Clinical Periodontal Parameter of Smokers with Periodontitis in Asia Following Periodontal Therapy: An Update Systematic Review and Meta-Analysis

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Abstract

Cigarette smoking is a well-established risk factor for periodontitis. The high prevalence of smoking in Asia therefore could affect the severity of periodontal disease and the outcome of periodontal therapy in Asia. This systematic review and meta-analysis aims to determine the clinical periodontal parameter of smokers with periodontitis in Asia following periodontal therapy. The protocol has been registered to PROSPERO database (CRD42020201607). Literature search followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guideline through electronic databases (PubMed, Scopus, EBSCO).

A total of 868 studies were identified from the electronic databases. Title and abstract were screened from the 415 remaining studies, and 357 irrelevant studies were excluded. Full text from the remaining 58 studies were assessed for potential eligibility, and only 19 studies met the inclusion criteria. Statistical Analysis used: Meta-analysis using random-effect model was performed using Exploratory Software for Confidence Intervals (ESCI) software.

Meta-analysis results for changes in periodontal pocket depth (PPD) demonstrated a reduction in periodontal pocket depth in both smokers and non-smokers group, with a mean difference of -0.83 mm (95% CI: -1.23 mm; -0.43 mm) and a mean difference of -1.13 mm (95% CI: -1.53 mm; -0.73 mm), respectively. Meta-analysis results for changes in clinical attachment level (CAL) demonstrated a gain in clinical attachment level (CAL) in both smokers and non-smokers group, with a mean difference of -0.98 mm (95% CI: -1.40 mm; -0.56 mm) and a mean difference of -0.97 mm (95% CI: -1.57 mm; -0.38 mm), respectively.

Smokers with periodontitis in Asia shows less reduction in periodontal pocket depth, indicating that smoking has a negative effect on the outcome of periodontal therapy.

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Introduction

Periodontitis is an inflammatory disease within the supporting tissues of the teeth, resulting in progressive destruction of the periodontal ligament and alveolar bone. [1,2] The destruction leads to loss of periodontal attachment and the formation of periodontal pocket .[3] Several risk factors affect the progress and onset of periodontitis, where cigarette smoking is one of the most important risk factor for periodontitis .[4] A meta-analysis study showed that smokers had approximately 80% higher risk for periodontitis than quitters and never-smokers.[5] Smoking can increase the risk of clinical attachment loss two to eight fold .[6] Smokers also have higher mean of probing depth and greater gingival recession compared to non-smokers.[6] Periodontitis initiation and progression depends on dysbiotic ecological changes in the microbiome, that is influenced by smoking. Smoking makes the dysbiotic microbiome changes more likely for some patients than others, and likely influence the severity of the disease.[3]

Prevalence of the periodontal disease varies in different regions of the world, and a

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higher prevalence and severity of periodontal disease is seen in Asian countries. [7,8]Tobacco smoking and betel chewing phenomenon in Asia are risk factors associated with the high prevalence and severity of periodontal disease in this region .[9] In 2015, more than 1.1 billion people in the world were smokers, dominated by men.[10] Global Burden of Disease Study 2015 reported that the global prevalence of current smoking in men is 25%, half of whom live in 3 Asian countries - China, India, and Indonesia .[11] Periodontal therapy is needed to treat periodontitis in smokers. However, smoking habit can also affect the response to periodontal therapy. Several studies have stated that the healing process of periodontal tissue after periodontal therapy is worse in smokers than in nonsmokers.[12–15] This can be related to the high quantity of Gram-negative bacteria in smokers compared to non-smokers.[16,17] Dysbiosis of the periodontal microbiome was presented in smokers despite of their periodontal condition and remained significant only in smokers even after the reduction of clinical signs of periodontitis with non-surgical periodontal treatment and over 3 months post-therapy. [18] Kanmaz, et al. also showed that smoker patients exhibit faster recolonization of Gram-negative bacteria in subgingival plaque samples 6 month after periodontal therapy .[17] Recurrence of periodontal disease is more common in smokers than in nonsmokers.

An appropriate strategy is needed to address the severity of periodontal disease in the Asian region [19]. This meta-analysis is devoted to studies conducted in Asia, so as to evaluate the results of periodontal therapy to treat smokers with periodontitis in the Asian region.

Materials and methods

Registration Protocol

This systematic review and meta-analysis protocol has been registered to PROSPERO database, under the registration number CRD42020201607.

Search Strategy

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guideline. Literature searches were performed on three electronic databases: PubMed, Scopus, and EBSCO. The publication period was restricted from August 2005-August 2020. Only full paper publication written in English were selected. The following search terms were “smoking”, “smokers”, “periodontitis”, “periodontal therapy”, “non-surgical periodontal therapy”, “periodontal flap”, “supportive periodontal”. References from eligible studies were scrutinized to identify additional studies.

Inclusion and Exclusion Criteria

The inclusion criteria for this study: (1) controlled clinical trials, randomized controlled trials, case-control studies, and cohort studies, (2) Studies conducted in Asia, (3) Published between 2005-2020, (4) Full paper publication written in English, (5) Studies that categorized subjects into ≥2 groups, include smoker and non-smoker with periodontitis, (6) Studies that report the periodontal pocket depth (PPD) and clinical attachment level (CAL) of smokers and non-smokers with periodontitis, before and after periodontal therapy. The exclusion criteria for this study: (1) Case series, case report, animal studies, cross sectional studies, (2) Studies that include patients with systemic condition and antibiotic consumption in the last 3 months.

