Site-specific treatment outcome in smokers following 12 months of supportive periodontal therapy

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Abstract

Aim: To evaluate the effect of cigarette smoking on periodontal health at patient, tooth, and site levels following supportive therapy.

Materials and Methods: Eighty chronic periodontitis patients, 40 smokers and 40 non-smokers, were recruited to a single-arm clinical trial. Periodontal examinations were performed at baseline (T0), 3 months following active periodontal therapy (T1), and 12 months following supportive periodontal therapy (T2). Smoking status was validated measuring serum cotinine levels. Probing depth (PD) ≥ 5 mm with bleeding on probing (BoP) was defined as the primary outcome. Logistic regression analyses adjusted for clustered observations of patients, teeth, and sites and mixed effects models were employed to analyse the data.

Results: All clinical parameters improved from T0 to T2 ($p < 0.001$), whereas PD, bleeding index (BI), and plaque index (PI) increased from T1 to T2 in smokers and non-smokers ($p < 0.001$). An overall negative effect of smoking was revealed at T2 (OR = 2.78, CI: 1.49, 5.18, $p < 0.001$), with the most pronounced effect at maxillary single-rooted teeth (OR = 5.08, CI: 2.01, 12.78, $p < 0.001$). At the patient level, less variation in treatment outcome was detected within smokers (ICC = 0.137) compared with non-smokers (ICC = 0.051).

Conclusion: Smoking has a negative effect on periodontal health following 12 months of supportive therapy, in particular at maxillary single-rooted teeth.

Active periodontal therapy (APT) followed by supportive periodontal therapy (SPT) has been demonstrated successful in a majority of patients (Axelsson & Lindhe 1981, Ramfjord 1987, Rosling et al. 2001, Axelsson et al. 2004). In perspective,

patients susceptible to recurrence of periodontal disease have been offered SPT at 3- to 4-month intervals with the intent to maintain treatment outcomes following APT, whereas less susceptible patients may be well served, using a less frequent SPT interval (Knowles et al. 1979, Lindhe & Nyman 1984). To facilitate identification of individuals at high risk for disease progression, a functional Periodontal Risk Assessment (PRA) diagram has been proposed (Lang & Tonetti 2003). In a longitudinal study validating the PRA

model, patients allocated to the high-risk category following APT showed a higher incidence of tooth loss compared with moderate- or low-risk patients (Eickholz et al. 2008).

In spite of clinical benefits, only a minority of patients appear to comply with recommended SPT regimens (Checchi et al. 1994, Demetriou et al. 1995), and efforts to optimize compliance being only partly successful (Wilson et al. 1993). Further, it appears that SPT compliance decreases as the risk profile of the

subject increases (Mendoza et al. 1991, Matuliene et al. 2010). Because of imperfect outcomes following APT (Bunæs et al. 2015) and inconsistent compliance (Matuliene et al. 2010, Ramseier et al. 2014), the selection of appropriate SPT intervals is of paramount importance for the maintenance of periodontal stability in cigarette smokers.

Smoking is a critical patient-related risk factor for chronic periodontitis and smokers exhibit fewer teeth and more advanced periodontal attachment loss compared with non-smokers (Kerdvongbundit & Wikesjo 2000, Calsina et al. 2002, Jansson & Lavstedt 2002). High cigarette consumption amplifies clinical manifestations of chronic periodontal disease and demands increased treatment needs (Dietrich et al. 2004, Susin et al. 2004, Do et al. 2008, Ramseier et al. 2015). Based on subjectively reported pack-year consumption, dose-dependent impaired clinical outcomes following SPT have been reported (Kaldahl et al. 1996a). It is unclear to what extent treatment response is influenced by a cumulative impact of smoking over years or by the consumption during SPT. However, a positive effect of smoking cessation on periodontal treatment outcomes may indicate the effect of present smoking exposure (Preshaw et al. 2005, Rosa et al. 2011).

Generally, optimal soft and hard tissue healing following APT is a critical point for successful treatment outcome. In a recently published study, Bunæs et al. (2015) reported impaired site-specific tissue responses to non-surgical and surgical APT in smokers compared with non-smokers. The multilevel approach using probing depth (PD) with bleeding on probing (BoP) as the primary outcome variable showed that plaque positive sites increased the risk for unfavourable treatment outcomes in smokers. A local additive detrimental effect of smoking is supported by studies reporting increased incidence of oral cancer and altered composition of the oral biofilm (Haffajee & Socransky 2001, Hashibe et al. 2007, Guglielmetti et al. 2014).

Longitudinal cohort studies have reported that smoking 20 or more cigarettes a day increased the risk of disease progression following APT (Kaldahl et al. 1996a, Matuliene et al. 2008). In contrast, long-term follow-up studies have not found an association between smoking status and tooth loss (Fisher et al. 2008, Saminsky et al. 2015). These inconclusive findings indicate that the effect of subjectively reported smoking habits on the outcome of SPT needs to be addressed in a prospective study with an objective measure of smoking exposure.

