the adverse effects of smoking on health has increased in developed countries, smoking rates continue to rise in developing countries. According to WHO, about 80% of smokers around the world live in low- and middle-income countries [1].

The link between smoking and lung cancer was first highlighted in the US Surgeon General's Report in 1964 [2]. Since then, smoking has been linked to many other diseases. According to a report in 2014, smoking is associated with illnesses of almost all organs and for pregnant women, severe damage to the fetus is almost unavoidable. Investigators continue to identify health problems caused by cigarette smoking, including common diseases such as cardiovascular diseases, diabetes, rheumatoid arthritis, and colorectal cancer [3]. In addition to general health issues, smoking is a risk factor for oral cancer, oral mucosal lesions, and periodontal disease [4].

As a major risk factor, smoking affects the prevalence, extent, and severity of periodontal disease. Cigarette smoking causes alteration in the microbial composition of subgingival plaque samples. Smoking cripples immune response by changing neutrophil function, fibroblast activities, antibody production, and vascular factors. As a consequence of these effects, smoking adversely impacts the outcome of periodontal therapy and implant success [5].

Dental practitioners should inform patients about the side effects of smoking and encourage them to quit. In this review, the effects of cigarette smoking on periodontal disease, etiology, and periodontal treatment have been emphasized and some findings of recent studies have been highlighted.

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Smoking as a Risk Factor for Periodontitis

Smoking is a strong but modifiable risk factor for periodontitis. Several studies in the literature have assessed the relationship between smoking and periodontal disease. The common result observed in the 1990s and 2000s is that smoking increases the risk of periodontal disease. According to the data from these studies, exposure to tobacco smoke and magnitude of the risk are proportional [6–11].

Studies from different populations globally demonstrate the association between smoking and periodontal disease severity. For instance, from 2004 to 2006, oral epidemiologic data was collected to evaluate smoking-attributable periodontal disease in Australian population. Unadjusted analyses revealed that former and current smokers had significantly higher periodontitis prevalence than did never smokers. In addition, 32% of moderate-severe periodontitis was attributable to smoking [12]. Similar to Australian population, smoking Greek adults exhibited severe periodontal tissue destruction compared to non-smokers [13]. Severe periodontitis can result in loss of teeth. In Japan, oral examination of 1088 participants was conducted to estimate the effect of smoking on oral health status. The odds ratio of having more than eight missing teeth and having periodontitis among current smokers was 1.67 and 1.74, respectively. Findings demonstrate that smoking has a positive association with missing teeth and periodontitis [14]. Parallel with previous observations, Khan et al. [15] reported 3.5 times higher risk of chronic periodontitis among smokers in Pakistan.

According to a well-known epidemiological study, current smokers were about four times likely to have periodontitis after adjusting for age, gender, race/ethnicity, education, and income. In terms of dose-response relationship, heavy smokers had a greater risk than light smokers (odds ratios 5.6 and 2.8, respectively) [16]. More recently, data from 2009 to 2012 National Health and Nutrition Examination Survey were used to determine the risk indicators for periodontitis in US adults. Results showed that there was at least a 50% greater likelihood of periodontitis in current smokers [17••].

Exposure to second-hand tobacco smoke or passive smoking has been causally linked to cancer and respiratory and cardiovascular diseases. In addition, it also has adverse effects on the health of infants and children [3]. Second-hand tobacco smoke is also referred to as "environmental" tobacco smoke (ETS). Sutton et al. studied the association of ETS and periodontal disease. In this study, NHANES data from 2009 to 2012 examination cycle were checked to determine the prevalence of periodontitis among US non-smokers and to evaluate the influence of ETS exposure on the occurrence of periodontitis. There was a 28% increase in the odds of periodontitis for those with any ETS exposure. This study concluded that ETS increases an individual's risk of developing periodontitis [18]. Evaluation of passive smoking is often subjective but cotinine levels can be used for an objective measurement. For instance, periodontal health in children exposed to passive smoking was determined by measuring the cotinine levels of saliva, urine, and gingival crevicular fluid (GCF). Findings showed that children exposed to passive smoking have elevated levels of cotinine in their saliva concomitant with an enhanced attachment loss [19••]. Since passive smoking has serious health consequences, dentists should inform their patients about potential effects of smoking on their dental health.