Risk of Bias

Risk of bias of included studies were assessed by two independent reviewer using RoB 2.0 tool for randomized controlled trial and ROBINS-I tool for non-randomized intervention or controlled clinical trials. Risk of bias in RoB 2.0 tool is judged with “low”, “moderate”, and “high”, meanwhile in the ROBINS-I tool is judged with “low”, “moderate”, “serious”, and “critical”.

Data Synthesis and Statistical Analysis

The qualitative synthesis was presented in a summary table, consisting of the first author’s name, publication year, demography data, periodontitis criteria, smokers criteria, intervention, and follow-up. Clinical periodontal parameters data such as periodontal pocket depth and clinical attachment level were presented in Supplementary Table 1 and Supplementary Table 2. Meta-analysis using random-effect model was performed using Exploratory Software for Confidence Intervals (ESCI) software (Cumming, 2012), for each main outcome (PPD and CAL). Results were presented with forest plot of mean difference and 95% confidence interval (CI).

Results

Study Selection

A total of 868 studies were identified from the electronic databases (Fig. 1). Duplicated studies from those electronic databases were removed. Title and abstract were screened from the 415 remaining studies, and 357 irrelevant studies were excluded. Full text from the remaining 58 studies were assessed for potential eligibility, and only 19 studies met the inclusion criteria.

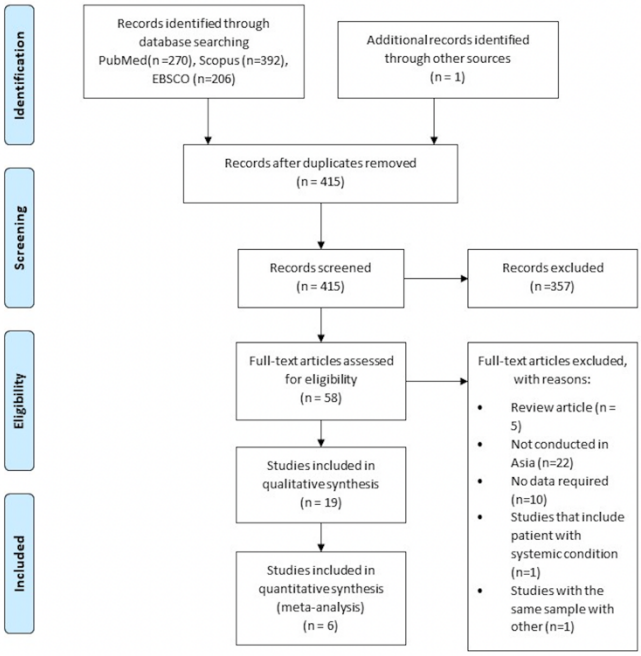

Figure 1. PRISMA flow diagram.

Characteristics of Included Studies

Nineteen studies met the inclusion criteria, that were published between 2008-2020 (Table 1). This systematic review and meta-analysis consist of studies that were carried out in Asia, with one study in Japan, one study in Hong Kong, one study in China, one study in Saudi Arabia, seven studies in India, and eight studies in Turkey. Of the 19 studies that were included, 17 studies were non-randomized intervention, and 2 studies were randomized controlled trial. The participants were dominated by male patients. The age of patients in included studies ranged from 18-80 year. All of the included studies stated the periodontitis patient criteria, with 18 studies include patient that is diagnosed based on the AAP 1999 classification, and 1 study include patient that is diagnosed based on the AAP 2017 classification.

There is a wide variation in smokers criteria among studies. Number of cigarettes per day and the smoking duration ranged from ≥5 cigarettes per day for at least 3 years, to ≥10 cigarettes per day for at least 10 years. Of the total of 19 studies, 17 studies categorized patient based on a self-reporting smoker's history or self-questionnaire, and 2 studies categorized patient based on a self-questionnaire and cotinine level measurement.18 studies were non-surgical periodontal therapy, and 1 study was regenerative therapy with platelet rich plasma combined with bovine derived xenograft.

Risk of Bias

The risk of bias assessment using the ROBINS-I tool was conducted in 17 studies with a non-randomized intervention design (Supplementary Fig. 1). A total of 11 studies have a low risk of bias, namely the study conducted by Ikezawa-Suzuki I, et al. (2008), Toker H, et al.(2012), Hendek MK, et al. (2015), Aziz, et al. (2015), Meenawat A, et al. (2015), Akbari G, et al. (2015), Turkoglu O, et al. (2016), Guru S, et al. (2018), Varghese J, et al. (2020), Kanmaz, et al. (2020), Hendek, et al. (2020) .[17,20–28] Six studies had a moderate risk of bias, namely the study conducted by Wan, et al. (2009), Buduneli N, et al. (2009), Mittal S, et al. (2017), Jiao J, et al. (2017), Padhye N, et al. (2019), Yilmaz S, et al.(2010). [12,29–33]

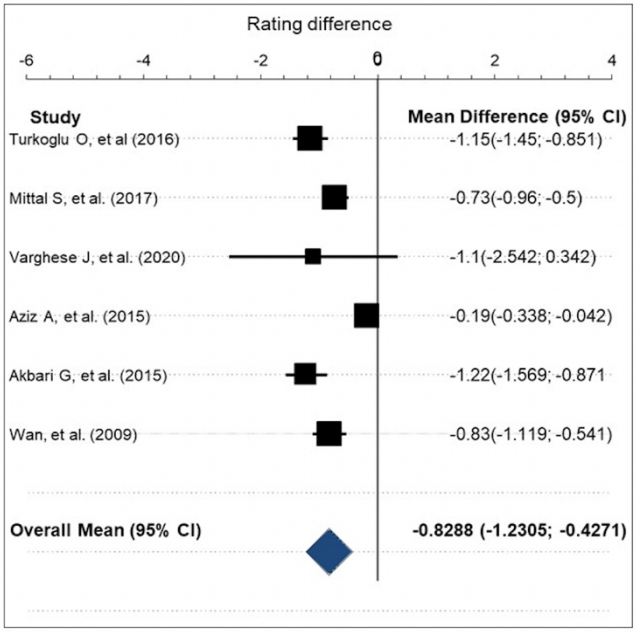

Figure 2. Forest Plot for Changes in Periodontal Pocket Depth in Smokers (3 Month Follow-Up).