To the best of our knowledge, there seems to be no prospective studies evaluating the patient, tooth, and site-related effects of cigarette smoking on the outcome of SPT in chronic periodontitis patients, using an objective measure of smoking status. Thus, the specific aims of this study were to determine the effect of smoking at patient, tooth, and site levels following 12 months of SPT and to compare the predictive value of clinical parameters for the outcome of SPT in smokers and non-smokers.

Material and Methods

The study protocol and informed consent approved by the Institutional Medical Research Ethics Committee (2011/151-6), University of Bergen, Norway, followed the Helsinki Declaration of 1975, version 2008. Participating subjects read and signed the informed consent prior to inclusion in the study.

Pre-study tests

Two pre-study exercises were performed. First, the intra-examiner (DFB) reproducibility was tested by measuring PD and clinical attachment levels (CAL) twice at six sites per tooth in 10 patients. Intra-class correlation coefficients (ICC) for repeated measures ranged between 0.92 and 0.96 for PD and between 0.93 and 0.96 for CAL. The sample size estimation was based on change in PD. A difference of 0.5 mm was considered clinically relevant. Standard deviation of the differences between repeated PD measurements from the intra-calibration amounted to 0.5 mm. A power analysis based on 40 subjects per group and with the level of significance (α) set to 0.05, gave an 88% power to detect a true difference of 0.5 mm. Second, masking of the operator (DFB) towards smoking status was tested in 30 chronic periodontitis patients. Twenty-eight of 30 patients (93%) were correctly identified as smokers or non-smokers ($p < 0.001$; for detail see Bunæs et al. 2015).

Eligibility criteria, patient sample, and smoking status

Inclusion criteria were healthy subjects aged 35–75 years, none using medication that could affect periodontal healing, having at least four non-adjacent teeth with an interproximal PD ≥ 6 mm and clinical attachment loss ≥ 5 mm with BoP without signs of apical pathology (Tonetti & Claffey 2005, Page & Eke 2007). The patients were either smokers (>10 cigarettes/day for at least 5 years) or non-smokers (never or not smoked within the last 5 years). Patients starting or discontinuing smoking during the study were not excluded. Exclusion criteria included any current medical condition affecting periodontal treatment, use of systemic antibiotics or subgingival scaling within 6 months prior initiation of the study, and delay of scheduled treatment visits by more than one month.

Eighty patients, 40 smokers and 40 non-smokers, with moderate to severe chronic periodontitis (Armitage 1999) referred for periodontal treatment from general practitioners in a rural district of Norway were consecutively enroled in this single-arm clinical trial March 2012 through September 2013 (Table 1). Medical, periodontal, and smoking history of the patients was obtained from clinical examinations, health forms, questionnaires, and by consulting their physicians. All referred patients were examined for eligibility and consecutively invited to participate.

The subjectively reported smoking status was calculated in pack years; the number of cigarettes smoked daily multiplied by the number of years divided by 20 (a standard pack of cigarettes) (Scott et al. 2001). Before and at the end of the study, smoking status was objectively validated by measuring cotinine levels in serum. Peripheral venous blood was collected from each participant using a glass vacutainer. After coagulation, blood was centrifuged (700 × g for 10 min.)

Table 1. Sociodemographic characteristics and health status in smokers and non-smokers at baseline (T0)

	Smokers n (%)	Non-smokers n (%)	p
≥60 years/<60 years	21/19 (52.5/47.5)	22/18 (55.0/45.0)	0.096
Male/female	15/25 (37.5/62.5)	23/17 (56.0/44.0)	0.121
Cohabitant/single	24/16 (60.0/40.0)	35/5 (87.2/12.8)	0.011
Elementary school/education beyond	30/10 (75.0/25.0)	20/20 (50.0/50.0)	0.025
Working/not working	18/22 (45.0/55.0)	28/12 (70.0/30.0)	0.069
Satisfaction/dissatisfaction with oral health	10/28 (26.3/73.7)	7/32 (18.0/82.1)	0.376
Alcohol consumption daily or weekly/ monthly or never	21/25 (58.3/41.7)	18/21 (46.2/53.9)	0.292
Dental visits regularly/irregularly	35/2 (94.6/5.4)	37/2 (94.9/5.1)	0.957

Students *t*-test and Chi-square: *p*-level <0.05.

and the serum was stored in aliquots at −80°C. Serum cotinine was assessed according to the instructions of the serum enzyme immunoassay kit (Cotinine ELISA Kit; MyBioSource, San Diego, CA, USA) measuring the absorbance at 450 nm with a microplate reader (FluoStar Optima V1.32 R2; BMG Labtech, Offenburg, Germany).

