

Dose-dependent effect of smoking and smoking cessation on periodontitis-related tooth loss during 10 - 47 years periodontal maintenance—A retrospective study in compliant cohort

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Abstract

Aim: We retrospectively explored effects of smoking on tooth loss due to periodontitis (TLP) in long-term compliant patients.

Materials and Methods: Chart data were collected from 258 patients undergoing post-non-surgical periodontal treatment (mean 2.24 visits/year) for 10–47.5 (mean 24.2) years. Patients were categorized as: (1) never smokers, (2) former smokers, (3) current light smokers (<10 cigarettes/day) and (4) current heavy smokers (≥10 cigarettes/day).

Results: Of 6,590 teeth present at baseline (mean 25.6 teeth/patient), 264 teeth were lost due to periodontitis, corresponding to 0.03, 0.05, 0.08 and 0.11 TLP annually among never smokers, former smokers, current light smokers and current heavy smokers, respectively. A tooth from a current heavy smoker had 4.4-fold, 2.7-fold and 2.6-fold greater risk of TLP than a tooth from a never smoker, a current light smoker and a former smoker, respectively. Both heavy and light former smokers needed washout periods of approximately 15 years to reach the TLP risk level of never smokers. The TLP risk decreased by 6%/year of smoking cessation.

Conclusions: It took almost 15 years of smoking cessation for the risk of TLP among former smokers to reach the level of never smokers. Hence, the 2018 periodontitis grading system should consider the impact of the “washout” period on former smokers.

KEYWORDS

cigarette smoking, mouth diseases, periodontitis, tooth extraction, validation study

1 | INTRODUCTION

Periodontal diseases are among the most prevalent diseases in adults (Albandar, 2005; Petersen & Ogawa, 2012). Periodontitis

affects around 75% of seniors (Albandar, 2005; Eke et al., 2018), and severe periodontitis is the sixth most prevalent chronic disease in the world (Kassebaum et al., 2014) affecting about 11%–15% of adults (Dye, 2012; Eke et al., 2018; Kassebaum et al., 2014).

The ultimate goal of periodontal therapy is to preserve the dentition in a state of health and function, with acceptable esthetics. Even though there is no known treatment modality that effectively can cure periodontitis, its precursor, gingivitis, can be prevented and managed by meticulous plaque biofilm control and lifestyle changes to alleviate the effect of modifiable risk factors, such as smoking cessation and prevention or management of hyperglycaemia in diabetes (Chapple et al., 2015). When such primary prevention efforts are not successful and destructive periodontitis develops, professional treatment and maintenance management are needed, with the ultimate goal of preventing tooth loss due to periodontitis (TLP) (Chapple et al., 2018; Lang & Bartold, 2018). Even though an abundance of studies reports TL, only a subset reported the number of teeth lost specifically due to periodontitis (TLP). In the following, the abbreviation "TLP" is used to denote "tooth loss due to periodontitis" or "teeth lost due to periodontitis," with similar use of TL for tooth loss (or teeth lost) for any reason.

Oliver (1969) reported TL among 442 patients (two-thirds aged >40 years; $n > 11,000$ teeth) treated in private practice that had received regular periodontal maintenance therapy (PMT). After an average of 10.1 years (range: 5–17 years) follow-up (FU) and having been seen every 4.6 months for PMT, there were 178 TLP (79.8% of all teeth lost [TL]), amounting to a mean of 0.40 teeth per patient over the 10.1 years, equivalent to 0.04 TLP/patient/year. Of note is that 22% of the patients did not lose any teeth with 11% losing only 1 tooth (Oliver, 1969).

Lindhe and Nyman (1984) reported 16 TLP in 7 of 61 patients undergoing PMT over 14 years, averaging 0.02 TLP/patient/year. Other studies also reported low annual rates of around 0.1 TLP/patient/year during long-term compliant PMT (Becker, Berg, & Becker, 1984; Bostanci & Arpak, 1991; Checchi, Montevicchi, Gatto, & Trombelli, 2002; Goldman, Ross, & Goteiner, 1986; Hirschfeld & Wasserman, 1978; McFall, 1982; McGuire, 1991; McLeod, Lainson, & Spivey, 1997; Nabers, Stalker, Esparza, Naylor, & Canales, 1988; Wood, Greco, & McFall, 1989). Interestingly, none of these early studies addresses the relationship of TLP to tobacco smoking, whereas the following more recent studies specifically report TLP during compliant long-term PMT while considering smoking.

Some studies were conducted in periodontics specialty offices in Spain, Norway and Italy and reported 0.05 TLP/patient/year with current smokers having a 70% statistically significantly increased risk for TLP [Risk Ratio (RR): 1.6; $p = .018$] (Martinez-Canut, 2015), 0.036 TLP/pt/year with smokers being fourfold more likely than non-smokers to have TLP [adjusted odds ratio (aOR) = 4.2; 95% CI: 1.4–13.8] (Fardal, Johannessen, & Linden, 2004) and 0.008 TLP/pt/year with smokers having almost 50% greater likelihood of TL (OR:1.49) (Carnevale, Cairo, & Tonetti, 2007), respectively.

Retrospective studies were performed based on patient charts at dental schools in Canada where a Dalhousie study reported a mean TLP of 0.06/patient/year (Matthews, Smith, & Hanscom, 2001) and one in Manitoba reported a mean TLP of 0.016/patient/year (Fisher et al., 2008). A Japanese multisite university-based study calculated

Clinical Relevance

Scientific rationale for the study: Long-term studies are unavailable regarding the dose and effects of smoking cessation on periodontitis-related tooth loss (TLP) during periodontal maintenance therapy.

