Review

Impact of Cigarette Smoking on Clinical Outcomes of Periodontal Flap Surgical Procedures: A Systematic Review and Meta-Analysis

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Background: Periodontal flap surgery is frequently used to remove subgingival deposits, yielding consequential reductions in gingival inflammation and probing depth (PD) with a gain in clinical attachment level (CAL) to treat advanced periodontal disease. However, clinical studies have reported diminished periodontal healing in smokers compared with non-smokers. The aim of the present systematic review and meta-analysis was to assess the impact of cigarette smoking on clinical outcomes following periodontal flap surgical procedures.

Methods: A systematic electronic review of articles relevant to periodontal flap surgical procedures in smokers was conducted from 1977 to March 2014 inclusive, using predefined, optimized search strategies. Meta-analyses were done separately for changes in the two primary outcomes of PD and CAL.

Results: The initial search yielded 390 titles and abstracts. After screening, eight controlled clinical studies were finally selected. Three studies were assessed as having a low risk of bias, two as having moderate risk of bias, and three as having a high risk of bias. Qualitative assessment of the articles consistently showed an improved treatment effect among non-smokers versus smokers. The reduction in PD in smokers and non-smokers ranged from 0.76 to 2.05 mm and 1.27 to 2.40 mm, respectively. For CAL, the gain in non-smokers versus smokers ranged from 0.29 to 1.6 mm and 0.09 to 1.2 mm, respectively. Meta-analysis on eight studies reporting on 363 study participants demonstrated an increased reduction in mean (95% confidence interval) PD of 0.39 (0.33 to 0.45) mm. Similar results were found for mean gain in CAL (0.35 [0.30 to 0.40] mm, n = 4 studies).

Conclusions: Considering the relatively homogenous information available, the authors conclude that active smokers could be candidates for periodontal flap surgical procedures. However, the magnitude of the therapeutic effect is compromised in smokers compared with non-smokers. Therefore, cigarette smokers should be: 1) encouraged to abstain from smoking; and 2) thoroughly informed preoperatively of substantial reduction in clinical outcomes compared with non-smokers. *J Periodontol 2015;86:254-263.*

KEY WORDS

Meta-analysis; periodontal debridement; periodontal pocket; periodontitis; review; smoking.

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doi: 10.1902/jop.2014.140452

Current data reveal an estimated 4.1 million smokers aged >30 years with severe periodontitis in the United States.[1] Smoking has been thoroughly investigated as a risk factor for periodontal disease, and several studies have shown the association between habitual cigarette use and deterioration of clinical indices of periodontal disease.[2-5] Nonetheless, smokers often exhibit lower scores of bleeding on probing (BOP) than non-smokers mainly because of the vasoconstrictive effect of nicotine on gingival blood vessels.[6] Therefore, smokers may remain unaware of their compromised periodontal health status until they present for examination and subsequent treatment at more advanced stages of periodontal disease. Thus, habitual smokers often represent a subpopulation with increased prevalence of advanced periodontal disease.[1]

In terms of periodontal treatment, non-surgical periodontal therapy is routinely performed as cause-related therapy for the control of periodontal inflammation. However, it may not always yield substantial reduction in probing depth (PD), especially among deeper pockets.[7-9] Periodontal flap surgery is often required to achieve adequate reduction in PD in patients with advanced periodontal disease, as in the case of habitual smokers.[10] Yet, results from clinical studies have reported diminished outcomes of the healing response following periodontal surgery in smokers compared with non-smokers.[11-14] In a randomized, controlled clinical trial, the treatment outcome in periodontal furcation defects following periodontal flap surgery was compared between cigarette smokers and non-smokers.[14] Six-month follow-up results revealed twice as much gain of clinical attachment level (CAL) in non-smokers than smokers.[14] Other studies have also supported a trend for less favorable healing following periodontal surgical procedures in smokers as well as increased risk for relapse during post-surgical maintenance.[13,15]