All the findings mentioned above reveal that both direct tobacco consumption and second-hand tobacco smoke are important modifiable risk factors for periodontitis and contribute to the etiology of periodontal disease.

Clinical and Radiographic Findings in Smokers

Periodontal inflammation leads to tissue destruction. Clinically, damage to the surrounding tissues of teeth due to inflammation is observed as bleeding on probing, periodontal pocket formation, gingival recession, pathologic mobility, and loss of teeth. These clinical manifestations are intensified in the presence of risk factors associated with periodontitis.

In 1940s, Pindborg et al. demonstrated the association of tobacco consumption with necrotizing ulcerative gingivitis for the first time. In the following years, epidemiological studies presented sufficient evidence about detrimental effects of smoking on periodontal tissues such as increased bone loss, attachment loss, gingival recession, and teeth loss [20–23].

To assess the impact of smoking on bone loss, the distance between cemento-enamel junction and interdental septum was measured. That distance was significantly greater in current smokers (1.71 mm) than non-smokers (1.45 mm) [24]. Furthermore, Baljoon et al. showed that the severity of vertical defects was clearly associated with smoking after adjustment of age [25]. Later, Edman et al. analyzed the impact of tobacco and socioeconomic factors on alveolar bone loss in four cross-sectional studies done in the preceding 30 years in a Swedish adult population. Individuals (787–1133) were examined clinically and radiographically. Results revealed that smoking was the strongest factor associated with alveolar bone loss, and socioeconomic factors had limited impact on the severity of bone loss [26].

To understand the impact of smoking on the occurrence of calculus deposition, Bergstrom et al. compared calculus deposition between smokers and non-smokers. The prevalence rates of supragingival calculus deposition for current smokers, former smokers, and non-smokers were 86, 66, and %65 respectively. This effect was independent of age, plaque, and inflammation [27]. Moreover, the same author observed

clinically suppressed hemorrhagic responsiveness in smokers [28]. Additionally, increased gingival recession [29] and enhanced attachment loss [30] were observed in smokers more than in non-smokers.

GCF volume has been altered by smoking as well. Mokeem et al. found obviously lower GCF volume in smokers than non-smokers. Furthermore, these subjects have greater attachment loss and deeper periodontal pockets than do non-smokers [31]. Kibayashi et al. tested the long-term influence of smoking on periodontal health. Probing depths were recorded in 1999 and 2003. Results showed that 38.5% of periodontal progression was attributable to current smoking [32]. In addition to local oral effects, smoking can cause alterations systemically. Erdemir et al. observed poor periodontal parameters in smokers with chronic periodontitis and anemia. Moreover, the number of erythrocytes and the levels of hemoglobin, hematocrit, and iron were lower in smokers compared to non-smokers [33••].

Researchers have also observed the impact of smoking cessation on periodontal tissues. A cross-sectional study in Thai population showed that smoking cessation appears to be beneficial to periodontium. The odds of having severe periodontitis for current smokers were 4.8 times greater than non-smokers. The same ratio for former smokers was 1.8 [34].