This systematic review consists of two studies with randomized controlled trial, which were assessed using the RoB 2.0 tool (Supplementary Fig. 2). These two studies, namely the study conducted by Pamuk F, et al. (2017), and AlAhmari F, et al. (2019) has a low risk of bias. [34,35]

Clinical Periodontal Parameters

A total of 19 studies that reported changes in pocket depth following periodontal therapy in smokers and non-smokers were included in this study. PPD in 16 studies were reported with mean (Supplementary Table 1), while in the other three studies were reported with median (Supplementary Table 2). Twelve studies conducted biochemical analysis of GCF samples before and after periodontal therapy in both smokers and non-smokers group (Supplementary Table 3).

PPD data in smokers and non-smokers from six studies were included in the meta-analysis. Data from other studies could not be included in the meta-analysis because of differences in study design, differences in follow-up time, and unavailability of mean and standard deviation. Meta-analysis for changes in pocket depth after periodontal therapy were performed in studies that had the same design, namely non-randomized intervention and at 3-month follow-up. Studies that would be included in the forest plot were Turkoglu O et al. (2016), Mittal S, et al. (2017), Varghese J, et al. (2020), Aziz A, et al. (2015), Akbari G, et al. (2015), and Wan, et al. (2009). [12,23–25,27,30]

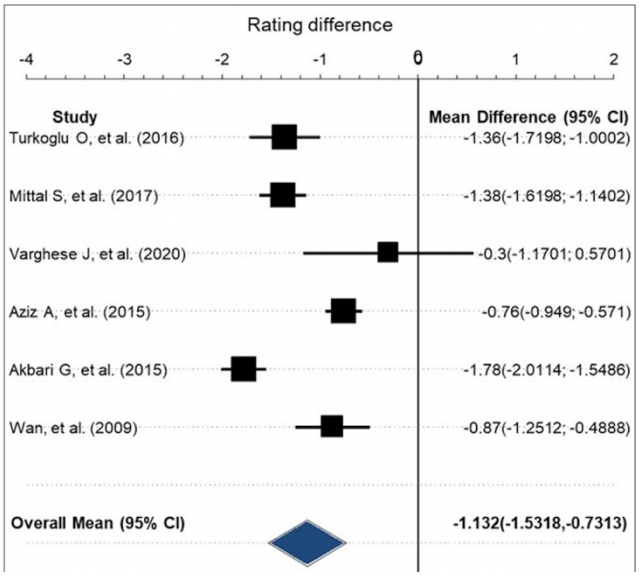

Figure 3. Forest Plot for Changes in Periodontal Pocket Depth in Non-Smokers (3 Month Follow-Up).

The results of the meta-analysis using the random effects model showed a significant reduction in pocket depth after periodontal therapy in smokers, with a mean difference or overall mean value of -0.8288 mm (95% CI: [-1.2305 mm; -0.4271 mm], p<0.001) (Fig. 2). The results of the meta-analysis using the random effects model also showed a significant reduction in pocket depth after periodontal therapy in non-smokers with a mean difference or overall mean of -1.132 mm (95% *CI*: [-1.532 mm; -0.731 mm], p<0.001) (Fig. 3). The overall mean value in both groups indicated that after periodontal therapy, the nonsmoking group experienced a higher pocket depth reduction compared to smokers.

Twelve of the 19 studies included in this study reported clinical attachment level data before and after periodontal therapy, in the smokers and non-smokers groups. Eight studies reported the mean and standard deviation, one study only reported the mean, (Supplementary Table 1) while the other three studies reported the CAL with median (Supplementary Table 2).

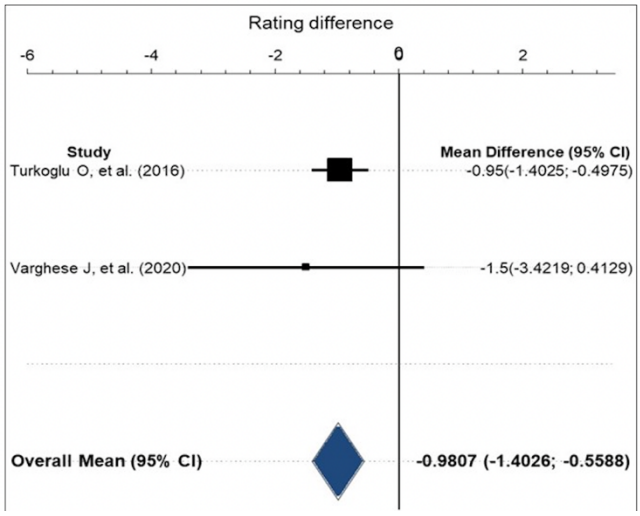

Figure 4. Forest Plot for Changes in Clinical Attachment Level in Smokers (3 Month Follow-Up).