Various mechanisms by which smoking impairs the healing response have been investigated to explain these unfavorable clinical findings.[16] These mechanisms encompass: 1) impaired neutrophilic function,[17] 2) decreased immunoglobulin A (IgA) and IgG production in saliva and serum,[18,19] 3) increased proliferation of periodontal pathogens,[20] and 4) impaired fibroblastic proliferation and function.[21] There have also been reports on the increase in expression of receptor of advanced glycation end products in gingival tissues as a potential mechanism of action that is currently under investigation.[22]

Results of a systematic review that assessed the effect of cigarette smoking on clinical outcomes following periodontal surgical procedures showed that periodontal wound healing is compromised in cigarette smokers compared with non-smokers.[23] The same review also reported that the hazardous effect of smoking manifests itself regardless of frequency or duration.[23] That systematic review included case reports and case series in addition to controlled studies and dealt with a range of surgical procedures including periodontal flap surgical procedures, root coverage procedures, and guided tissue regeneration. To the authors' knowledge, a meta-analysis of studies assessing the effect of cigarette smoking on periodontal flap procedures has not been previously performed. Thus, the aim of the present systematic review and meta-analysis is to assess the impact of cigarette smoking on the clinical outcomes following periodontal flap surgical procedures (flap debridement surgery, modified Widman flap, apically positioned flap).

MATERIALS AND METHODS

Search Strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the participants, interventions, control, outcomes (PICO) principle:[24] participants (P)—persons in the included studies must have been smokers diagnosed with moderate and/or advanced periodontitis; types of interventions (I)—the intervention of interest was periodontal flap surgery; control intervention (C)—non-smoker patients receiving the same intervention were considered as controls; and outcome measures (O)—changes in CAL and PD post-surgically were set as efficacy outcomes. Adverse events associated with surgical treatment in smokers were recorded as safety outcomes.

To identify studies relevant to the PICO question, the Medline (Ovid) database, the EMBASE database, and the Cochrane Central Register of Controlled Trials (CENTRAL) were electronically searched for available data. The search included articles published from January 1946 up to and including March 2014. Articles available online in electronic form ahead of print were considered eligible for inclusion.

The first phase of the evaluation of the literature included a search of the electronic databases using both Medical Subject Heading terms and free text relevant to periodontal flap procedures (i.e., flap debridement surgery, modified Widman flap, apically positioned flap) and smoking/tobacco use. The complete search strategy for Medline (Ovid) is available in Table 1. An additional search of the Medline (Ovid) In-Process database was conducted to capture the latest relevant articles.

Selection Criteria

Two reviewers performed the screening independently (GK, FJ) after reviewing the title and abstract of each potentially relevant article according to the following

Table 1.

Optimization of Keyword Combinations With Boolean Operators Used in the Search of Medline (Ovid) (March 4, 2014)

Advanced Search in Medline (Ovid)	Number of Articles
1. exp Surgical Flaps/	46,065
2. (surg$4 adj3 flap).mp.	2,325
3. open flap debridement.mp.	181
4. modified widman flap.mp.	97
5. apically positioned flap.mp.	42
6. flap procedure.mp.	539
7. periodontal surgery.mp.	1,145
8. 1 or 2 or 3 or 4 or 5 or 6 or 7	47,841
9. exp "Tobacco Use"/	124,799
10. exp Tobacco Products/	3,192
11. Smoking/	116,416
12. (smoker$ or smoking).mp.	196,718
13. 9 or 10 or 11 or 12	198,231
13. exp Periodontal Diseases/	69,601
14. periodont$4.mp.	66,791
15. 13 or 14	89,078
16. 8 and 13 and 15	114

inclusion criteria: 1) original articles; 2) human controlled, clinical studies; 3) ≥10 participants; 4) ≥6 months of follow-up post-intervention; and 5) surgical interventions that included flap debridement surgery, modified Widman flap, and apically positioned flap procedures in smokers and non-smokers.

Exclusion criteria were: 1) review articles; 2) case series; 3) case reports; 4) surgical interventions for correction of mucogingival defects (i.e., soft tissue grafting procedures); 5) use of biologic factors and/or grafting procedures; and 6) animal studies.