Clinical assessments

A full-mouth intra-oral radiographs series was recorded before the clinical examination. Clinical recordings were collected at baseline pre-ATP (T0), at 3 months post-APT (T1), and following 12 months of SPT (T2). PD was recorded as the distance from the gingival margin to the probeable base of the pocket, CAL as the distance from the cemento-enamel junction or the margin of a dental restoration to the probeable base of the pocket. PD and CAL were measured using a periodontal probe (PCPUNC 15; Hu-Friedy, Chicago, IL, USA) at six sites per tooth rounding up to the nearest mm. Full mouth gingival bleeding scores were recorded as the percentage of sites showing bleeding on gentle probing (Ainamo & Bay, 1975) and full mouth dental plaque scores as the percentage of tooth surfaces with visible plaque following staining with disclosing solution (O'Leary et al. 1972). As a supplement to staining, the periodontal probe was used to discriminate between plaque and pellicle.

Treatment

APT (T0-T1) and SPT (T1-T2) were performed by the same operator (DFB). APT included nonsurgical

and surgical periodontal therapy individualized to optimize treatment outcomes for each patient. Following ATP, a programme with regular appointments every three months was scheduled for SPT (Knowles et al. 1979, Lindhe et al. 1984). The 60-min appointments included re-motivation and re-instruction in oral hygiene, full mouth plaque removal, and supra- and subgingival debridement as needed. In addition, smokers were motivated to reduce or quit smoking, and encouraged to participate in a public smoking cessation programme (Røyketelefonen, Helsedirektoratet, Oslo, Norway). Mechanical debridement was carried out using conventional hand-instruments (Hu-Friedy, Chicago, IL, USA; and American Eagle Instruments, Missoula, MT, USA) and ultrasonic scalers (EMS, Nyon, Switzerland). For plaque removal, rotating rubber cups and glycine powder (EMS – Air Flow-Perio) in an air-polishing device (Dentsply Prophy-Jet ®; Dentsply, York, PA, USA) were used.

Statistical analysis

The Shapiro–Wilk test was used to check for the assumption of normal distributed data. According to the test, the data were considered normally distributed. Means and standard deviations of secondary outcome variables (number of teeth, PD, CAL, BI, PI) were calculated and differences were tested, using the two sample *t*-test and Mann–Whitney test. Chi-square test was applied for testing of differences in frequencies and percentages between the categorical variables.

In an adjusted logistic regression model, gender was categorized as male (1) and female (0), age as ≥60 years (1) and <60 years (0), self-reported education as ≤9 years (1) and >9 years (0), and marital status as married/cohabitant (1) and living alone (0). The primary outcome variable PD ≥ 5 mm with BoP was dichotomized as (1) present and (0) absent. Each site, corrected for clustering of data within teeth and patients, was the unit of analysis. Sites presenting PD ≥ 5 mm with BoP at teeth extracted between T0 and T1 were not included in the analysis. Associations between PD ≥ 5 mm with BoP at T2 and clinical variables at T0 and T1 were tested using adjusted logistic regression analysis. Plaque positive sites categorized as (0) and plaque negative sites as (1), BoP positive sites as (0) and BoP negative sites as (1), and overall mean values calculated at T0 and T1 for PD and CAL were tested. For the smoking effect model following T1, specific teeth and sites were tested at T1 and T2. Two dummy variables were made for time and smoke and included in the adjusted model: (T2 = 1 and Smoke = 0) as (1) and (T2 = 1 and Smoke = 1) as (0) and (T1 = 1 and Smoke = 0) as (1) and T1 = 1 and Smoke = 1) as (0). Intra-class correlation coefficients (ICC) within patients, teeth, and sites were calculated using linear mixed effects models.

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A *p*-value <0.05 was considered statistically significant. All analyses were conducted using Stata version 13 (Stata Corp., College Station, TX, USA).