Earlier studies generally evaluated the effects of tobacco smoke. However, recent research, within roughly the last 4 to 5 years, has focused on the effect of alternative smoking types. For instance, Javed et al. evaluated a group of water pipe smokers in terms of periodontal changes. Periodontal condition of water pipe smokers was observed to be as bad as tobacco smokers [35]. Similarly, Kulkarni et al. compared the effect of cigarette smoking and smokeless tobacco use on periodontal tissues. In this cross-sectional study, clinical parameters from smokeless tobacco users were similar to the smoking group [36••]. Katuri et al. aimed to determine the impact of various forms of tobacco consumption on periodontal health. Cigarette smoking or smokeless tobacco both negatively impacted periodontal status, and moreover, smokeless tobacco users had more attachment loss [37••]. Similar to previous studies cigar, pipe, and cigarette smoking were checked whether they were a risk factor for periodontitis and tooth loss. Different forms of smoking cause an increase in the prevalence of periodontitis, extent of attachment loss, and gingival recession compared to non-smokers. Consequently, cigar and pipe may have similar adverse effects on periodontal health and tooth loss as cigarette smoking [38]. Findings showed that long-term effects of different types of tobacco need to be evaluated.

Overall, previous and current clinical observations confirm the association between different forms of tobacco consumption and severe chronic periodontitis (Table 1).

Microbiological Findings in Smokers

Earlier investigations suggested that cigarette smoking does not affect bacterial flora [50, 51]; however, recent studies showed differences between microbial populations of smokers and non-smokers. Microbiological changes reflect detrimental influence of smoking on periodontal tissue breakdown. For this reason, it needs to be elucidated to what extent microbiological alterations exist between smokers and non-smokers.

Haffajee et al. evaluated the prevalence and proportions of the subgingival species among current, former, and non-smokers. They observed that species from red and orange complexes were significantly higher in current smokers. Interestingly, the difference is observed in areas with a probing depth of < 4 mm [52]. Similar to these findings, Eggert et al. also observed significantly higher levels of *P. gingivalis* and *P. intermedia* in probing depths ≤ 5 mm [53]. These observations confirm that smoking creates a favorable environment for pathogenic species especially in shallow sites.

More recent studies focused on microbial profiles and bacterial colonization in smokers (Table 2). By utilizing 16S sequencing, subgingival microbiome of smokers and non-smokers were compared. Smokers had higher levels of disease-associated pathogens like *Parvimonas*, *Fusobacterium*, *Campylobacter*, *Bacteroides*, and *Treponema* [57]. Kumar et al. identified the biofilm composition during plaque formation by 16S ribosomal RNA (rRNA) gene cloning and sequencing. Results showed that the characteristics of bacterial colonization in smokers were different than in non-smokers, and smoking induced early colonization of periodontal pathogens [58]. Recently, Karasneh et al. evaluated the impact of smoking on the subgingival bacterial profile in both healthy participants and chronic periodontitis patients. Higher odds were observed for *Treponema* species in chronic periodontitis patients [59].

Investigators studied the impact of smoking on the virulence of specific periodontopathogens. For instance, *P. gingivalis* cells treated with cigarette smoke extract induced a lower pro-inflammatory response from monocytes and peripheral blood mononuclear cells than did untreated cells [60]. Another study showed that cotinine, one of the major cigarette's derivatives, may cause increased *P. gingivalis* invasion in epithelial cells [61].These findings show that cigarette consumption may cause alterations in bacterial virulence.

Resilience to pathogenic organisms plays an important role in susceptibility to future diseases. Joshi et al. collected gingival plaque and GCF samples from smokers and non-smokers. The findings were early colonization of the pathogens, higher levels of pathogenic species, and enhanced pro-inflammatory response in smokers compared to non-smokers. These results suggest that smoking reduces the resistance of the ecosystem [62••].