For articles that were considered potentially relevant by at least one reviewer, the full-text articles were obtained for eligibility evaluation against the predetermined inclusion criteria. An additional manual search of the following journals was performed from January 1990 to March 2014: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *The International Journal of Periodontics & Restorative Dentistry*, and *Journal of Periodontal Research*. The reference list of each of the selected full-text articles was also reviewed for article titles suggesting surgical periodontal treatment in smokers. If required, an attempt was made to contact the corresponding authors to obtain missing, unclear, or unpublished data.

As in the first phase of selection, the two reviewers conducted the second phase independently and in duplicate. κ scores (Cohen's κ coefficient) were used to determine the level of agreement between the two reviewers.[25]

Data Extraction

Two reviewers independently mined data regarding the year of publication, location of data, source of funding, patient characteristics, baseline plaque levels, number of participants in each group, number of interventions, smoking frequency and duration, and outcomes for each study and entered them in electronic spread sheets.

Outcome Variables

The effects of smoking on CAL and PD were evaluated as the primary outcome variables.

Assessment of Bias Within Studies

A specific protocol was used independently by the two reviewers for the assessment of the screened articles. The clinical studies included in the present systematic review were assessed using criteria from the revised Consolidated Standards of Reporting Trials (CONSORT) statement criteria for evaluation of randomized, controlled trials according to a previously described protocol.[26-28] The aim of the assessment was to identify within-study bias related to reporting of randomization, masking, follow-up, statistical analysis, and reporting of outcomes for the selected studies. A cumulative score was formed for each study following quality assessment, and an overall estimation of risk of bias was assigned to each included randomized clinical trial.[27,29] Studies in which all of the criteria were met were assigned a low risk of bias. A moderate risk was considered when at least one of the criteria was partially met, and a high risk of bias was estimated when one or more of the criteria were not met.[27,29]

Statistical Analyses

Meta-analyses were conducted separately for each of the two primary outcomes: PD and CAL, as previously described.[27] In case of missing data for the meta-analyses, the corresponding authors were contacted twice and the response rate was recorded. The mean differences between the reduction in PD and gain in CAL in smokers versus non-smokers groups were estimated as the effect-size measures. By definition, a mean difference <0 indicated a greater effect size in non-smokers. Heterogeneity among the included studies for each outcome was assessed using the q statistic and I^2 statistic.[30]

Outcome measures were combined with a random-effects model using the DerSimonian-Laird method