Principal findings: Among 258 patients followed for 10–47.5 years, a tooth from a former smoker had 2.6 times greater TLP risk than one from a never smoker. Within 15 years upon smoking cessation, a tooth in a former heavy smoker (≥ 10 cigarettes/day) had 12 times (OR = 12.20; 95% CI: 4.64–31.90)—and in a former light smoker (< 10 cigarettes/day) almost four times (OR = 3.74; 95% CI: 1.50–9.34)—greater risk of TLP compared to a tooth from a never smoker. This risk decreased 6%/year after quitting smoking.

Practical implications: Potential TLP during periodontal maintenance therapy among former smokers for ≤ 15 years after smoking cessation should be expected by clinicians and be considered in a revised 2018 periodontitis grading system.

a mean of 0.040 TLP/patient/year among PMT compliant patients (Hirata, Fuchida, Yamamoto, Kudo, & Minabe, 2019). These three studies found smoking to not be associated with TLP.

A German study found smoking to be a significant risk factor for TLP in 142 patients with an initial mean age of 46 years (range 23–72 years) that had PMT lasting 10.5 (± 1.6) years, but no estimates of the magnitude of its effect were provided (König, Plagmann, Ruhling, & Kocher, 2002). In a Chinese dental school, 94 compliant post-periodontal surgery patients were followed for a mean of 3.8 years (Huang, Lai, Huang, & Lu, 2016). Current smoking was associated with recurrence of periodontitis, but not with tooth loss, possibly due to the short FU duration and only 5.3% (5/94) being current smokers. A dental school/specialist centre in Singapore followed 239 compliant PMT patients (mean age 49.3 years; range 26–70 years) for an average of 10.7 years (range: 7.0–20.4 years) and reported 0.03 TLP/patient/year (Ng, Ong, Lim, Koh, & Chan, 2011). Even though smoking habits were recorded in detail, smoking was not included in the regression model to identify risk factors due to the participation of only one current and one former smoker. A Swiss dental school study followed 270 PMT patients for a mean of 5.6 (± 3.8) years during which 150 TLP occurred, namely 0.099 TLP/patient/year. Despite 39.6% being current and 27.8% former smokers, smoking had no significant role in TL (Tonetti, Muller-Campanile, & Lang, 1998; Tonetti, Steffen, Muller-Campanile, Suvan, & Lang, 2000).

Several factors play important roles in pathogenesis and progression of periodontitis (Giannobile et al., 2013), and synergistic effects of two factors simultaneously, such as diabetes/hyperglycaemia and smoking, may be greater than the sum of the effects of the individual factors (Ganesan et al., 2017). Such genetic, epigenetic

and behavioural or environmental factors may lead to tooth loss due to hopeless periodontitis, despite standard professional and home care to which a minority, currently estimated to 20–25 per cent of patients, do not respond adequately and predictably (Giannobile et al., 2013). This situation presents a challenge in assigning the Grade as per the 2018 periodontitis classification (Kornman & Papapanou, 2019) as well as in clinical management, which requires experienced and knowledgeable professional judgement.

Overall, existing literature demonstrates that periodontal treatment with subsequent compliant long-term PMT successfully can maintain a dentition with minimal TLP. While some studies report that cigarette smoking increases the risk for TLP, detailed estimates of such effect by various smoking subcategories are lacking.

Therefore, the specific goals of our study were to answer the following questions [PICO/PECO elements (Higgins et al., 2019; Miller & Forrest, 2001; Richardson, Wilson, Nishikawa, & Hayward, 1995):

1. What is the overall effect of smoking on TLP during compliant PMT for at least 10 years? P (patient/participant/population): dental school patients treated for periodontitis; I (intervention)/E (exposure): cigarette smoking; C (comparison/control): non-smokers; O (outcome): TLP
2. What are the specific effects of smoking on TLP during compliant PMT for at least 10 years? P (patient/participant/population): dental school patients treated non-surgically for periodontitis; I (intervention)/E (exposure): (a) cigarette smoking intensity and frequency; and (b) duration of smoking cessation; C (comparison/control): non-smokers or smokers of varying intensity, frequency, and duration; O (outcome): tooth loss due to periodontitis (TLP)]

2 | MATERIAL AND METHODS

This study was conducted in agreement with the Helsinki Declaration of 1975 (World Medical Association [WMA], 1975) as most recently revised in 2013 (WMA, 2013). The study was approved by the University of Michigan Medical School Institutional Review Board (IRBMD) with study identifier HUM00157260/HUM00160933.