Table 1 Summary of clinical findings on the association between smoking and periodontitis from 2015 to 2017

Reference	Sample size	Principal parameters evaluated	Principal findings
Dugue et al. [39]	578 (smoker166, non-smoker 412)	Clinical attachment loss Questionnaire about smoking Blood sample for serum cotinine levels	Serum cotinine showed greater association with severity of clinical attachment loss than self-report.
Katuri et al. [37]	120 (current smokers 40 smokeless tobacco 40 current smokers with habit of chewing smokeless tobacco 40)	Oral Hygiene Index-Simplified (OHI-S) and Community Periodontal Index (CPI) for Probing Depth (CPI-PD) and Attachment Loss (CPI-AL)	Smokers and smokeless tobacco users both have poor periodontal parameters. Smokeless tobacco users have more attachment loss.
Lee et al. [40]	18,488 (smokers periodontitis prevalence 35% non-smokers periodontitis prevalence 27%)	Questionnaire about smoking, drinking, andcommunity periodontal index	The prevalence of periodontitis in smokers and drinkers are significantly higher than only in smokers or only in drinkers.
Simila et al. [41]	5540 (current smokers 1757 former smokers 1525 never smokers 3062)	Number of teeth	Long-term smoking affects tooth loss even after cessation.
Khan et al. [15]	443 (smoker 244, non-smoker 199)	Probing depth	Smokers had 3.5 times higher risk of chronic periodontitis.
Jang et al. [42]	8336 (current smokers 1882 former smokers 1263 never smokers 5191)	Community periodontal index	Current smokers had higher risk of periodontitis than did non-smokers. Risk for disease presented a dose-dependent relationship with increasing pack-years.
Shereef et al. [43]	30 (current smokers 10 former smokers 10 never smokers 10)	Periodontal parameters	Current smokers presented greater probing depth and clinical attachment loss than former and non-smoker.
Dietrich et al. [44]	23,376 (current smokers 4394 former smokers 7268 never smokers 11.714)	Tooth loss	Smoking was associated with higher prevalence of tooth loss. The association was stronger in men than women and stronger in younger versus older individuals.
Lee et al. [45]	6011 (current smokers 6573 noncurrent smokers 3960)	Serum vitamin D concentrations Community periodontal index	Current smokers had a significant association between vitamin D deficiency and periodontal status.
Bibars et al. [46]	190 (cigarette smokers 30 water pipe smokers 72 dual smokers 50 non-smokers 38)	Periodontal parameters	Cigarette smokers, water pipe smokers and dual smokers were more likely to have periodontal disease compared to non-smokers. Water pipe smoking is not a safe way of smoking.
Kitagawa et al. [47]	36,110 (men 12.784; women 22.896 smokers 32.5–51.1% in men; 11.7–21.49% in women)	Medical check up Community periodontal index	Smoking, oral hygiene status, and factors related with metabolic syndrome are associated with periodontitis.
Ilhan et al. [48]	743 (current smokers 268 never smokers 475)	Community periodontal index Clinical attachment level	Among females, older age, low education status, smoking 11–40+ cigarettes a day, being employed and presence of high number of missing tooth surfaces were associated

Table 1 (continued)

Reference	Sample size	Principal parameters evaluated	Principal findings
			with attachment loss greater than 3 mm. Among males, attachment loss greater than 3 mm was related with older age, use of alcohol, and unemployment.
Sutton et al. [18]	Non-smoking 4329 adults	Probing depth Clinical attachment level	The odds of periodontitis increased 28% in non-smokers with any environmental tobacco smoke exposure than with no measurable exposure.
Carson et al. [49]	23,376 (current smokers 11.662 never smokers 11.714)	Tooth loss	Current smokers had more tooth loss than did former and non-smokers. Strong dose-dependent association between cigarette smoking and the risk of tooth loss was observed.

It is a known fact that periodontal therapy causes changes in the subgingival microbial profile. Haffajee et al. observed significantly decreased levels of *P. gingivalis*, *T. forsythia*, and *T. denticola* in non-smokers after scaling and root planing, but not in smokers [63]. Additionally, Meulman et al. demonstrated that supragingival periodontal therapy causes modest changes in smoker's subgingival biofilm but not in non-smokers [64]. Healing after therapy depends on sufficient reduction in periodontal pathogens. These findings may elucidate the inefficiency of scaling and root planing in smokers. Hence, dental practitioners should consider more efficient treatment approaches in smokers.