Data on changes in clinical attachment levels in smokers from two studies were included in the meta-analysis. Data from other studies could not be included in the meta-analysis because of differences in study design, differences in follow-up time, and unavailability of data in mean and standard deviations. Meta-analysis for changes in clinical attachment levels

after periodontal therapy in smokers and nonsmokers were carried out in studies that had the same design, namely non-randomized intervention and at 3-month follow-up.

The results of the meta-analysis using the random effects model showed a significant improvement in CAL after periodontal therapy in smokers with a mean difference or overall mean of -0.9807 mm (95% CI: [-1.4026 mm; -0.5588 mm], p<0.001) (Fig. 4). The results of the meta-analysis using the random effects model as well showed a significant improvement in CAL after periodontal therapy in nonsmokers with a mean difference or overall mean of -0.9746 mm (95% CI: [-1.566 mm; -0.383 mm], p<0.001) (Fig. 5). The overall mean value in the two groups indicated that after periodontal therapy, the nonsmokers group experienced a lower CAL gain compared to smokers.

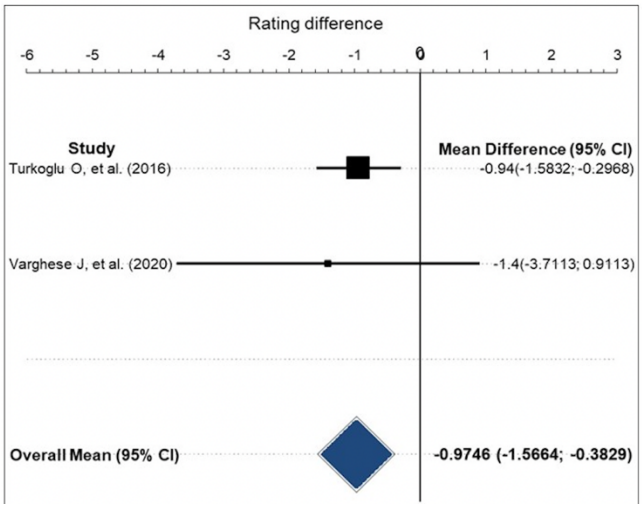

Figure 5. Forest Plot for Changes in Clinical Attachment Level in Non-Smokers (3 Month Follow-Up).

Discussion

Periodontitis can be influenced by various risk factors, smoking is one of the most influential risk factors. Smoking habit is one of the risk factor associated with the high prevalence and severity of periodontal disease in the Asian region.[9] This systematic review and meta-analysis aims to determine the clinical periodontal parameter of smoker with periodontitis in Asia following periodontal therapy, so as to evaluate the results of periodontal therapy to treat smokers with periodontitis in the Asian region.[7]

This meta-analysis study begins with a qualitative synthesis or systematic review. There were 19 studies included in the systematic review, 17 studies were non-randomized intervention and two studies were randomized-controlled trial. A total of 18 studies were non-surgical periodontal therapy, and other study was surgical periodontal therapy. The follow-up of each study that was included varied, namely 1 month, 2 months, 3 months, 6 months, and 12 months. This systematic review and meta-analysis study showed that there was a reduction in pocket depth after periodontal therapy, in both smokers and non-smokers. The reduction in pocket depth was seen in all follow-ups, namely 1 month, 2 months, 3 months, 6 months, and 12 months' follow-up.

The meta-analysis study showed that the reduction in pocket depth in smokers was worse (-0.8288 mm; 95% CI: [-1.2305 mm; -0.4271 mm], p <0.001) compared to non-smokers. (-1.132 mm (95% CI: [-1.532 mm; -0.731 mm], p <0.001). This supports the theory that smoking has a negative effect on periodontal therapy. The results of this study support previous research conducted by Labriola. et al. regarding the effects of smoking on non-surgical therapy of periodontal.[36].Labriola, et al. conclude that smoking has a negative impact on non-surgical periodontal therapy, with a weighted mean difference between smokers and nonsmokers of 0.433 mm.[36]

Smoking is an important risk factors on periodontal disease. Several studies have shown that smokers have a higher pocket depths compared with non-smokers.[13,37,38] This is also supported by the periodontal pocket depth data obtained in the included studies in this meta-analysis. Thirteen out of 19 studies, which were included in a qualitative synthesis or systematic review, showed higher pocket depth in smokers prior to periodontal therapy, eight of which, showed significant differences between the smokers and nonsmokers groups.[20,22,23,26,28,30,32,39] Clinical periodontal parameters before and after periodontal therapy were worse in smokers than non-smokers, regarding the effect of smoking on the response immune-inflammatory of the host.[6,40]

Twelve studies that were included in this study conducted an analysis of inflammatory biomarkers in the smokers and non-smokers groups. Aziz, et al. conducted an analysis of

levels of IL-10, an anti-inflammatory cytokine and IL-6, a pro-inflammatory cytokine.[23] Oxidative stress markers such as superoxide dismutase, GPx (glutathione peroxidase), and malondialdehyde were also investigated in this study. The results of this study indicated that prior to periodontal therapy, malondialdehyde was significant ($p < 0.05$) higher in smokers, whereas levels of IL-6, C-Reactive protein, and superoxide dismutase were higher in smokers, but there was no significant difference. The high level of these biomarkers in smokers compared to non-smokers indicated that the periodontal tissue damage was worse in smokers. Meanwhile, markers such as IL-10, GPx (gluthatione peroxidase), and vitamin C levels were worse in smokers. This study shows that there is an improvement of these inflammatory biomarkers after scaling and root planing was performed. Scaling and root planing significantly increased IL-10, GPx activity, and vitamin C levels in both groups. Meanwhile, other biomarkers such as IL-6, C-reactive protein, malondialdehyde, and superoxide dismutase decreased significantly after scaling and root planing. These results show improvements in inflammatory biomarkers in smokers and non-smokers, but improvements in these biomarkers are worse in smokers.[23] Studies conducted by Padhye et al. also performed an analysis of levels malondialdehyde in the saliva of smokers and nonsmokers, where malondialdehyde levels were higher in smokers prior to periodontal therapy. After periodontal therapy, there was a reduction in levels in malondialdehyde both groups, but the levels of malondialdehyde in smokers were still high.[32]