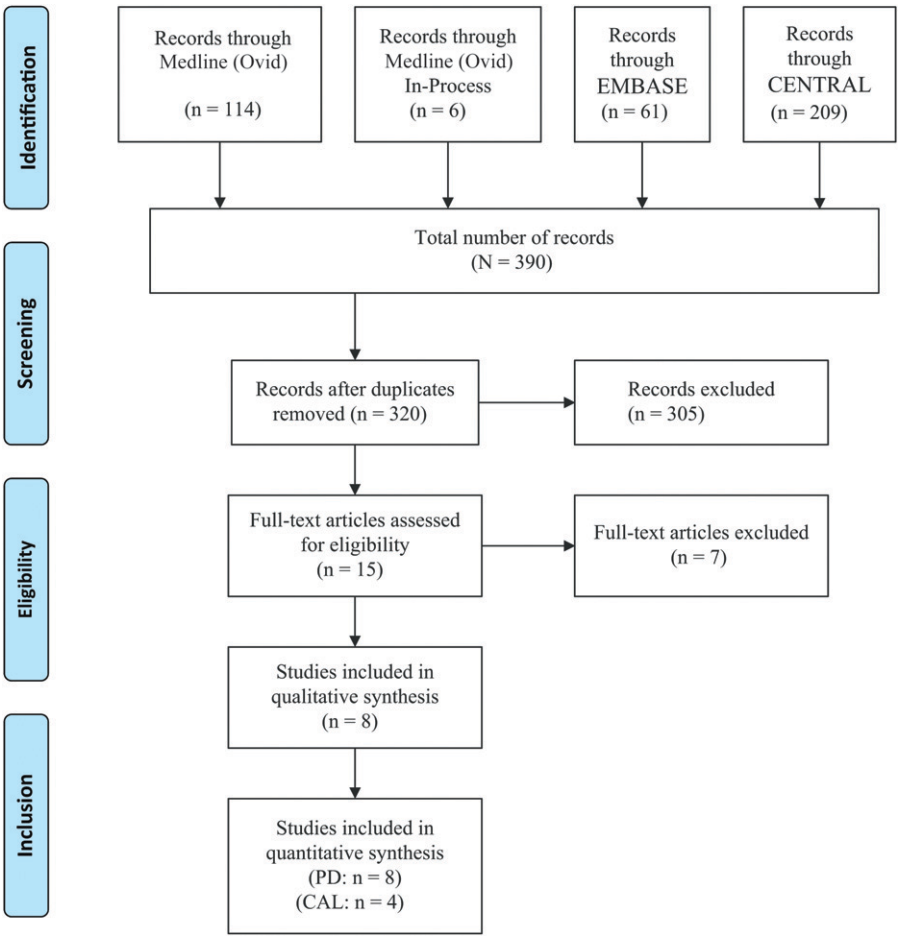

Figure 1.
Flowchart showing study selection based on PRISMA guidelines.

due to its robustness in comparison to fixed-effects models in the case of small sample sizes.[31] Forest plots were produced reporting weighted average of outcomes and 95% confidence intervals (CIs). The α level was set at 0.05. Funnel plots were constructed to explore potential publication bias across studies. All the statistical analyses were carried out with a specialized statistical software.¶

RESULTS

A total of 390 titles and abstracts were identified after the electronic search using the prespecified search strategy (Fig. 1). No additional studies were identified as relevant after a search of the reference lists and manual search of the selected journals. After removal of duplicates (n = 70), initial screening of titles and abstracts was performed, and 305 articles were excluded as irrelevant to the PICO question (κ score for inter-reviewer agreement [95% CI]: 0.92 [0.88 to 0.97]). Scrutiny of the full-text articles from the remaining 15 articles led to the exclusion of seven studies after application of the prespecified exclusion criteria, due to either lack of clinical data on smoking status,[32-35] use of regenerative techniques only,[36] or multiple reports from the same study population[12,37] (κ score for inter-reviewer agreement [95% CI]: 0.87 [0.62 to 0.99]) (see Supplementary Fig. 1 in online *Journal of Periodontology*). In total, eight clinical trials fulfilled the inclusion criteria and were included in this review.[11,13-15,38-41]

Risk of Bias Assessment of Included Studies

Three studies were assessed as having a low risk of bias,[11,38,39] two as having moderate risk of bias,[13,14] and three as having a high risk of bias.[15,40,41] In the three studies that were assessed as having a high risk of bias, at least four of the six methodologic criteria were fully or partially met (see Supplementary Fig. 2 in online *Journal of Periodontology*).[15,40-42]

Qualitative Results of Studies

All studies reported changes in PD as an outcome,[11,13-15,38-41] whereas four studies also reported on gain in CAL post-treatment.[11,14,15,39] In total, the included studies reported on 363 study participants with ages ranging from 23 to 80 years. The mean ages of smokers and non-smokers ranged from 39.6 to 59.7 years and 42.9 to 61.9 years, respectively. In none of the studies were there any significant differences between mean ages of smokers and non-smokers.[11,13-15,38-41] Duration of smoking was reported in three studies and ranged from ≥1 year to up to 27.8 years.[13,40,41] Smoking frequency thresholds for patient inclusion were reported in six studies and ranged from ≥1 cigarette per day to at least 20 daily (Table 2).[11,13,14,39-41] Periodontal treatment was performed by means of modified Widman flap in three studies and[13,38,41] flap debridement surgery with or without osseous recontouring in four studies,[14,15,39,40] and both treatment approaches were used in the remaining study.[11] The follow-up period ranged from 6 months up to 7 years.[11,13-15,38-41]

In terms of clinical results, similar reduction in BOP was noted overall for smokers and non-smokers (Table 3). All studies reported significantly less reduction in PD among smokers compared with

¶ R metafor package, R Development Core Team, Vienna, Austria.

Table 2.