Immunoinflammatory Effects of Smoking on Periodontal Tissues

Studies indicate that tobacco use alters both the innate and adaptive immune response to periodontal pathogens [65, 66]. Although it is not clear which mechanism enhances the periodontal breakdown in smokers, investigators have found that there are alterations in neutrophil function, antibody production, fibroblast activities, vascular factors, and inflammatory mediator production.

Studies have evaluated the effects of tobacco products on different types of cells, including epithelial cells, immune cells, bone cells, and fibroblasts. They all agree that smoking causes harmful effects in the functioning of these cells. Guntsch et al. observed low levels of neutrophil viability and damaged phagocytosis function in smokers compared to non-smokers with evidence of a dose-response effect [67]. It has been shown that white blood cell count was higher in smokers than in non-smokers. Moreover, the serum folic acid concentration of smokers was lower than that of non-smokers [68••]. Another study observed inhibition of superoxide anion and hydrogen peroxide production in human blood neutrophils in response to nicotine treatment. This finding demonstrated negative impact of nicotine on the bactericidal activity of neutrophils [69].

Nicotine significantly inhibited human periodontal ligament fibroblast (HPDLF) proliferation and decreased protein synthesis in a dose-dependent manner [70]. Gamal et al. demonstrated a significant decrease of attachment in periodontal ligament cells in response to nicotine [71]. Impaired attachment of cells to root-planed surfaces suggests that smoking might affect periodontal therapy outcomes. Additionally, various studies have identified the harmful effects of nicotine on HPDLF functions such as proliferation, attachment, and chemotaxis [72–74]. Moreover, Tipton et al. found increased collagen breakdown by gingival fibroblasts in response to nicotine treatment [75]. Strong cell-extracellular matrix (ECM) interaction is important in cell survival. Recently, Lallier et al. demonstrated the effect of smoking on HPDLF-ECM

Table 2 Summary of current microbiological findings on the association between smoking and periodontitis

Reference	Findings
Coretti et al. [54]	16S rRNA sequencing was utilized to assess the subgingival microbiota in smokers and non-smokers with chronic periodontitis. Both smokers ($n = 6$) and non-smokers ($n = 14$) had higher levels of *Parvimonans, Desulfubulbus, Paludibacter*, *Haemophilus*, and *Sphaerochaeta*. A major microbial community change was evident in smokers, suggesting an association between smoking and severity of subgingival dysbiosis.
Medikeri et al. [55]	*Selenomonas sputigena* were detected by PCR in severe chronic periodontitis patients with ($n = 15$) or without smoking (n = 15) and periodontally healthy subjects ($n = 30$). There is no significant difference between periodontitis and healthy group. Smoking has no influence on *Selenomonas sputigena*.
Moon et al. [56]	16S rRNA sequencing was used to investigate subgingival bacterial species of smokers ($n = 57$) and non-smokers ($n = 36$) with moderate chronic periodontitis. *Fusobacterium*, *Fretibacterium*, *Streptococcus*, *Veillonella*, *Corynebacterium*, and *Filifactor* were abundant in smokers. On the other hand, *Prevotella*, *Campylobacter*, *Aggregatibacter*, *Veillonella*, and *Haemophilus* were less abundant in smokers. Species richness was more in smokers than non-smokers.

interactions. HPDLF exposed to cigarette smoke extract had lower level of attachment to fibronectin and type-1 collagen [76••].