Akbari, et al. showed that the reduction in pocket depth after periodontal therapy was higher in non-smokers than in smokers, indicating the presence of sites of persistent inflammation. This is also supported by the MMP-8 analysis conducted in this study. MMP-8 is a matrix metalloproteinase associated with collagen breakdown in periodontal tissues, seen on GCF and saliva from periodontitis patients. This study showed that MMP-8 in smokers was higher than in non-smokers, but that the reduction of MMP-8 after periodontal therapy was higher in non-smokers.[24]

This systematic review and meta-analysis also showed an improvement in clinical attachment level in the smokers and nonsmokers groups. The improvement in clinical attachment level was seen at all follow-ups, namely 1 month, 2 months, and 3 months' follow-up. The results of the meta-analysis in the smokers group showed that there was a significant improvement in the clinical attachment level after periodontal therapy, namely -0.9807 (95% CI: [-1.4026; -0.5588], $p < 0.001$). The results of the meta-analysis in non-smokers also showed that there was a significant improvement in the clinical attachment level, namely -0.9746 (95% CI: [-1.566; -0.383], $p < 0.001$). Both overall mean indicated that there was a significant improvement of clinical attachment level in smokers and nonsmokers after periodontal therapy, but the improvement in the clinical attachment level after periodontal therapy in non-smokers was worse than smokers. These results are consistent with previous research, conducted by Labriola, et al. regarding the effects of smoking on non-surgical periodontal therapy.[36] Studies conducted by Labriola, et al. showed that smoking had a negative effect on non-surgical periodontal therapy, but it was only associated with a higher reduction in pocket depth in nonsmokers, whereas the mean difference of improvement in clinical attachment level between smokers and nonsmokers showed no significant difference. This could be caused by reduced edema in the periodontal tissue of the smoker prior to therapy. Increased vasoconstriction in smokers is associated with reduced bleeding and edema, so smokers have less potential for resolution of inflammation and less potential for gingival recession. Labriola, et al. stated that this may lead to no significant differences in the improvement of clinical attachment levels between smokers and nonsmokers.[36]

Conclusions

Clinical periodontal parameter of smokers with periodontitis in Asia following periodontal therapy showed a significant change compared to baseline. However, non-smokers show a greater reduction in periodontal pocket depth, indicating that smoking has a negative effect on the outcome of periodontal therapy.

Acknowledgments

The authors thank Universitas Indonesia for the financial support in this study.

Study	Country	Study Design	Sample Characteristic		Periodontitis Criteria	Smokers Criteria	Intervention	Follow-Up
			Smokers	Non-Smokers				
Ikezawa-Suzuki I, et al. (2006)	Japan	Clinical trial	Age (Mean±SD) 51.8±2.2 years M/F= 8/4	Age (Mean±SD) 56.9±1.6 years M/F= 1/22	Chronic periodontitis (AAP 1999)	Smokers consist of active smokers and passive smokers, 28.2±7.6 pack/years	NSPT	1 month
Wan, et al. (2009)	Hongkong	Clinical trial	Age (Mean±SD) 46.2±6.8 years M/F= 20/-	Age (Mean±SD) 45±5.9 years M/F= 20/-	Chronic periodontitis (AAP 1999)	≥ 10 cigarettes/day for at least 10 years, 20.8±8.7 pack/years	NSPT	3 month, 6 month, 12 month
Buduneli N, et al. (2009)	Turkey	Clinical trial	Age (Mean±SD) 48±4.4 years M/F= 6/4	Age (Mean±SD) 44.54±5.53 years M/F= 4/6	Moderate chronic periodontitis (AAP 1999) (two interproximal sites with CAL ≥4 mm and PD ≥5 mm	≥ 10 cigarettes/day for >5 years, -	NSPT	4 weeks
Toker H, et al. (2012)	Turkey	Clinical trial	Age (Mean±SD) 38.4±5.5 years M/F= 6/9	Age (Mean±SD) 38.7±5.9 years M/F= 8/9	Generalized chronic periodontitis (AAP 1999) (>30% of sites with CAL and PD ≥5 mm	≥ 20 cigarettes/day, -	NSPT	6 weeks
Hendek MK, et al. (2015)	Turkey	Case-control with interventi on arm	Age (Median (IQR)) 45.0 (12.0) years M/F= 15/9	Age (Median (IQR)) 44.01 (5.0) years M/F= 12/11	Chronic periodontitis (AAP 1999) (30% periodontal bone loss and ≥2 non-adjacent sites per quadrant with PD ≥ 5mm and BOP	≥10 years and a minimum of 10 cigarettes per day	NSPT	1 month. 3 months
Aziz A, et al. (2015)	India	Clinical trial	Age (Mean±SD) 44.1±5.81 years M/F= 80/-	Age (Mean±SD) 40.9±4.6 years M/F= 51/-	Chronic periodontitis (AAP 1999) (clinical attachment loss ≥5 mm)	≥5 cigarettes/day, smoking habit for over 3 years	NSPT	3 months
Meenawat A, et al. (2015)	India	Clinical trial	Age (Mean±SD) 43.58±4.36 years M/F= 12/-	Age (Mean±SD) 43.25±4.16 years M/F=12/-	Chronic periodontitis (4 tooth sites with	>10 cigarettes/day for >2 years,	NSPT	1 month