Main Characteristics for Studies Included After Second Phase of Selection

Reference	Year	Funding	Intervention	Follow-Up	Medical History	Periodontal Status	Baseline Plaque Levels	Smoking Duration	Smoking Dosage (cigarettes/day)
Preber and Bergström[41]	1990	Swedish health and dental care company*	MWF	12 months	NA	Moderate-to-severe periodontitis	<0.5 PI	≥5 years	≥20/day
Kaldahl et al.[11]	1996	United States federal grant	MWF; FDS with osseous surgery	Yearly, ≤7 years	NA	Moderate-to-severe periodontitis	<30% plaque control record	NA	Overall: ≥10/day; heavy smokers > 20/day; light smokers < 19/day; past smokers: history of daily smoking in the past
Boström et al.[13]	1998	Swedish Dental Association; Swedish health and dental care company*	MWF	5 years	Non-contributory	Moderate periodontitis	28.5% ± 15.71% plaque control record	Current smoker: 27.8 years; past smokers: 21 years	Current smoker: 19.9/day; past smoker: 16.6/day
Scabbia et al.[15]	2001	Ministrio Dell' Universita e della Ricerca, Italy	FDS without osseous recontouring	6 months	Non-contributory	Moderate-to-severe periodontitis	43% ± 21% plaque control record	NA	≥10/day (range: 10 to 60 cigarettes)
Orbak et al.[40]	2003	NA	FDS	NA	NA	CP	1.99 ± 0.5 PI	≥1 year	≥15/day
Trombelli et al.[14]	2003	Ministrio Dell' Universita e della Ricerca, Italy	FDS without osseous recontouring	6 months	Non-contributory	Moderate-to-severe periodontitis	47% ± 24% plaque control record	NA	≥10/day
Hellström et al.[38]	2008	Specialty pharmaceutical company†	MWF	6 months	Non-contributory	Moderate-to-severe CP	44% ± 31% plaque control record	NA	NA
Kim et al.[39]	2007	Private dental products company‡	FDS	3 and 6 months	Non-contributory	Moderate-to-severe CP and AgP	0.16 ± 0.51 PI	NA	≥1/day

MWF = modified Widman flap, PI = plaque index, FDS = flap debridement surgery, NA = information not available.
* Praktikertjanst, Stockholm, Sweden.
† OraPharma, Horsham, PA.
‡ Ivoclar Vivadent, Schaan, Liechtenstein.

Table 3.
Outcomes Assessment of Included Studies (n or mean ± SD)

Reference	Smokers	Non-Smokers	Smokers			Non-smokers		
			Reduction in BOP/GI (%)	Reduction in PD (mm)	Gain in CAL (mm)	Reduction in BOP/GI (%)	Reduction in PD (mm)	Gain in CAL (mm)
Preber and Bergström et al.[41]	24	25	NA	0.76 ± 0.36	NA	NA	1.27 ± 0.43	NA
Kaldahl et al.[11]	Heavy smokers = 31, light smokers = 15	Non-smokers = 18, past smokers = 10	6	1.30 ± 0.10	0.65 ± 0.1	12	1.70 ± 0.20	1.0 ± 0.10
Boström et al.[13]	20	Non-smokers = 17, past smokers = 20	NA	0.9 ± 1.70	NA	NA	past smokers = 1.6 ± 1.83, non-smokers = 1.2 ± 1.40	NA
Scabbia et al.[15]	28	29	22 ± 23	1.9 ± 0.7	1.20 ± 0.70	25 ± 21	2.4 ± 0.9	1.60 ± 0.70
Orbak et al.[40]	25	25	0.45 ± 0.45	1.21 ± 0.67	NA	0.64 ± 0.41	1.58 ± 0.67	NA
Trombelli et al.[14]	19	12	28 ± 24	1.90 ± 1.40	1.0 ± 1.30	33 ± 23	1.80 ± 1.30	1.30 ± 1.10
Hellström et al.[38]	17	13	54 ± 4	2.05 ± 0.09	NA	59 ± 6	2.37 ± 0.22	NA
Kim et al.[39]	3	Non-smokers = 5, past smokers = 7	NA	0.80 ± 0.86	0.09 ± 0.44	NA	0.95 ± 0.87	0.29 ± 0.31

GI = gingival index, NA = information not available.

non-smokers.[11,13-15,38-41] The reduction in PD in smokers and non-smokers ranged from 0.76[41] to 2.05 mm[38] and 1.27[41] to 2.40 mm,[38] respectively. For CAL, the gain in non-smokers versus smokers ranged from 0.29[39] to 1.6 mm[15] and 0.09[39] to 1.2 mm,[15] respectively. All studies reported greater CAL gain in non-smokers compared with smokers but also consistently noted a mean gain in post-surgical CAL for smokers (Table 3). None of the studies reported any adverse events associated with smoking status.