2.1 | Study population

Data were retrospectively retrieved from charts of patients who underwent non-surgical periodontal treatment between January 1966 and January 2008 at the University of Michigan School of Dentistry, Ann Arbor, Michigan, USA. Inclusion criteria, data collection and patient allocation according to the 2017 World Workshop periodontitis case definitions that include stage (1–4), grade (A, B and C) and extent (localized, generalized) (Tonetti, Greenwell, & Kornman, 2018) are described elsewhere (Ravidà et al., 2020). Diabetes was added as an exclusion criterion to eliminate this important confounding factor in the current study that seeks to specifically assess the role of smoking. Given that there is no evidence for generally appropriate

PMT intervals (Farooqi, Wehler, Gibson, Jurasic, & Jones, 2015; Mombelli, 2019), patients who underwent at least one initial, active treatment session of non-surgical (scaling and root planing) periodontal treatment and subsequently underwent at least one PMT visit per year throughout the entire FU period were included in the study. Data on pertinent patient characteristics, the number of PMT visits per year and relevant medical history were collected. Radiographic bone loss (BL, % of root length) at baseline (time zero, T0) was measured from periapical radiographs to assess periodontitis stage and grade (Pepelassi, Tsiklakis, & Diamanti-Kipiotti, 2000). The date of the last PMT visit for which data were available was called T1. Tooth-specific data on clinical parameters, such as periodontal probing depth (PPD), clinical attachment level (CAL) [formerly calculated and recorded in the chart as the difference between PPD and the distance from the free gingival margin (FGM) to the cemento-enamel junction (CEJ)], bleeding on probing (BOP), furcation involvement, presence of restorations and crowns on inter-proximal surfaces, apical pathology, endodontic root filling, endodontic post and presence of vertical bone defects were collected at T0 and T1.

Patient charts were searched for tooth loss (TL) by comparing the number of natural teeth present at T0 and T1. For each non-third molar tooth that was lost, the date and cause of extraction were recorded. Importantly, the reason for any extraction was always recorded as per school policy. To evaluate the effect of smoking habits on TL, patients were divided at T0 into four groups with the current smokers further allocated to one of two groups by smoking intensity: (a) never smokers; (b) former smokers (ex-smokers); (c) low-intensity (light) current smokers who smoked <10 cigarettes/day; and (d) high-intensity (heavy) current smokers who smoked ≥10 cigarettes/day. The number of years since smoking cessation was recorded for patients who were ex-smokers at T0 (Group 2) as well as for patients in Groups 3 and 4 who had quit smoking during the FU period. Furthermore, any change in the smoking habits for the other groups was recorded and taken in consideration in the statistical analyses. Any patient with incomplete data for any of the collected information was excluded from the study.

2.2 | Statistical analysis

Statistical analysis was conducted using SPSS 22 (IBM Corporation) and R 3.5.1 (R Core Team, 2018).

At the patient-level, a simple binary logistic regression model was created to assess the probability of medium–high risk for having TLP (TLP > 1) according to smoking classification. Multiple models were constructed while adjusting for potentially confounding factors (sex, age, number of PMT visits, FU duration and baseline clinical data).

Based on the number of TLP during the study, participants were categorized as well-maintained (0–3 TLP), downhill (4–9 TLP) and extreme downhill (≥10 TLP) (Hirschfeld & Wasserman, 1978), with this index modified to include only TLP, not any TL. At the tooth-level, the outcome TLP (yes/no or ≥1/0) was related to the smoking classification of the patient until the occurrence of the event or at T1

(in case of no change in smoking status) using multilevel logistic regression with generalized estimation equations (GEE). Raw ORs and 95% CIs were calculated and tested for significance of the included variables with the Wald chi-squared test. Again, multiple models were constructed to estimate the need to adjust for potential confounding factors (sex, age, number of PMT visits, FU duration and baseline clinical data). The goodness of fit of different estimates (for different matrix correlations) was assessed by QIC (Quasi-likelihood under the Independence model Criterion) goodness of fit statistic for GEE models.

Upon initial analyses, ex-smokers were further subdivided based on both the former smoking intensity (number of cigarettes smoked per day) and duration of time since cessation in order to study the washout period within former smokers, comparing risk of TLP between categories.

Time to event of extraction due to periodontitis was analysed using survival analysis techniques. In particular, to consider dependence between observations (tooth-level data clustered by patient), univariate and multivariate multilevel Cox regression models with clustering by patient were built to analyse the influence of the smoking condition. The proportional hazard assumption was tested by means of Schoenfeld's tests.

The statistical significance level was set at 5% ($\alpha = .05$). These calculations are the basis for the subdivision of the group of current smokers by smoking intensity as described earlier with Group 3 smoking < 10 cigarettes/day (light smokers) and Group 4 smoking ≥ 10 cigarettes/day (heavy smokers).

3 | RESULTS

3.1 | Study population

A total of 258 patients (123 males and 135 females) with a baseline mean age of 46.6 (± 11.8) years (range: 17–76 years) were included in the study. Patients with at least one annual PMT visit were followed for a mean duration of 290.7 (± 81.1) months (range: 120–570 months), equivalent to 24.2 \pm 6.7 years (range: 10–47.5 years). The average number of annual PMT visits was 2.24. Demographic and clinical characteristics of the study population at T0 are shown in Table 1.

The sex distribution in the smoking categories was significantly different ($p = .008$, χ^2) with more women among never smokers (~60% vs. 40%) and fewer women among ex-smokers (~30% vs. ~70%). All the other characteristics were similar among groups.