Study	Country	Study Design	Sample Characteristic		Periodontitis Criteria	Smokers Criteria	Intervention	Follow-Up
			Smokers	Non-Smokers				
					PD >4mm, CAL >2mm)	11,13±5,02 pack/years		
Akbari G, et al. (2015)	India	Clinical trial	Age range= 30-39 years		Chronic periodontitis (CAL ≥5 mm and 2 non adjacent sites	≥10 cigarettes/day for ≥5 years, -	NSPT	3 months
Turkoglu O, et al. (2016)	Turkey	Clinical trial	Age (Mean±SD) 43.5±7.7 years Age range= 29-60 years M/F= 9/6	Age (Mean±SD) 46.4±7.1 years Age range= 36-61 years M/F= 8/6	Moderate-severe chronic periodontitis (4 non-adjacent teeth with CAL ≥4 mm and PD ≥5 mm)	≥10 cigarettes/day for ≥10 years, 19,01±12,1 pack/years	NSPT	1 month, 3 months
Mittal S, et al. (2017)	India	Clinical trial	Age (Mean) 35.32 years M/F= 20/-	Age (Mean) 37.4 years M/F= 24/46	Chronic periodontitis (at least 4 teeth with pocket depth >3-5 mm and attachment loss 1-3 mm)	History of tobacco consumption for a minimum duration of 2 years	NSPT	1 month, 2 month, 3 month
Jiao J, et al. (2017)	China	Observati onal, retrospecti ve	Age (Mean±SD) 45.12±18.00 years Age range=18-80 years		Chronic periodontitis (PD ≥4 mm and AL ≥3 mm)	Patients who still smoked at the last visit	NSPT	≥ 6 weeks
Pamuk F, et al. (2017)	Turkey	Randomiz ed clinical trial	Age range= ≥35 years		Generalized chronic periodontitis (AAP 1999) (>30% sites with (CAL) (PD) ≥ 5mm)			
Guru S, et al. (2018)	India	Clinical trial	Age (Mean±SD) 36.4±8.2 years Age range 25-50 years M/F= 25/-	Age (Mean±SD) 36.3±8.4 years Age range 25-50 years M/F= 25/-	Generalized moderate-sever chronic periodontitis (clinical attachment loss ≥ 3 mm)	≥20 cigarettes/day for ≥2 years, -	NSPT	1 month

Study	Country	Study Design	Sample Characteristic		Periodontitis Criteria	Smokers Criteria	Intervention	Follow-Up
			Smokers	Non-Smokers				
Padhye N, et al. (2019)	India	Clinical trial	-	Age (Mean) 36.7 years Age range= 21-53 years	Chronic periodontitis	≤10 cigarettes/day for a minimum 2 years	NSPT	6 weeks, 12 weeks
Varghese J, et al. (2020)	India	Clinical trial	Age range= 40-65 years M/F= 10/-	Age range= 40-65 years M/F= 10/-	Chronic periodontitis (AAP 1999) (30% teeth with pockets > 5 mm)	≥10 cigarettes/day for > 5 years, -	NSPT	3 months
Hendek MK, et al. (2020)	Turkey	Clinical trial	Age (Mean±SD) 44.60±7.8 years Age range 36-54 years M/F= 11/9	Age (Mean±SD) 44.10±7.54 years Age range 31-56 years M/F= 10/10	Chronic periodontitis (AAP 1999) (30% periodontal bone loss, presence at least two non-adjacent sites per quadrant with probing pocket depths of ≥5 mm and BOP	≥10 cigarettes/day for ≥10 years, -	NSPT	6 weeks-8 weeks
Kanmaz, et al. (2020)	Turkey	Clinical trial	Age (Mean±SD) 32.93±3.37 years Age range 26-38 years M/F= 10/4	Age (Mean±SD) 31.00±4.90 years Age range 22-38 years M/F= 4/9	Periodontitis Stage III or IV Grade C	>10 cigarettes/day for >5 years, 11,75±4,76 pack/years	NSPT	1 month, 3 months
Yilmaz S, et al. (2010)	Turkey	Clinical trial	Age range= 32-50 years		Advanced chronic periodontitis with intrabony defect	≥10 cigarettes/day for ≥10 years, -	Regenerative treatment with platelet-rich plasma combined with a bovine-derived xenograft	12 months

Table 1. Characteristic of Included Studies.

Conflict of Interest

The authors declare no conflict of interest regarding the content, design, and result presented in the study.