Quantitative Results of Studies

After data extraction and, when necessary, communication with authors (authors' response rate: one of four), eight studies[11,13-15,38-41] were included in the meta-analysis of the weighted mean differences of PD and four[11,14,15,39] in the meta-analysis of the weighted mean differences of CAL (Fig. 1). The remaining four studies were excluded from the latter meta-analysis due to lack of CAL data in accordance with smoking status.[13,38,40,41] For both outcomes (PD and CAL), no evidence of publication bias was demonstrated across the included studies (see Supplementary Figs. 3 and 4 in online *Journal of Periodontology*). Figures 2 and 3 present the forest plots and summary estimates for weighted mean differences of PD and CAL between smokers and non-smokers, respectively. Tests for heterogeneity demonstrated non-significant heterogeneity for both PD (q = 3.85, degrees of freedom = 7, P = 0.80, I^2 = 0%) and CAL (q = 0.58, degrees of freedom = 3, P = 0.87, I^2 = 0%). The pooled effect sizes for reduction in PD were found to be highly significant in favor of non-smokers in the range of 0.39 mm (P <0.001). Similarly, 0.35 mm more CAL gain was

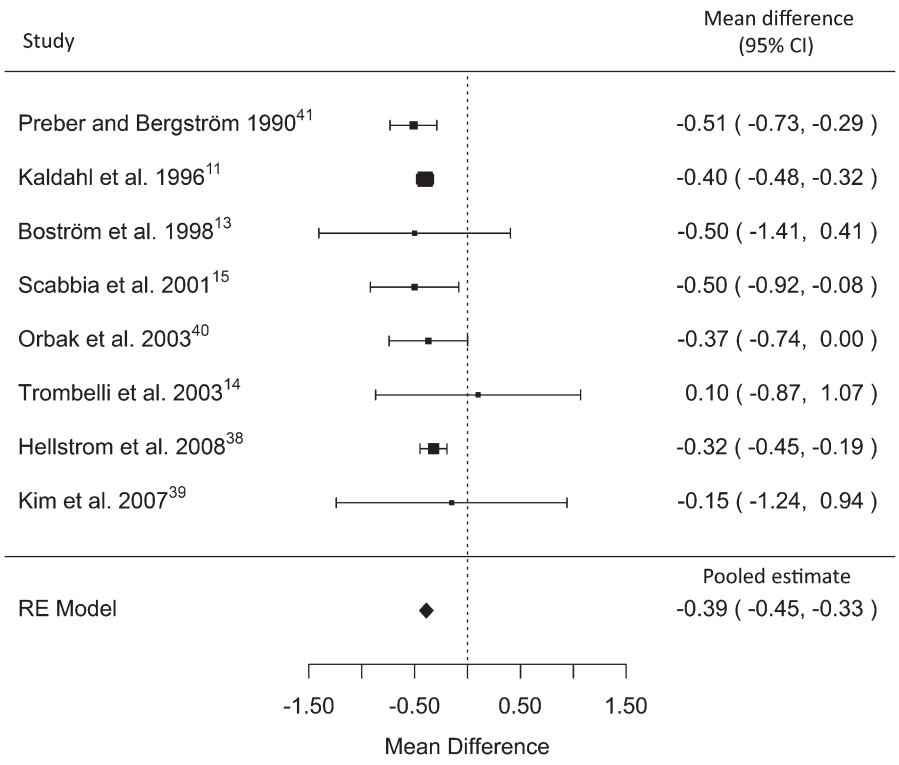

Figure 2.
Forest plot for included studies that reported PD in smokers versus non-smokers showing weighted mean differences and 95% CIs. Weighted mean differences were estimated by a random effects (RE) model. Mean difference <0 indicates greater PD reduction in non-smokers versus smokers.

found in non-smokers versus smokers (P <0.001).