T-lymphocyte levels were lower in gingiva of smokers than non-smokers [77]. Loos et al. showed that heavy smokers had elevated T-cell production [78]. Since the major function of B-cells is immunoglobulin syntheses, smoking and B-cell association were evaluated by studying immunoglobulin (Ig) levels. Lower serum levels of IgG and IgA were reported in smokers than non-smokers [79]. IgG2 is known to be protective against periodontal destruction. Granswickel et al. found that smokers have lower levels of total IgG and IgG2 than non-smokers [80]. Zeller et al. demonstrated that smoking causes decreased total IgG response against *P. gingivalis* strains which may enhance *P. gingivalis* infectivity [81]. Moreover, IgA, IgG, and IgM levels in the saliva of smokers were significantly lower than in non-smokers [82]. Decreased Ig level in salivary fluid of smokers may lower the host defense against periodontitis. These findings corroborate that in response to tobacco products, alterations have been seen in immune cells, and these changes shift towards destructive activities.

Inflammatory mediators have been assessed in smokers; however, inconclusive findings have been reported. GCF levels of TNF-α is higher in smokers than in non-smokers [83]. On the other hand, the same investigators did not find any significant changes in the GCF levels of interleukin-6, interleukin-1β, and interleukin-1 receptor antagonist in response to smoking [84]. In periodontally diseased subjects, the total amounts of IL-1β, IL-6, and IL-8 were significantly increased as compared to healthy controls, whereas IL-4 showed an inverse relationship to periodontal status and higher amounts were found in the control group. IL-6 and IL-8 levels were significantly correlated to smoking [85]. In contrast to these findings, Erdemir et al. did not observe any significant changes on the levels of TNF-α and IL-6 in the GCF of chronic periodontitis patients [86]. Javed et al. compared the whole salivary cytokine production among smokers and non-smokers with or without prediabetes. Among healthy subjects, IL-1β and IL-6 levels were higher in smokers than non-smokers. Among participants with prediabetes, the same cytokine levels were similar between smokers and non-smokers [87]. Wendell et al. demonstrated that nicotine can induce human gingival fibroblasts' IL-6 and IL-8 production. Moreover, nicotine in combination with LPS synergistically upregulates cytokine production. It seems that bacterial LPS and nicotine may induce pro-inflammatory fibroblast phenotype [88].

Investigators revealed that smoking influences bone metabolism as well. It is known that osteoprotegerin (OPG) suppresses osteoclastogenesis. Cigarette smokers have significantly lower levels of serum OPG than non-smokers do [89]. Similar to these findings, Ozcaka et al. found increased RANKL/OPG ratio in smokers [90].

Matrix metalloproteinases (MMPs) have an important role in tissue destruction. Katona et al. observed increased expression of MMP-1,-2,-3 and decreased expression of tissue inhibitor of matrix metalloproteinase (TIMP)-1, -3, -4 in osteoblasts treated with nicotine or in combination with LPS [91]. A recent study revealed significantly lower levels of PDGF-AB in GCF samples of smokers; however, MMP-1, MMP-8, TGF-β1, and VEGF levels did not show any significant difference [92]. Furthermore, significantly higher levels of MMP-9 were found in smokers compared with healthy controls. MMP-8 levels were elevated only in the diseased sites in smokers [93]. Another study assessed the impact of smoking on messenger RNA (mRNA) expression of MMP-8 and TIMP-1 in chronic periodontitis

patients and periodontally healthy participants. The authors observed significantly higher mRNA expression of MMP-8 in chronic periodontitis smokers compared to chronic periodontitis non-smokers [94]. Similarly, serum levels of MMP-9 were elevated and TIMP-1 decreased in smokers with chronic periodontitis. In addition to these changes, myeloperoxidase and neutrophil elastase levels were significantly higher in smokers [95].

Based on these findings, we can say that in general, smokers have decreased levels of mediators required for pathogen elimination and increased levels of mediators associated with tissue breakdown. This may explain the enhanced susceptibility to periodontitis in smokers.