Results

Eighty patients, 40 smokers (mean age 57.6 years, range 37–70 years) and 40 non-smokers (mean age 58.7 years, range 35–73 years), entered this study. Socio-demographic characteristics according to smoking status at baseline (T0) are summarized in Table 1. The experimental protocol started April 2012 to end March 2015. Thirty-six (90%) smokers and 36 (90%) non-smokers completed the study (Fig. 1). Dropouts did not alter the socio-demographic characteristics at T1 and T2.
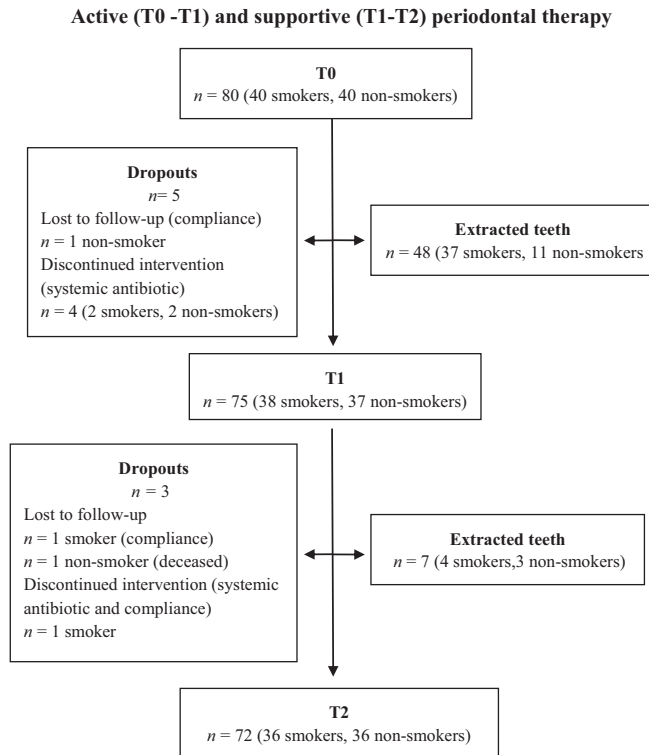
Active (T0 -T1) and supportive (T1-T2) periodontal therapy

T0
n = 80 (40 smokers, 40 non-smokers)

Dropouts
n = 5
Lost to follow-up (compliance)
n = 1 non-smoker
Discontinued intervention
(systemic antibiotic)
n = 4 (2 smokers, 2 non-smokers)

Extracted teeth
n = 48 (37 smokers, 11 non-smokers)

T1
n = 75 (38 smokers, 37 non-smokers)

Dropouts
n = 3
Lost to follow-up (compliance)
n = 1 smoker (compliance)
n = 1 non-smoker (deceased)
Discontinued intervention (systemic
antibiotic and compliance)
n = 1 smoker

Extracted teeth
n = 7 (4 smokers, 3 non-smokers)

T2
n = 72 (36 smokers, 36 non-smokers)

Fig. 1. Study flow chart.

Three (7.9%) smokers reported discontinuing smoking between T1 and T2, only one exhibited a cotinine level at T2 consistent with non-smokers (<10 ng/ml).

Compared with non-smokers, smokers presented significantly higher mean PD and CAL at all time-points (Table 2). Between T0 and T2 both groups responded favourable to periodontal therapy with significant reductions in mean PD, CAL, BI, and PI ($p < 0.001$) (not tabulated). However, during SPT, from T1 to T2, mean PD, BI, and PI increased in both groups. In smokers mean PD increased from 2.63 to 2.80 mm ($p = 0.007$) and in non-smokers from 2.27 to 2.42 mm ($p = 0.002$), BI in smokers from 22.42 to 27.00 ($p = 0.011$) and in non-smokers from 22.81 to 30.50 ($p = 0.001$), and PI in smokers from 18.45 to 30.09 ($p < 0.001$) and in non-smokers from 21.49 to 32.78 ($p < 0.001$) (not tabulated). From T1 to T2, mean CAL did not change significantly in either smokers or non-smokers (not tabulated).

An overall distribution of PD ≥ 5 mm with BoP was 11.3% in smokers and 7.1% in non-smokers. In comparison, the corresponding percentages for PD ≥ 5 mm only were 14.8% in smokers and 8.3% in non-smokers. Compared with non-smokers, smokers had 4.2% more number of sites with PD ≥ 5 mm with BoP compared with 6.5% more PD ≥ 5 mm. The number of sites with PD ≥ 5 mm with BoP at T0, T1, and T2 are summarized in Table 3. At T1, the total number in smokers were 132 (2.6%) and 52 (1.0%) in non-smokers ($p < 0.001$), increasing at T2 to 180 (3.8%) in smokers and 79 (1.6%) in non-smokers ($p < 0.001$). From T1 to T2, the increase was significant for all teeth and sites in smokers and non-smokers, except for multi-rooted buccal sites in non-smokers. At T2, a higher number of PD ≥ 5 mm with BoP was observed in smokers compared with non-smokers at maxillary molar palatal sites ($p = 0.040$), at maxillary single-rooted palatal and buccal sites ($p = 0.001$ and $p = 0.002$, respectively), and at mandibular single-rooted lingual sites ($p = 0.032$).