DISCUSSION

The present study is, to the authors' knowledge, the first meta-analysis to assess the magnitude of therapeutic effect of periodontal flap surgical procedures in terms of non-smokers versus smokers. Results reveal that although periodontal flap procedures performed in active smokers generally moderately improved clinical measures of periodontal disease, the magnitude of benefit was significantly less than that observed in non-smokers.[11,13-15,38-41] Comparison of weighted estimates among the included studies demonstrated that non-smokers exhibited a 0.4-mm greater reduction in mean PD response following surgical treatment compared with smokers. A similar difference in enhanced gain of CAL for non-smokers was also noted.

The present results support the 2007 findings of Johnson and Guthmiller, who compiled the information available on periodontal therapy in smokers and concluded that smokers do benefit from periodontal surgical procedures.[16] The same authors also suggested that periodontal surgery may be recommended to smokers for pocket reduction, but the results should be expected to range from 50% to 75% of those observed in non-smokers.[16] The present meta-analysis verified these findings but also provided a quantitative estimate of the magnitude of the difference within groups for PD and CAL. The 0.4-mm difference in PD reduction in smokers versus non-smokers is not only statistically significant but also clinically relevant. Previous studies have shown that a PD reduction in this range can significantly increase the clinical response to treatment.[38,43] Williams et al. found that the additional benefit of ≈0.3-mm reduction in PD, when using minocycline microspheres as an adjunct to scaling and root planing, significantly improved the response to treatment by augmenting the percentage of treatment sites that experienced ≥2-mm reductions in PD.[43] Hellström et al. reported that the use of a local antimicrobial following a modified Widman flap further reduced the mean PD by 0.3 mm beyond the effect of modified Widman flap, which led to significantly more pockets experiencing >2-mm PD reduction.[38] Thus, the calculated 0.4 mm greater reduction in mean PD observed in non-smokers in the present study is also expected to translate to a greater number of sites meeting or exceeding the threshold of 2-mm reduction in PD.[43]

The strength of the aforementioned results is supported by the very narrow 95% CIs found for the weighted differences in PD and CAL in the meta-analyses (–0.45 to –0.33 and –0.39 to –0.30, respectively). Based on the lack of heterogeneity across the included studies, it is unlikely that the reduced healing response noted in smokers was a result of chance. Therefore, clinicians could interpret these findings as a guideline for preoperatively setting smokers' expectations. Because the mean magnitude of expected PD reduction after periodontal surgery has been shown to not exceed 3 mm, a reduced effect in smokers may account for fewer pockets with a baseline depth of ≥7 mm that achieve adequate reduction.[44] In such cases, it may be advisable to inform smokers before periodontal flap surgery that additional therapy may be required.

A limitation of this study on an outcome level is the lack of standardized reporting of smoking status in the included studies. Most of the studies reported