TABLE 1 Demographic and clinical characteristics at baseline (T0) by smoking status (N = 258)

Characteristics	Number (%) or Mean (\pm SD)	Smoking status at baseline (T0) Mean (\pm SD) or n (%)			
		Never smokers n (%) or Mean (\pm SD)	Former smokers n (%) or Mean (\pm SD)	Current smokers	
				Light smokers <10 cig/day n (%) or Mean (\pm SD)	Heavy smokers ≥ 10 cig/day n (%) or Mean (\pm SD)
N, n (%)	258	146 (56.6)	50 (19.4)	37 (14.3)	25 (9.7)
Age, years	46.6 (± 11.8)	46.7 (± 12.2)	49.5 (± 10.0)	43.1 (± 11.6)	45.1 (± 12.1)
Sex					
Male	123 (47.7)	59 (40.4)	34 (68.0)	19 (51.4)	11 (44.0)
Female	135 (52.3)	87 (59.6)	16 (32.0)	18 (48.6)	14 (56.0)
Periodontitis stage ^a	258				
1	27 (10.5)	19 (13.0)	4 (8.0)	3 (8.1)	1 (4.0)
2	78 (30.2)	43 (29.5)	18 (36.0)	10 (27.0)	7 (28.0)
3	130 (50.4)	70 (47.9)	26 (52.0)	20 (54.1)	14 (56.0)
4	23 (8.9)	14 (9.6)	2 (4.0)	4 (10.8)	3 (12.0)
Extent	258				
Localized	189 (73.3)	105 (71.9)	36 (72.0)	29 (78.4)	19 (76.0)
Generalized	68 (26.4)	41 (28.1)	14 (28.0)	7 (18.9)	6 (24.0)
Molar/incisor pattern	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)
Follow-up duration (FU), months	290.7 (± 81.1)	292.1 (± 81.6)	273.8 (± 70.4)	291.4 (± 79.0)	315.3 (± 97.1)
# PMT visits/year	2.24 (± 0.68)	2.23 (± 0.68)	2.28 (± 0.60)	2.19 (± 0.62)	2.26 (± 0.95)
# Teeth present	25.5 (± 3.0)	25.8 (± 2.7)	25.2 (± 3.6)	25.3 (± 2.8)	25.3 (± 3.4)

Abbreviations: # or N or n, number; cig, cigarettes; PMT, periodontal maintenance therapy; SD, standard deviation.

^a2018 periodontitis classification (Tonetti et al., 2018).

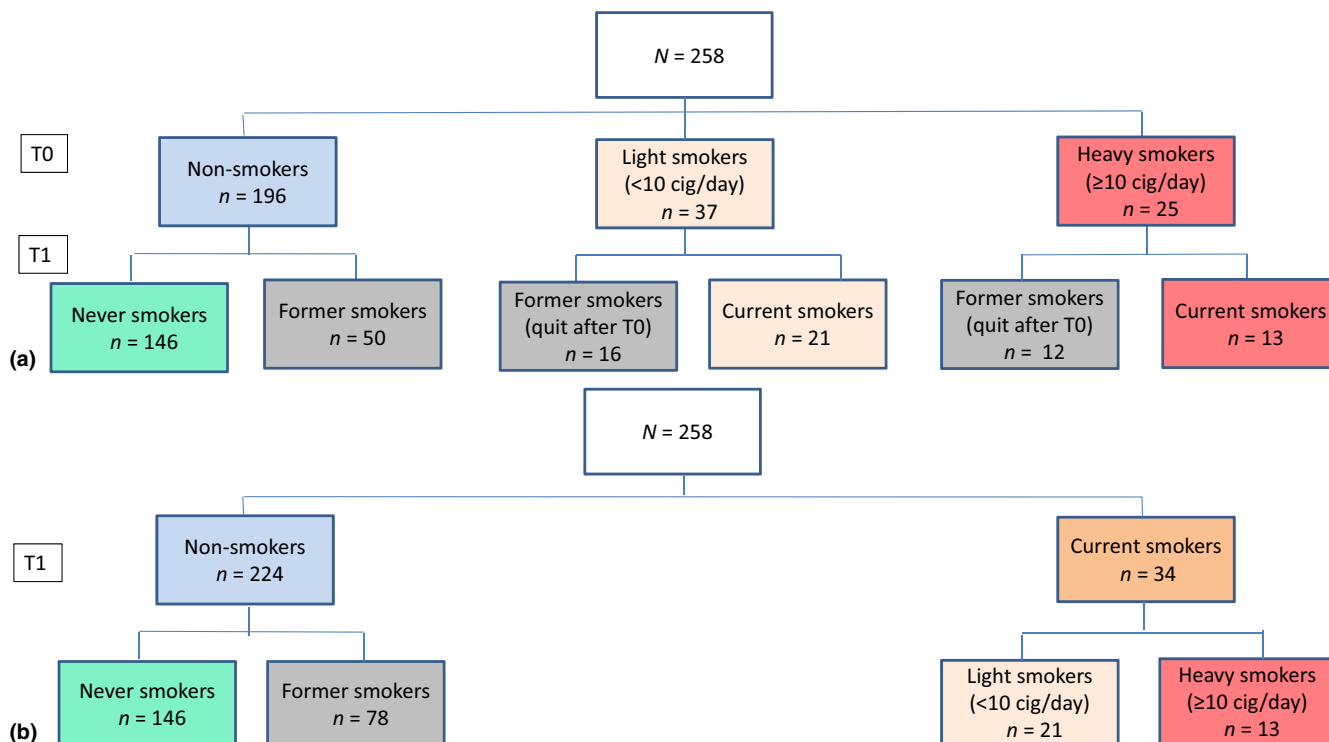


FIGURE 1 Patient-level distribution of the study population by smoking habits at baseline (T0) and at the last periodontal maintenance therapy visit (T1) (Panel a). Final smoking habits at T1 (Panel b) (N = 258). Abbreviations: cig, cigarettes; N or n, number of patients; T0, baseline; T1, last study visit

Smoking status was initially determined at T0 (Figure 1, Panel a) and was also recorded for each subsequent PMT visit. Such repeated recording provided the basis for calculating detailed information about any changes in smoking habits, including cessation, during the FU period between T0 and T1 as illustrated in Panel a in Figure 1. Twenty-eight smokers stopped smoking and thus became ex-smokers between T0 and T1, namely 43.2% (16/37) of the initially light smokers and 48.0% (12/25) of the initially heavy smokers. None of the patients originally designated as never smokers at T0 became smokers during the study period, and none of the patients quit smoking and started again. The final smoking status at the last PMT visit is shown in Panel b in Figure 1.