References

1. Hinrichs JE, Kotsakis GA. Classification of Diseases and Conditions Affecting the Periodontium. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, eds. *Carranza's Clinical Periodontology*. 13th ed. Philadelphia: Elsevier Inc.; 2019:55-79.
2. Slots J. Periodontitis: Facts, Fallacies and The Future. *Periodontol 2000*. 2017;75(1):7-23. doi:10.1111/prd.12221
3. Tonetti MS, Greenwell H, Kornman KS. Staging and Grading of Periodontitis: Framework and Proposal of A New Classification and Case Definition. *J Periodontol*. 2018;89(January):S159-S172. doi:10.1002/JPER.18-0006
4. Genco RJ, Borgnakke WS. Risk Factors for Periodontal Disease. *Periodontol 2000*. 2013;62(1):59-94. doi:10.1111/j.1600-0757.2012.00457.x
5. Leite FRM, Nascimento GG, Baake S, Pedersen LD, Scheutz F, López R. Impact of Smoking Cessation on Periodontitis: A Systematic Review and Meta-analysis of Prospective Longitudinal Observational and Interventional Studies. *Nicotine Tob Res*. 2019;21(12):1600-1608. doi:10.1093/ntr/nty147
6. Johnson GK, Guthmiller JM. The Impact of Cigarette Smoking on Periodontal Disease and Treatment. *Periodontol 2000*. 2007;44(1):178-194. doi:10.1111/j.1600-0757.2007.00212.x
7. Corbet EF, Zee KY, Lo ECM. Periodontal Diseases in Asia and Oceania. *Periodontol 2000*. 2002;29(1):122-152. doi:10.1034/j.1600-0757.2002.290107.x
8. Bokhari S, Suhail A, Malik A, Imran M. Periodontal Disease Status and Associated Risk Factors in Patients Attending a Dental Teaching Hospital in Rawalpindi, Pakistan. *J Indian Soc Periodontol*. 2015;19(6):678-682. doi:10.4103/0972-124X.156882
9. Corbet EF, Leung WK. Epidemiology of Periodontitis in the Asia and Oceania Regions. *Periodontol 2000*. 2011;56(1):25-64. doi:10.1111/j.1600-0757.2010.00362.x
10. WHO. WHO Prevalence of tobacco smoking. World Health Organization. https://www.who.int/gho/tobacco/use/en/. Published 2015.
11. Yang B-Y. Tobacco Smoking in Asia-A Public Health Threat. *J Am Med Assoc*. 2019;2(3):e191471. doi:10.1001/jamanetworkopen.2019.1471
12. Wan CP, Leung WK, Wong MCM, et al. Effects of Smoking on Healing Response to Non-Surgical Periodontal Therapy: A multilevel modelling analysis. *J Clin Periodontol*. 2009;36(3):229-239. doi:10.1111/j.1600-051X.2008.01371.x
13. Apatzidou DA, Riggio MP, Kinane DF. Impact of Smoking on the Clinical, Microbiological and Immunological Parameters of Adult Patients with Periodontitis. *J Clin Periodontol*. 2005;32(9):973-983. doi:10.1111/j.1600-051X.2005.00788.x
14. Patel RA, Wilson RF, Palmer RM. The Effect of Smoking on Periodontal Bone Regeneration: A Systematic Review and Meta-Analysis. *J Periodontol*. 2012;83(2):143-155. doi:10.1902/jop.2011.110130
15. Kotsakis GA, Javed F, Hinrichs JE, Karoussis IK, Romanos GE. Impact of Cigarette Smoking on Clinical Outcomes of Periodontal Flap Surgical Procedures: A Systematic Review and Meta-Analysis. *J Periodontol*. 2015;86(2):254-263. doi:10.1902/jop.2014.140452
16. Bunæs DF, Mustafa M, Mohamed HG, Lie SA, Leknes KN. The Effect of Smoking on Inflammatory and Bone Remodeling Markers in Gingival Crevicular Fluid and Subgingival Microbiota Following Periodontal Therapy. *J Periodontal Res*. 2017;52(4):713-724. doi:10.1111/jre.12438
17. Kanmaz B, Lappin DF, Nile CJ, Buduneli N. Effects of Smoking on Non-Surgical Periodontal Therapy in Patients with Periodontitis Stage III or IV, and Grade C. *J Periodontol*. 2020;91(4):442-453. doi:10.1002/JPER.19-0141
18. Hanioka T, Morita M, Yamamoto T, et al. Smoking and periodontal microorganisms. *Jpn Dent Sci Rev*. 2019;55(1):88-94. doi:10.1016/j.jdsr.2019.03.002
19. Corbet EF. Periodontal diseases in Asians. *J Int Acad Periodontol*. 2006;8(4):136-144.
20. Ikezawa-Suzuki I, Shimada Y, Tai H, Komatsu Y, Tanaka A, Yoshie H. Effects of Treatment on Soluble Tumour Necrosis Factor Receptor Type 1 and 2 in Chronic Periodontitis. *J Clin Periodontol*. 2008;35(11):961-968. doi:10.1111/j.1600-