Effects of Smoking on Periodontal Therapy

Complete wound healing is an important step to achieve the desired outcomes after periodontal therapy. Various animal studies have evaluated the impact of tobacco products on periodontal and peri-implant tissue healing. For instance, Benatti et al. created fenestration defects on the mandibular first molar region in rats. They found that cigarette smoke inhalation (CSI) caused significant negative impact on new bone formation [96]. Another group exposed animals to CSI and the expression of alkaline phosphatase, bone morphogenetic protein (BMP)-2 and -7, receptor activator of nuclear factor κB ligand, OPG were assessed. Except BMP-7, CSI significantly affected the expression pattern of all of the studied genes [97].

Clinical studies have investigated the response of smokers and non-smokers to different types of periodontal therapies. In general, consuming tobacco products causes poor clinical response [98–102]. A meta-analysis demonstrated that probing depth reduction was significantly greater in non-smokers than smokers, and clinical attachment level was not significant but the results favored outcomes in non-smokers [103]. The adverse effect of smoking is not limited to periodontal parameters in response to non-surgical therapy. Erdemir et al. found significantly lower level of folic acid and vitamin B12 in the serum samples of smokers following non-surgical therapy [104]. Since smoking reduces the effectiveness of non-surgical periodontal treatment, clinicians apply adjunctive antimicrobial agents to increase the effectiveness of treatment. For instance, Machion et al. assessed the clinical effects of locally delivered doxycycline as an adjunctive to scaling and root planing (SRP) in smokers and observed greater attachment gain in doxycycline gel-applied sites [105]. Minocycline microspheres (MM) were also applied with SRP in smoking subjects with periodontitis. Adjunctive use of MM significantly improved clinical outcomes after therapy. Moreover, MM reduced the number of red and orange complex bacteria in current smokers [106].

Systemic antimicrobial therapy adjunctive to SRP has been evaluated in smokers. Adjunctive use of azithromycin reduced probing depths and improved attachment level in smokers with periodontitis [107]. In another study, smokers with chronic periodontitis were treated with metronidazole and amoxicillin combination as an adjunctive to SRP. Antimicrobial combination improved both clinical and microbiological outcomes [108]. These observations showed that adjunctive use of antimicrobials either locally or systemically is important to deal with the limitations of SRP in smokers.

Some studies evaluated the impact of smoking on soft tissue grafting and periodontal-regenerative therapies. Results revealed that smokers exhibit less amount of root coverage than non-smokers do [109]. In addition to soft tissue interventions, surgical therapies of periodontal bone defects and furcation problems in smokers were examined in various studies. For example, Class II furcation defects were treated with polytetrafluoroethylene membrane both in smokers and non-smokers. During the follow-up period, smokers had significantly higher residual defects than did non-smokers [110]. Yilmaz et al. utilized platelet-rich plasma combined with bovine-derived xenograft in intrabony defects of smokers and non-smokers. Healing was compromised in smokers [111]. A meta-analysis reported that smoking causes negative impact on bone regeneration and less bone gain in two- or three-wall intrabony defects treated with guided bone regeneration [112]. Supportive periodontal therapy following regenerative treatments maintains clinical outcomes; however, it is unsatisfactory in smokers. For instance, Matuliene et al. observed less progress in disease sites during supportive periodontal treatment in smokers [113].

Smoking has been known as a pre-disposing factor in implant failure [114]. Various studies focused on the outcomes of implant therapy in smokers. After three or more years following the installation, Lambert et al. observed 8.9% implant failure in smokers. For non-smokers, it was 6%. The same authors also reported that use of preoperative antibiotics reduced failures in smokers [115].

A recent study compared peri-implant soft tissue parameters and bone loss around immediately loaded and delayed loaded implants in smokers and non-smokers. Tobacco products increased inflammation and bone loss around implants. Nevertheless, loading protocol did not cause a significant change on hard and soft tissues in healthy smokers or non-smokers [116••]. A meta-analysis compared the implant failure rate between smokers and non-smokers and reported higher implant failure in smokers [117]. Gurlek et al. observed more peri-implantitis and mucositis cases among smokers than non-smokers. Furthermore, suppuration, bleeding, and plaque scores around the implants were significantly higher in smokers [118••].