3.2 | Patient-level results

Clinical characteristics at T1 by smoking group are shown in Table 2. A statistically significant association was found between increasing smoking intensity (number of cigarettes/day) and TLP. For patient-level comparison, the number of TLP was dichotomized into the two groups: low (≤ 1 tooth) and high (> 1 tooth). Overall, former smokers had 2.59 times the odds of high (> 1) TLP compared to never smokers (95% CI: 1.27–5.26) (Table S1). Current light smokers (< 10 cigarettes/day) did not have any statistically significantly excess risk for TLP when compared to never smokers upon adjustment for sex, age, FU duration and number of PMT (Tables S1 and S2) or to former smokers overall (Table S2).

In contrast, current heavy smokers (> 10 cigarettes/day) had 18.9 times greater risk of high TLP (> 1 tooth) compared to never smokers (95% CI: 4.82–74.1; $p < .001$) upon adjustment for sex, age, FU duration and number of PMT (Tables S1 and S2) and a statistically significant nine-fold greater risk compared to either former smokers overall (aOR = 9.07; 95% CI: 2.09–39.5; $p < .01$) or to current light smokers (aOR = 8.79 (1.49–51.8; $p < .01$) (Table S1). A binary logistic regression model showed that whereas sex, age and number of PMT visits per year were not important confounders, the FU duration was a statistically significant variable.

Based on the number of TLP during the study, more than 9 in 10 (91.9%) of the participants were categorized as well-maintained (0–3 TLP), 7.4% as downhill (4–9 TLP) and 0.8% as extreme downhill (≥ 10 TLP) (Table 2).

3.3 | Tooth-level results

At baseline, 6,590 teeth were present in the 258 study participants (mean 25.5 teeth/patient). A total of 631 teeth were lost during FU, of which 264 (41.8%) were lost due to periodontitis, amounting to 3.65% (95%CI: 3.22%–4.09%) of all teeth present at baseline. The proportions of TL by smoking status at T1 and reason for TL are illustrated in Figure 2. The mean number of TLP during the study period ranged from 0.03 (± 0.06) TLP/patient/year in never smokers to 0.11 (± 0.08) TLP/patient/year in heavy smokers (Table 2). The vast majority of TL between times T0 and T1 occurred in current heavy smokers, who on average lost almost a quarter (24.0%) of their teeth,

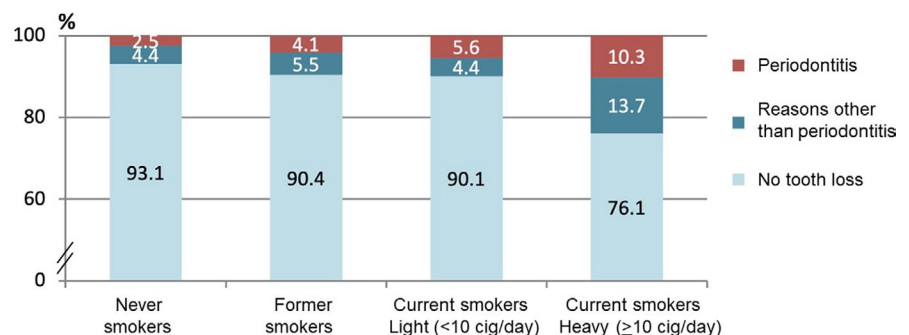
TABLE 2 Clinical characteristics by smoking group at last follow-up visit (T1) by smoking status (N = 258)