Based on the number of PD ≥ 5 mm with BoP, patients were allocated into four different groups: (1) patients with 0 sites; (2) patients with 1–4 sites; (3) patients with 5-8 sites; and (4) patients with ≥9 sites. For both smokers and non-smokers at T0, 97.5% ($n = 39$) had ≥9 sites and 2.5% ($n = 1$) 5-8 sites. For smokers at T1, 13.2% ($n = 5$) had ≥9 sites, 13.2% ($n = 5$) 5-8 sites, 55.3% ($n = 21$) 1–4 sites, and 18.4% ($n = 7$) had 0 numbers of PD ≥ 5 mm with BoP (not tabulated). At T2, the corresponding percentages were 16.7% ($n = 6$), 25.0% ($n = 9$), 38.9% ($n = 14$), and 19.4% ($n = 7$). For non-smokers at T1, 0 patients had ≥9 sites (group 4) and 8.1% ($n = 3$) had 5-8 sites (group 3) and at T2, the respective percentages were 2.8% ($n = 1$) and 13.9% ($n = 5$). The mean level of three different cigarette measures was recorded and presented for each patient group at T0 and T2 (Fig. 2). Compared with subjectively reported

Table 2. Patient-related clinical measures in smokers and non-smokers at T0, T1, and T2

Clinical measures	T0 (n = 80)			T1 (n = 75)			T2 (n = 72)		
	Smokers mean (±SEM)	Non-smokers mean (±SEM)	*p*	Smokers mean (±SEM)	Non-smokers mean (±SEM)	*p*	Smokers mean (±SE)	Non-smokers mean (±SEM)	*p*
Number of teeth	23.35 (5.14)	25.08 (2.88)	0.069	22.53 (5.65)	24.81 (3.30)	0.036	22.11 (6.24)	24.61 (3.15)	0.058
PD	3.80 (1.63)	3.36 (1.52)	<0.001	2.63 (1.02)	2.27 (0.85)	<0.001	2.80 (1.11)	2.42 (0.88)	<0.001
CAL	4.55 (1.80)	3.97 (1.48)	0.001	3.57 (1.34)	3.06 (1.12)	<0.001	3.60 (1.52)	3.13 (1.11)	<0.001
BI	66.68 (17.93)	67.33 (15.57)	0.864	22.42 (8.41)	22.81 (10.97)	0.864	27.00 (8.02)	30.50 (9.78)	0.050
PI	54.62 (21.72)	54.63 (21.72)	0.607	18.45 (10.89)	21.49 (14.13)	0.304	30.09 (16.14)	32.78 (14.59)	0.352

BI, bleeding index; CAL, clinical attachment level; SEM, standard error of the mean, PD, probing depth; PI, plaque index.

Table 3. Numbers of sites with probing depth ≥5 mm with BoP before (T0), following active (T1), and supportive periodontal therapy (T2) at arch and tooth level

Localization	T0			T1			T2		
	Smokers n (%)	Non-smokers n (%)	p	Smokers n (%)	Non-smokers n (%)	p	Smokers n (%)	Non-smokers n (%)	p
Overall	1471 (26.4)	1049 (17.5)	<0.001	132 (2.6)	52 (1.0)	<0.001	180 (3.8)	79 (1.6)	0.001
Maxillary multi-rooted									
Buccal	131 (39.7)	136 (32.6)	0.105	10 (3.8)	7 (2.0)	0.209	11 (3.6)	12 (4.6)	0.731
Palatal	175 (53.0)	198 (47.5)	0.309	27 (10.2)	15 (4.2)	0.009	31 (12.0)	21 (6.4)	0.040
Maxillary single-rooted									
Buccal	214 (20.8)	124 (11.2)	0.680	16 (1.7)	2 (0.2)	0.121	26 (2.9)	6 (0.6)	0.002
Palatal	374 (46.4)	180 (16.2)	0.030	25 (2.6)	8 (0.8)	0.159	48 (5.4)	12 (1.3)	0.001
Mandibulary multi-rooted									
Buccal	99 (33.0)	86 (24.9)	0.269	9 (3.0)	7 (2.3)	0.617	10 (3.4)	3 (1.1)	0.055
Lingual	137 (41.5)	125 (36.2)	0.326	12 (4.0)	9 (2.9)	0.561	17 (5.7)	12 (4.2)	0.473
Mandibulary single-rooted									
Buccal	154 (14.1)	95 (8.4)	0.148	14 (1.4)	2 (0.2)	0.628	21 (2.2)	5 (0.5)	0.164
Lingual	187 (17.1)	105 (9.3)	0.011	19 (1.9)	2 (0.2)	0.190	16 (1.7)	8 (0.8)	0.032