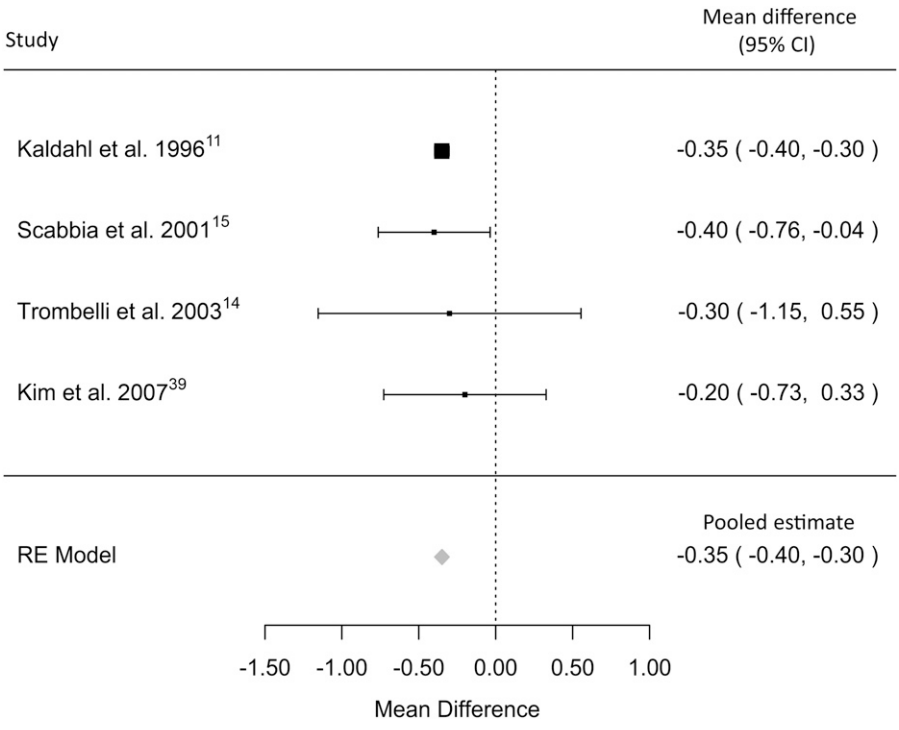

Figure 3.
Forest plot for included studies that reported CAL in smokers versus non-smokers showing weighted mean differences and 95% CIs. Weighted mean differences were estimated by a random effects (RE) model. Mean difference <0 indicates greater CAL in non-smokers versus smokers.

arbitrarily selected thresholds for the inclusion of smokers that ranged from ≥1 to ≥20 cigarettes per day.[39,41] Although this variation in smoking dosage may be expected to strengthen or attenuate the deleterious effect of smoking on periodontal healing accordingly, Javed et al. previously reported that a dose-dependent effect of smoking in periodontal healing has not been consistently shown in published studies.[23] In particular, Kaldahl et al. actually compared the response of heavy smokers, defined as smoking ≥20 cigarettes per day, to that of light smokers (≥10 and <20 cigarettes per day).[11] Results from Kaldahl et al. showed a trend for less PD reduction in heavy smokers versus light smokers that was found to be significant only after 6 years of follow-up.[11] One plausible explanation for the lack of a significant dose-dependent effect of smoking may be the high concentration of nicotine in the crevicular fluid even after limited exposure. Nicotine's concentration in the crevicular fluid has been found to be ≤300-fold that of plasma.[16] Thus, even light cigarette consumption may cause a disproportionately harmful effect to periodontal tissue healing. Future studies that will use established definitions of smoking are needed to definitively address the equivocal association between smoking duration and dosage and impaired periodontal healing.

One example of this is pack-years. A pack-year is quantified as the number of packs of cigarettes smoked per day, multiplied by the number of years the individual has been a smoker.[45] Consequently, 1 pack-year means that a person has been smoking one pack (20 cigarettes) per day for a year, or approximately 7,300 cigarettes for a year.[45] Using such an approach would allow for direct comparisons between studies and would most likely provide more information on the potential effect of dosage and/or duration on periodontal wound healing. Another implication for future research could be the use of the comprehensive smoking index (CSI).[46] Similar to pack-years, the CSI provides a record of smoking duration and dosage. In addition to this information, CSI also captures information on the recency of smoking and allows for the estimation of the half-life of the smoking effect.[46] Using the CSI may be advantageous in periodontal research, as the robustness of this index for estimating the effect of smoking on periodontal health has been previously verified.[46]

CONCLUSIONS

Overall, periodontal surgical treatment benefited patients irrespective of smoking status. However, the magnitude of the therapeutic effect was significantly more beneficial in non-smokers compared with smokers in terms of both PD and CAL. Clinicians should use findings of the present study during preoperative treatment planning to caution smokers about the potential need for further therapeutic interventions following periodontal flap surgery.

ACKNOWLEDGMENTS

The authors are grateful to Amy Claussen, MLIS, University of Minnesota, Minneapolis, Minnesota, for her expert contribution in the construction of the search strategy and electronic search of the literature. The authors also wish to thank Prof. Dr. Eickholz, Goethe-Universität Frankfurt am Main, Frankfurt, Germany, for devoting the time and effort to provide additional data from his original study. The authors report no conflicts of interest related to this study.

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Submitted August 5, 2014; accepted for publication September 16, 2014.