Characteristics	Smoking status at last follow-up visit (T1) Mean (\pm SD) or n (%)				
	Total N (%) or Mean (\pm SD)	Never smokers n (%) or Mean (\pm SD)	Former smokers n (%) or Mean (\pm SD)	Current smokers	
				Light smokers <10 cig/day n (%) or Mean (\pm SD)	Heavy smokers \geq 10 cig/day n (%) or Mean (\pm SD)
N, n (%)	258	146 (56.6)	78 (30.2)	21 (8.1)	13 (5.0)
Age, years	46.6 (\pm 11.8)	46.7 (\pm 12.2)	46.6 (\pm 10.4)	45.8 (\pm 13.5)	46.7 (\pm 13.6)
# Teeth present	23.0 (\pm 4.5)	23.8 (\pm 3.8)	22.4 (\pm 4.8)	21.7 (\pm 6.3)	19.8 (\pm 4.0)
# TL since baseline (T0)	2.54 (\pm 3.05)	1.96 (\pm 2.59)	3.01 (\pm 3.38)	2.76 (\pm 3.79)	5.84 (\pm 2.94)
# TLP (% of all teeth lost)	1.01 (39.8%)	0.67 (\pm 1.50) (34.2%)	1.28 (\pm 1.95) (42.5%)	1.43 (\pm 2.50) (51.8%)	2.46 (\pm 1.94) (42.1%)
# teeth lost due to reasons other than periodontitis (% of all teeth lost)	1.53 (60.2%)	1.29 (\pm 1.78) (65.8%)	1.73 (\pm 2.47) (57.5%)	1.33 (\pm 2.18) (48.2%)	3.38 (\pm 1.94) (57.9%)
TL pattern ^a	258				
Well-maintained (0–3)	191 (74.0)	119 (81.5)	54 (69.2)	14 (66.7)	4 (30.8)
Downhill (4–9)	55 (21.3)	24 (16.4)	18 (23.1)	5 (23.8)	8 (61.5)
Extreme downhill (\geq 10)	12 (4.7)	3 (2.1)	6 (7.7)	2 (9.5)	1 (7.7)
Mean # TL for any reason/Pt/year	0.101	0.08 (\pm 0.10)	0.12 (\pm 0.12)	0.15 (\pm 0.25)	0.25 (\pm 0.12)
Mean # TLP/pt/year	0.042	0.03 (\pm 0.06)	0.05 (\pm 0.07)	0.08 (\pm 0.19)	0.11 (\pm 0.08)
TLP pattern ^a	258				
Well-maintained (0–3)	237 (91.9)	139 (95.2)	70 (89.7)	19 (90.5)	9 (69.2)
Downhill (4–9)	19 (7.4)	6 (4.1)	8 (10.3)	1 (4.8)	4 (30.8)
Extreme downhill (\geq 10)	2 (0.8)	1 (0.7)	0 (0.0)	1 (4.8)	0 (0.0)

Abbreviations: # or N or n, number; cig, cigarettes; PMT, periodontal maintenance therapy; pt, patient; SD, standard deviation; TL, tooth loss (teeth lost) due to any reason; TLP, tooth loss (teeth lost) due to periodontitis.

^aHirschfeld and Wasserman (1978).

FIGURE 2 Tooth-level distribution of tooth loss (TL) during the follow-up period by reason for tooth loss and smoking status at the last periodontal maintenance therapy (PMT) visit (T1) (N = 6,590). Abbreviations: cig, cigarettes



with 10.3% being TLP and 13.7% lost due to other reasons (Figure 2). A dose–response pattern for TLP is seen by smoking status from never smokers through former and current light to current heavy smokers having lost 2.5%, 4.1%, 5.6% and 10.3% of their teeth (Figure 2).

At the tooth-level overall, former smokers (at the time of the event) had 73% greater odds of TLP compared to never smokers

(aOR = 1.73; 95% CI: 1.08–2.75; $p = .022$) (Table 3, Table S3). This risk was substantially greater for teeth in current heavy smokers whose odds for any TLP were 438 per cent or 4.4-fold greater than in never smokers (OR = 4.38; 95% CI: 2.67–7.21; $p < .001$), 2.6-fold greater than in former smokers and 2.7-fold greater than in current light smokers (Table 3, Table S3).

TABLE 3 Tooth-level association between any teeth lost due to periodontitis (TLP) (yes/no) and smoking status at the last follow-up visit (T1)^a (N = 6,590)

Smoking group	Reference category			
	Never smokers aOR (95% CI)	Former smokers aOR (95% CI)	Current smokers	
			Light smokers <10 cig/day aOR (95% CI)	Heavy smokers ≥10 cig/day aOR (95% CI)
Never smokers	1	n/a	n/a	n/a
Former smokers	1.73 (1.08–2.75)	1	n/a	n/a
Current smokers				
Light smokers <10 cig/day	1.89 (0.91–3.94)	1.05 (0.54–2.07)	1	n/a
Heavy smokers ≥10 cig/day	4.38 (2.67–7.21)	2.56 (1.55–4.22)	2.74 (1.26–5.94)	1

Note: **Bolded** font, statistically significant at $p < .05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cig, cigarettes; n/a, not available or not applicable

^aAdjusted for sex, age, follow-up duration, number of maintenance visits/year and periodontitis stage (Tonetti et al., 2018).

Characteristics	Odds ratio ^a (OR)	95% Confidence interval (95% CI)
Former smoking intensity		
Light smokers < 10 cig/day	1	n/a
Heavy smokers ≥10 cig/day	4.89	2.30–10.4
Duration of smoking cessation (# years since quitting smoking)	0.94	0.89–0.99
Intensity × duration	1.03	0.94–1.14

Note: **Bolded** font, statistically significant at $p < .05$.

Abbreviations: #, number; cig, cigarettes; n/a, not available or not applicable; T0, baseline; T1, last follow-up visit.

^aBinary logistic regression model using GEE without adjustment.

TABLE 4 Tooth-level association between any teeth lost to periodontitis (TLP) (yes/no) and characteristics of former smokers at last follow-up (T1) (N = 2,163 teeth present in former smokers at T0)

In order to assess differences in tooth survival by smoking status, while taking into consideration the time to TLP for each tooth, we built a frailty multilevel Cox regression multivariate model with data clustered for each patient. Results of this analysis revealed no significant difference in risk for TLP between a tooth from never smokers and former light smokers of <10 cigarettes/day. In contrast, a tooth from former heavy smokers of ≥10 cigarettes/day (aHR = 3.34; 95% CI: 2.08–5.37; $p < .001$) and current heavy smokers (aHR = 4.69; 95% CI: 2.84–7.75; $p < .001$) had significantly greater risk of TLP compared to never smokers during FU (Table S4).