BoP; bleeding on probing; multi-rooted, molars; single-rooted, premolars and incisors; buccal, two proximal-buccal and one mid-buccal; palatal, two proximal-palatal and one mid-palatal; lingual, two proximal-lingual and one mid-lingual.
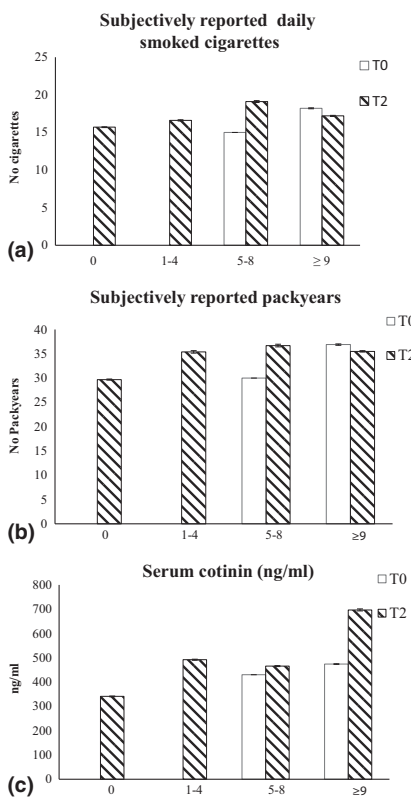

Fig. 2. Means of smoking measures in patients with 0, 1–4, 5–8, and ≥9 sites of probing depth ≥5 mm and bleeding on probing at T0 and T2.

consumption, the serum cotinine levels were higher for smokers presenting ≥9 sites with PD ≥ 5 mm with BoP at T2. For this group, the objectively validated cigarette consumption showed 37.9% higher mean serum cotinine level at T2 (697 ng/ml) compared with the mean serum cotinine level in the groups presenting a lower number of PD ≥ 5 mm with BoP (433 ng/ml).

At the site level, clinical parameters and numbers of teeth at T0 and T1 were tested in smokers and non-smokers as predictors for PD ≥ 5 mm with BoP at T2 (Table 4). All variables significantly increased the OR, except for number of teeth at T0 and T1 and for plaque positive sites at T0 in smokers. BoP at T0 was a strong predictor in smokers (OR: 8.93, CI: 3.28, 24.36, $p < 0.001$) and non-smokers (OR: 10.99, CI: 3.33, 36.23 $p < 0.001$). Compared with BoP at T0, BoP at T1 increased the OR in smokers (OR = 13.26, CI: 5.12, 34.38, $p < 0.001$), but not in non-smokers (OR = 4.68, CI: 1.32, 16.61, $p < 0.001$). Plaque positive sites at T0 predicted PD ≥ 5 mm with BoP only in non-smokers (OR = 3.05, CI: 1.19, 7.82, $p = 0.020$), whereas an association was revealed between plaque positive sites at T1 in smokers (OR = 5.83, CI: 2.74, 12.42, $p < 0.001$) and non-smokers (OR = 2.29, CI: 1.03, 5.07, $p < 0.041$).

The overall effect of smoking at T2 on the number of sites with PD ≥ 5 mm and BoP was tested at different teeth and sites using adjusted logistic regression analysis (Table 5). An overall negative effect of smoking was demonstrated (OR = 2.78, CI: 1.49, 5.18, $p = 0.001$) particularly at maxillary single-rooted buccal and palatal sites (OR = 6.21, CI: 2.05, 18.88, $p = 0.001$ and OR = 4.55, CI: 1.61, 12.85, $p = 0.004$ respectively), mandibular single-rooted buccal sites (OR = 4.35, CI: 1.06, 17.82, $p = 0.041$), and mandibular multi-rooted buccal sites (OR = 4.10, CI: 1.09, 15.38, $p = 0.036$). The overall ICC were reported within patients (ICC = 0.114), teeth (ICC = 0.509), and sites (ICC = 0.761). The variation was highest at the patient level and least at the site level and was consistent within different teeth and sites (Table 5). At the patient level, the overall ICC for smokers (ICC = 0.137) was higher than for non-smokers (ICC = 0.051; not tabulated).

Discussion

The present study evaluated the effect of cigarette smoking at patient, tooth, and site levels following 12 months of SPT. During SPT, smokers and non-smokers presented increased numbers of PD ≥ 5 mm with BoP with the greatest increase at maxillary single-rooted teeth in smokers; from 10 to 16 at buccal sites and from 25 to 48 at palatal sites. An overall negative effect of smoking was revealed at T2 with the strongest effect at maxillary single-rooted teeth. To a great extent, the site-specific effects explain the outcomes of periodontal therapy (D'Aiuto et al. 2005) and the patient-related effect of smoking seems to act as a modifier at the

Table 4. Clinical parameters and number of teeth as predictors for probing depth (PD) ≥ 5 mm with bleeding on probing (BoP) at T2 in smokers and non-smokers