051X.2008.01317.x
21. Toker H, Akpinar A, Aydin H, Poyraz O. Influence of Smoking on Interleukin-1beta Level, Oxidant Status and Antioxidant Status in Gingival Crevicular Fluid from Chronic Periodontitis Patients Before and After Periodontal Treatment. *J Periodontal Res*. 2012;47(5):572-577. doi:10.1111/j.1600-0765.2012.01468.x
22. Hendek MK, Erdemir EO, Kisa U, Ozcan G. Effect of Initial Periodontal Therapy on Oxidative Stress Markers in Gingival Crevicular Fluid, Saliva, and Serum in Smokers and Non-Smokers With Chronic Periodontitis. *J Periodontol*. 2015;86(2):273-282. doi:10.1902/jop.2014.140338
23. Aziz A, Kalekar M, Benjamin T, Suryakar A, Patil S, Bijle M. Short-Term Effectiveness of Scaling and Root Planning on Periodontal Parameters, Systemic Inflammatory, and Oxidative Stress Markers in Smokers with Chronic Periodontitis. *J Int Oral Heal*. 2015;7(10):16.
24. Akbari G, Venkatesh Prabhuji M, Karthikeyan B, Raghunatha K, Narayanan R. Analysis of Matrix Metalloproteinase-8 Levels in Gingival Crevicular Fluid and Whole Mouth Fluid Among Smokers and Nonsmokers Using Enzyme-Linked Immune-Sorbent Assay and A Novel Chair-Side Test. *J Indian Soc Periodontol*. 2015;19(5):525-530. doi:10.4103/0972-124X.162201
25. Türkołlu O, Eren G, Emingil G, Azarsiz E, Kutukculer N, Atilla G. Does Smoking Affect Gingival Crevicular Fluid LL-37 Levels Following Non-Surgical Periodontal Treatment in Chronic Periodontitis? *Arch Oral Biol*. 2016;61:98-105. doi:10.1016/j.archoralbio.2015.10.018
26. Guru S, Sam SE, Rajan S, Padmanabhan S. Comparative Evaluation of Salivary Hepatocyte Growth Factor in Smokers and Non-smokers with Chronic Periodontitis. *J Investig Clin Dent*. 2018;9(2):e12306. doi:10.1111/jicd.12306
27. Varghese J, Bhat V, Chianeh YR, Kamath V, Husain NAH, Özcan M. Salivary 8-hydroxyguanosine Levels in Smokers and Non-Smokers with Chronic Periodontitis. *Odontology*. 2020;108(4):569-577. doi:10.1007/s10266-020-00496-x
28. Karsiyaka Hendek M, Kisa U, Olgun E. The Effect of Smoking on Gingival Crevicular Fluid Peptidoglycan Recognition Protein-1 Level Following Initial Periodontal Therapy in Chronic Periodontitis. *Oral Dis*. 2020;26(1):166-172. doi:10.1111/odi.13207
29. Buduneli N, Buduneli E, Kütükçüler N. Interleukin-17, RANKL, and Osteoprotegerin Levels in Gingival Crevicular Fluid From Smoking and Non-Smoking Patients With Chronic Periodontitis During Initial Periodontal Treatment. *J Periodontol*. 2009;80(8):1274-1280. doi:10.1902/jop.2009.090106
30. Mittal S, Dani N, Abullais SS, Al-Qahtani NA, Shah K. Effect of Smoking and Tobacco Chewing on Periodontal Disease and Non-Surgical Treatment Outcome: A Clinical and Biochemical Study. *J Int Acad Periodontol*. 2017;20(1):12-18.
31. Jiao J, Shi D, Cao ZQ, et al. Effectiveness of Non-Surgical Periodontal Therapy in A Large Chinese Population with Chronic Periodontitis. *J Clin Periodontol*. 2017;44(1):42-50. doi:10.1111/jcpe.12637
32. Padhye N, Padhye A, Gupta H. Quantification and Comparison of The Impact of The Smoking Status on Oral Polymorphonuclear Leukocyte and Malondialdehyde Levels in Individuals with Chronic Periodontitis: A Double-Blinded Longitudinal Interventional study. *Contemp Clin Dent*. 2019;10(3):517-524. doi:10.4103/ccd.ccd_906_18
33. Yilmaz S, Cakar G, Ipci SD, Kuru B, Yildirim B. Regenerative Treatment with Platelet-Rich Plasma combined with a Bovine-Derived Xenograft in Smokers and Non-smokers: 12-month Clinical and radiographic results. *J Clin Periodontol*. 2010;37(1):80-87. doi:10.1111/j.1600-051X.2009.01509.x
34. Pamuk F, Lütfioğlu M, Aydoğdu A, Koyuncuoglu CZ, Cifcibasi E, Badur OS. The Effect of Low-Level Laser Therapy as an Adjunct to Non-Surgical Periodontal Treatment on Gingival Crevicular Fluid Levels of Transforming Growth Factor-beta 1, Tissue Plasminogen Activator and Plasminogen Activator Inhibitor 1 in Smoking and Non-smoki. *J Periodontal Res*. 2017;52(5):872-882. doi:10.1111/jre.12457
35. AlAhmari F, Ahmed HB, Al-Kheraif AA, Javed F, Akram Z. Effectiveness of Scaling and Root Planning with and without adjunct Antimicrobial Photodynamic Therapy in the Treatment of Chronic Periodontitis among Cigarette-smokers and Never-smokers: A Randomized Controlled Clinical Trial. *Photodiagnosis Photodyn Ther*. 2019;25(December 2018):247-252. doi:10.1016/j.pdpdt.2019.01.006
36. Labriola A, Needleman I, Moles DR. Systematic Review of The Effect of Smoking on Nonsurgical Periodontal Therapy. *Periodontol 2000*. 2005;37:124-137. doi:10.1111/j.1600-0757.2004.03793.x
37. Putri F, Lessang R, Soeroso Y. The difference in pocket depth and gingival recession between both smokers and non-smokers with chronic periodontitis. *J Int Dent Med Res*. 2018;11(3):1007-1010.
38. Fageeh HN, Ibraheem WI, Meshni AA, Preethanath RS. Serum Nitric Oxide Levels in Smokers with Chronic Periodontitis. *J Int Dent Med Res*. 2020;13(2):663-668.
39. Varghese J, Bhat V, Chianeh YR, Kamath V, Husain NAH, Özcan M. Salivary 8-hydroxyguanosine levels in smokers and non-smokers with chronic periodontitis. Odontology. 2020. doi:10.1007/s10266-020-00496-x
40. Eshghipour B, Tofighi H, Nehal F, Vohra F, Javed F, Akram Z. Effect of Scaling and Root Planing on Gingival Crevicular Fluid Cytokine/Chemokine Levels in Smokers with Chronic Periodontitis: A Systematic Review. J Investig Clin Dent. 2018;9(3):e12327. doi:10.1111/jicd.12327