3.4 | Washout period for former smokers

3.4.1 | Tooth-level results

Both the intensity of former smoking and the duration of the cessation period significantly influenced the estimated probabilities of TLP during the study period.

The probability of TLP exhibited a dose-dependent response as a tooth from a former heavy smoker (≥10 cigarettes/day) was greater than for a tooth from a former light smoker (<10 cigarettes/day) at all time points. Moreover, the longer the duration since smoking cessation, the lower the probability of TLP became for teeth from both light and heavy former smokers. In fact, the predicted probability of TLP for teeth from heavy and light former smokers tended to approximate one another as time since smoking cessation increased (Not shown).

Results of binary logistic regression modelling using GEE estimated that each additional year since quitting smoking reduced the risk of TLP by 6% (OR = 0.94; 95% CI: 0.89–0.99; $p = .031$) (Table 4). Furthermore, teeth from former heavy smokers had almost 5 times greater risk of TLP compared to those from former light smokers (OR = 4.89; 95% CI: 2.30–10.04) (Table 4).

The washout period for former smokers was defined as the duration of time it took for the risk of TLP for a former smoker to approximate the baseline risk of a never smoker. The GEE model at the tooth level showed that the washout period was 15 years for both heavy and light former smokers (Table 5). A tooth in a former

TABLE 5 Tooth-level association between any lost teeth due to periodontitis (TLP) (yes/no) and smoking status at last follow-up visit (T1) adjusted for the other independent factors shown in the table ($N = 6,590$ teeth at T0)

Characteristics	Smoking intensity	Duration of cessation (# years since quitting smoking)	Adjusted odds ratio (aOR)	95% Confidence interval (95% CI)
Smoking status at T1				
Never smokers			1	
Former smokers	Light smokers <10 cig/day	>40	0.58	0.18–1.86
		31–40	0.26	0.03–2.09
		16–30	0.52	0.24–1.12
	Heavy smokers ≥10 cig/day	<15	3.74	1.50–9.34
		>40	1.76	0.54–5.72
		31–40	1.70	0.38–7.67
Current smokers	Light smokers <10 cig/day	16–30	1.75	0.64–4.82
		<15	12.20	4.64–31.90
	Heavy smokers ≥10 cig/day	n/a	1.94	0.93–4.05
		n/a	4.32	2.63–7.08
Sex				
Male	n/a	n/a	1	
Female	n/a	n/a	0.92	0.62–1.37
Age, years	n/a	n/a	0.98	0.96–1.01
Follow-up (FU), months	n/a	n/a	1.004	1.001–1.007
# Maintenance visits/year	n/a	n/a	0.81	0.53–1.23
Periodontitis stage at T0 ^a				
1	n/a	n/a	1	
2	n/a	n/a	1.62	0.70–3.77
3	n/a	n/a	3.03	1.37–6.74
4	n/a	n/a	7.27	2.81–18.8

Note: **Bolded** font, statistically significant at $p < .05$

Abbreviations: #, number; cig, cigarettes; n/a, not available or not applicable; T0, baseline; T1, last follow-up visit.

^a2018 periodontitis classification (Tonetti et al. 2018).

light smoker showed almost four times greater risk of TLP compared to that from a never smoker within the first 15 years of smoking cessation (OR = 3.74; 95%CI: 1.50–9.34). Within the same time-frame, a tooth in a former heavy smoker had 12 times greater risk of TLP compared to that from a never smoker (OR = 12.20; 95% CI: 4.64–31.90). However, the TLP risk was not statistically significantly different for neither light nor heavy former smokers relative to never smokers after 15-year cessation (Table 5). A tooth from a never smoker had 2.5% risk for TLP during the study period. This was the reference probability ($p = .025$) of TLP at T1 because 103 teeth were lost to periodontitis among the 4,088 teeth originally present in never smokers at T0, so $p = 103/4,088 = .025$.

4 | DISCUSSION

In accordance with prior studies, we found that frequent and consistent PMT subsequent to active non-surgical periodontal

treatment can result in tooth preservation for the majority of the dentition (94.4%–97.5%). However, heavy smokers lost 23.9% over this same period. Our study's finding of 0.042 TLP/patient/year is of a similar magnitude to that in the study of a mean duration of 10.7 years in Singapore of 0.03 TLP/patient/year (Ng et al., 2011), despite the latter study's 239 participants with a very low smoking rate (only one current and one former smoker). Compared to the 0.099 TLP/patient/year during a mean of only 5.6 years reported in a Swiss study that included 67.4% former or current smokers, our patients exhibited less than half their reported TLP (Tonetti et al., 1998, 2000). However, direct, numeric comparisons with results from past studies are somewhat inaccurate due to heterogeneous study designs and case definitions used for periodontitis diagnosis, as well as differences in intensity of initial active non-surgical periodontal treatment, philosophies regarding tooth extraction, definitions of compliant PMT, inclusion of non-compliant patients, duration of PMT and FU and parameters reported.

In our study, TLP accounts for 39.8% of the total teeth extracted (Table 2). This finding was lower than in a German dental school study, in which 48% of the tooth loss during PMT occurred due to periodontitis (König et al., 2002), and the Swiss study, where 64% of the extractions (including third molars and primary teeth) were due to periodontitis (Tonetti et al., 1998, 2000).