	Smokers		Non-smokers	
	OR (95% CI)[a]	*p*	OR (95% CI)[a]	*p*
T0				
Teeth	1.02 (0.94, 1.10)	0.699	1.16 (1.01, 1.34)	0.035
CAL	1.48 (1.19, 1.83)	<0.001	1.63 (1.32, 2.02)	<0.001
PD	2.12 (1.74, 2.59)	<0.001	2.25 (1.68, 3.01)	<0.001
BoP	8.93 (3.28, 24.36)	<0.001	10.99 (3.33, 36.23)	<0.001
Plaque	2.21 (0.70, 6.36)	0.185	3.05 (1.19, 7.82)	0.020
T1				
Teeth	1.03 (0.94, 1.12)	0.527	1.16 (1.03, 1.31)	0.017
CAL	2.25 (1.80, 2.82)	<0.001	2.81 (2.14, 3.67)	<0.001
PD	5.63 (3.46, 9.16)	<0.001	7.39 (4.25, 12.85)	<0.001
BoP	13.26 (5.12, 34.38)	<0.001	4.68 (1.32, 16.61)	<0.001
Plaque	5.83 (2.74, 12.42)	<0.001	2.29 (1.03, 5.07)	0.041

T0-T2, baseline before active periodontal therapy (T0)-12 months of supportive periodontal therapy (T2), T1-T2; following completion of active periodontal therapy (T1)-12 months with supportive periodontal therapy (T2).
[a]Logistic regression showing effect of tooth and site-related conditions at T0 and at T1 adjusted for gender, age, marital status, and education.

Table 5. The effect of smoking on probing depth ≥5 mm with bleeding on probing at T2 presented with intra-class correlation coefficients (ICC) within patients, teeth, and sites

	OR (95% CI)	*p*	ICC[a]	ICC[b]	ICC[c]
Overall	2.78 (1.49, 5.18)	0.001	0.114	0.509	0.761
Maxillary multi-rooted	1.55 (0.74, 3.23)	0.238	0.165	0.472	0.758
Buccal sites	1.12 (0.46, 2.75)	0.802	0.161	0.286	0.686
Palatal sites	1.81 (0.84, 3.88)	0.129	0.182	0.371	0.746
Maxillary single-rooted	5.08 (2.01, 12.78)	0.001	0.184	0.476	0.752
Buccal sites	6.21 (2.05, 18.88)	0.001	0.156	0.351	0.754
Palatal sites	4.55 (1.61, 12.85)	0.004	0.210	0.406	0.733
Mandibular multi-rooted	2.51 (1.01, 6.23)	0.047	0.163	0.355	0.691
Buccal sites	4.10 (1.09, 15.38)	0.036	na	0.117	0.746
Lingual sites	2.12 (0.82, 5.49)	0.120	0.168	0.231	0.642
Mandibular single-rooted	3.09 (1.01, 9.43)	0.048	0.171	0.575	0.763
Buccal sites	2.34 (0.75, 7.26)	0.143	0.257	0.401	0.755
Lingual sites	4.35 (1.06, 17.82)	0.041	0.136	0.664	0.781

Logistic regression showing main effect of patient-related conditions at T2 adjusted for gender, age, marital status, and education.
[a]ICC, intra-class correlation coefficients within patients.
[b]ICC, intra-class correlation coefficients within teeth.
[c]ICC, intra-class correlation coefficients within sites na; not available.

site-specific level. As suggested, the magnitude of changes during SPT appears related to the initial defect size at site level and to heavy smoking at patient level (Matuliene et al. 2008). Moreover, a local effect of smoking appears to be superimposed on the systemic effect, particularly affecting maxillary single-rooted teeth. In smokers, the percentage of PD ≥ 5 mm with BoP at these teeth increased from 31% at T1 to 41% at T2, whereas the percentage for maxillary multi-rooted teeth declined from 28% to 23%, respectively. The percentage at T2 were comparable with baseline registration and in accordance with previous findings

demonstrating a high percentage of PD ≥ 5 mm in single-rooted teeth in smokers (van der Weijden et al. 2001). Interestingly, the results show slightly different site-specific treatment outcomes following APT and SPT, indicating altered local tissue responses to cigarette smoking during APT compared with SPT.

Including BoP in the primary outcome variable could introduce a bias due to less BoP in smokers compared with non-smokers (Preber & Bergström 1985, Bergström & Boström 2001). On the other hand, a site level periodontal diagnose including BoP seems to correlate with disease progression and

periodontal instability irrespective of smoking status (Ramseier et al. 2015). At a site level, absence of BoP is considered to predict long-term stability following treatment of chronic periodontitis patients (Lang et al. 1990), whereas presence of BoP predicts disease progression in both smokers and non-smokers (Ramseier et al. 2015). However, it is not clear whether BoP to the same extent is associated with disease progression at a site level in smokers and non-smokers. In this study, the association between BoP at T1 and PD ≥ 5 mm with BoP at T2 was stronger in smokers compared with non-smokers. More intense bleeding from deep pockets following non-surgical periodontal therapy in smokers (Ardais et al. 2014) can be explained by a hyper-inflammatory condition in gingival tissues, thus making BoP a strong predictor for disease progression during SPT.