Some studies focused on the impacts of smoking on peri-implant health status. A cross-sectional study evaluated the

Table 3 Summary of some current studies related to therapeutic outcomes in smokers and non-smokers

Reference	Type of periodontal therapy	Outcome
Sharma et al. [121]	1% alendronate (ALN) adjunct to SRP for the treatment of chronic periodontitis in smokers ($n = 46$).	1% ALN stimulated a significant increase in probing depth reduction, attachment gain, and an improved bone fill compared to placebo gel.
Javed et al. [122]	Mechanical debridement (MD) with and without adjunct antimicrobial photodynamic therapy (aPDT) in peri-implant inflammation among smokers ($n = 84$) and non-smokers ($n = 82$).	MD with adjunct aPDT is more effective in reducing peri-implant probing depth than MD alone in smokers and non-smokers in short-term. In the long term, outcomes of MD either with or without aPDT findings are comparable.
Camargo et al. [123]	Oral hygiene education and SRP in smokers ($n = 24$) and non-smokers ($n = 24$).	Treatment lowered the levels of periodontopathogens after 3 months for non-smokers and after 6 months for both groups. The prevalence of Candida species was significantly higher in smokers than in non-smokers at all time points.
Bunaes et al. [124]	Non-surgical and surgical periodontal therapy in smokers ($n = 40$) and non-smokers ($n = 40$).	Smokers showed less improvement in clinical parameters in response to non-surgical and surgical periodontal therapy compared with non-smokers, in particular at plaque-positive sites.
Reino et al. [125]	Heavy smokers ($n = 20$) with gingival recessions treated. One side received a coronally positioned flap (CPF), while the contralateral side received the extended flap technique (EFT), both procedures carried out in conjunction with a subepithelial connective tissue graft (SCTG).	Regardless of the technique used, heavy smoking markedly limits root coverage.

peri-implant crevicular fluid of regular follow-up patients. Clinical parameters including gingival index, probing depth, peri-implant bone loss, and peri-implant crevicular fluid volume were significantly higher in smokers; the only exception was plaque scores. Moreover IL-1β, TNF-α, and PGE2 levels were increased in smokers. Clinical parameters and the cytokine levels are positively correlated in smokers. Findings suggest that implants are relatively at risk in smokers, even if they seemed to be healthy [119]. Ata-Ali et al. also evaluated peri-implant crevicular fluid of heavy smokers. Heavy smokers had poorer clinical parameters, greater number of periodontal pathogens, and elevated cytokine levels; however, these alterations in smokers were not statistically significant [120]. Further studies are needed to delineate the effects of smoking on implant therapy.

Smokers are more likely to have periodontitis than non-smokers, and overall findings suggest that smoking affects adversely periodontal and implant therapies. Dental professionals should help smokers quit tobacco products and offer them information about cessation treatment (Table 3).

Conclusion

It is known that consumption of tobacco products cause harmful effects on oral tissues. Several studies reported that smoking enhances the susceptibility to periodontal disease, and the severity and progression of the disease depends on the dose as well as the frequency of exposure. Despite the enhanced severity of disease in smokers, clinical signs of inflammation are less prominent. Since gingival inflammation is suppressed in smokers, clinicians should be attentive in detecting diseased sites. Microbiological profile in smokers seems to be different than in non-smokers. Changes in microbial composition decrease resistance of the microenvironment. The underlying immune-inflammatory mechanisms of the periodontitis in smokers have not been totally understood yet. Current literature supports the notion that altered immune response seems to have an important role in the pathogenesis. Changes in microbiome and inflammatory response result in unsatisfactory outcomes of non-surgical, surgical, and implant therapy. To improve the outcome of treatments, adjunctive antimicrobial approaches could be suggested to treat periodontal disease in smokers. As an important part of health system, dental practitioners should inform patients about the beneficial effects of smoking cessation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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