A tendency towards recurrence of periodontitis during SPT was supported by a significant increase in PD, BI, and PI in both smokers and non-smokers. These findings are in agreement with previous studies showing a slight disease progression during the first years following ATP (Knowles et al. 1979, Preshaw & Heasman 2005). These longitudinal trends of treatment progression might reflect lack of compliance from highly susceptible patients during the first years of SPT. In this study, to compensate for variation in compliance among smokers

(Ramseier et al. 2014), a 3-month SPT frequency compatible with maintenance of highly susceptible patients, was offered. Preferably, the frequency of SPT should reflect the individual risk profile. However, in this prospective study, the SPT interval was standardized regardless of the susceptibility for recurrence of periodontitis, and patients exceeding a 4-month interval were excluded. The effort to adjust for compliance should be considered a merit in the analyses of evaluating the effect of smoking exposure on the efficacy of SPT.

The exposure of smoking was quantified and objectively validated by measuring serum cotinine concentration. At T2, an association was revealed between ≥ 9 sites of PD ≥ 5 mm with BoP per patient and high cotinine levels. Heavy smoking during periodontal treatment, quantified by high levels of cotinine, negatively influenced the outcome of SPT. This association was not detected at T0, indicating that doses of current smoking exposure do not to the same extent influence the level of periodontal disease. Consequently, when smoking cessation is not successful, reduced smoking exposure during therapy should be encouraged. A dose-related treatment response has been documented (Kaldahl et al. 1996a), however, not by objective measures of smoking exposure during therapy. In this study, 86% of the patients with ≥ 9 sites of PD ≥ 5 mm with BoP at T2 were heavy smokers. These findings are in agreement with a former study concluding that 90% of non-responders are smokers (Magnusson & Walker 1996). Non-responding periodontitis, characterized by multiple progressing sites following therapy, is considered a patient-specific more than site-specific entity. Smoking as a patient-related risk factor has previously been recognized (Kornman et al. 1997, Matuliene et al. 2010) and in this study, smoking outweighed other patient-related risk factors documented by a smaller variation in PD ≥ 5 mm with BoP at T2 within smokers compared with non-smokers.

A few limitations of this study, however, should be discussed. The lack of masking has been addressed previously (Bunæs et al. 2015).

Further, a follow-up period of 12 months is a relatively short time to study the effect of smoking on the outcome of SPT. An extension of the observation period might provide more substantiated information. On the other hand, during a longer follow-up period, more patients are prone to drop out and a higher number of smokers might quit smoking. Both factors could definitely have undermined the statistical analysis and the validity of the results. Three smokers reported smoking cessation between T1 and T2 and yet were not excluded from the study. Matching serum cotinine concentration confirmed smoking cessation for one, whereas the other two reported the use of snuff to substitute cigarette nicotine. In Scandinavia, the use of snuff has increased significantly during recent years, especially among adolescents (Hergens et al. 2014). Unregistered use of snuff may have disturbed the measured cotinine concentrations in serum and might be considered a confounder.

In summary, both smokers and non-smokers showed a slight recurrence of disease following 12 months of SPT. However, both smokers and non-smokers responded to periodontal therapy with significant reductions in mean PD, CAL, BI, and PI ($p < 0.001$). An overall negative effect of smoking on PD ≥ 5 mm with BoP was demonstrated with a site-specific tissue response to smoking. Further, BoP at T1 in smokers was a strong site-specific predictor for PD ≥ 5 mm with BoP at T2. At the patient level, elevated cotinine measures at T2 were associated with ≥ 9 sites of PD ≥ 5 mm with BoP. The study reveals that cigarette smoking as a patient-related risk factor may modulate site-associated variables affecting outcomes of SPT. The magnitude of the effect of cigarette smoking on local tissue responses should be further explored in prospective studies with objective quantification of smoking exposure.

Acknowledgements

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Clinical Relevance

Scientific rationale for the study: In general, smokers respond less favourably to periodontal therapy compared with non-smokers. To predict the long-term outcome of periodontal therapy in smokers, the effect of smoking needs to be evaluated at patient, tooth, and site level following active therapy.

Principal findings: An overall negative effect of smoking was demonstrated following 12 months of supportive periodontal therapy, especially at maxillary single-rooted teeth. At patient level, high serum cotinine levels were associated with ≥9 disease progressing sites. At site level, bleeding on probing following active periodontal therapy predicted an increased risk of disease progression in smokers compared with non-smokers.

Practical implications: In perspective, smoking cessation or even smoking reduction may benefit treatment outcomes following supportive periodontal therapy.