4.1 | Tooth loss for any reason among former smokers

While we did not identify any prior studies that reported specifically on TLP among former smokers, some longitudinal studies have focused on the effect of having quit smoking on TL for any reason. For example, Dietrich and colleagues demonstrated that smoking quitters among male US health professionals had a significantly lower risk for TL compared with current smokers. Although this TL risk decreased gradually over time, it did not reach the level of never smokers until after 10–20 years after cessation (Dietrich, Garcia, de Pablo, Schulze, & Hoffmann, 2007). Another study among men (Veterans Administration) also found that TL due to any cause decreased over time after smoking cessation (Krall, Dietrich, Nunn, & Garcia, 2006). A 1997 study concluded that “smoking cessation significantly benefits an individual's likelihood of tooth retention, but it may take decades for the individual to return to the rate of tooth loss observed in non-smokers” (Krall, Dawson-Hughes, Garvey, & Garcia, 1997). Women who quit showed no difference due to their low number ($n = 14$). During the study that lasted 18 (± 7) years, male quitters ($n = 167/N = 813$) lost more teeth on average [$0.223(\pm n/a)$ /participant/year] than non-smokers [$0.133(\pm n/a)$ /participant/year] and had 70% greater risk for incident TL (RR = 1.7; 95% CI: 1.5–1.8) compared to non-smokers ($n = 529$) (Krall et al., 1997). These results, as well as the results of the present study, demonstrate that former smokers have a residually elevated risk for TL compared to non-smokers for a substantial duration of time immediately after quitting.

4.2 | Years long washout period after smoking cessation

When taking into consideration the broad range of detrimental effects and physiological mechanisms that are at play, it is understandable that it takes a long time to revert to healthy tissues in former smokers after smoking cessation. The oral epithelium and its cover of saliva together represent a barrier to protect the underlying tissues. However, this protection is likely compromised in smokers due to the desiccation and toxic effects of tobacco and its smoke, which facilitates the transfer of bacteria and their toxins into the bloodstream by which they are disseminated throughout the body and contribute to chronic systemic inflammation (Borgnakke, 2019).

In smokers, changes in the oral microbiota that favour anaerobic species occur (Beghini et al., 2019), so the subgingival biofilm in smokers displays less species diversity than non-smokers (Bizzarro, Loos,

Laine, Crielaard, & Zaura, 2013). Moreover, interactions occur between periodontal clinical manifestations and bacterial antibody profiles and are mediated by antibody responses (Nagarajan, Miller, Dawson, Al-Sabbagh, & Ebersole, 2017). Both host genetic factors (Zhang, Yu, & Arce, 2020) and epigenetic modifications (non-DNA encoded changes in gene expression caused by environmental and other factors) play important roles in the pathogenesis of periodontitis (Larsson, Castilho, & Giannobile, 2015; Martins et al., 2016). Neutrophil function is also altered in smokers (Armitage, 2020). However, the specific cellular and molecular mechanisms that may contribute towards the washout period in former smokers are still largely unknown. Overall, we found that both current and former heavy smokers had more TLP than current and former light smokers. However, we did not identify any past study that provided such detailed reporting of TLP by intensity of current and former smoking habits in a compliant population with long-term PMT. Hence, we cannot make any direct comparisons regarding the impact of smoking on TLP by smoking intensity.

4.3 | 2018 periodontitis case definitions

The 2017 World Workshop aligned and updated the periodontitis classification to the current understanding of periodontal diseases. Among the five major recommendations of the 2017 World Workshop Consensus pertaining to future research, is the use of existing databases to validate and refine the newly introduced classification system (Papapanou et al., 2018). In a previous study, our team validated the capability of the staging and grading system to predict future TLP (Ravidà et al., 2020). In the present study, we advocate for the refinement of the new classification when allocating former smokers a periodontitis grade (Tonetti et al., 2018). Firstly, our finding of great differences between light and heavy former smokers is a factor that we believe should be incorporated. That is, the category former smokers should be divided into two subgroups, distinguishing between heavy (≥ 10 cigarettes/day) and light (< 10 cigarettes/day) former smokers. Secondly, instead of considering a patient a non-smoker once he/she quits smoking, our findings suggest that the periodontitis grade for a former smoker should be changed only after a sufficient washout period has passed and not immediately upon smoking cessation.

4.4 | Strengths

To the best of our knowledge, this study is one of the largest studies of its kind, as the 258 participants underwent compliant PMT for an unusually extended FU period [mean 24.2 (± 6.7) years] ranging from 10 to 47 years with the participants undergoing a mean of 2.24 PMT visits/year. Due to the high number of patients available, we could exclude those with less than 10 years of PMT. Furthermore, Ravidà and team (2020) are the first to allocate each patient to one of the 2018 clinical periodontitis case definitions (Tonetti et al., 2018) and explore the effects of smoking on tooth loss caused by periodontitis while applying the 2018 smoking history categories (Ravidà

et al., 2020). Historically, smoking was not generally recognized as an important risk factor for progression of periodontitis until the 1990s. The US Surgeon General's report on oral health of 2000 was the first such report to mention smoking as an evidence-based risk factor for periodontitis (U.S. Department of Health & Human Services, 2000). To avoid the confounding influence of diabetes on TLP and heterogeneity in reported glycaemic measurements (HbA1c vs. blood glucose), patients with diabetes were not included. It is known that the additive effects of putative risk factors (such as smoking, diabetes and the presence of interleukin-1 polymorphisms) increase the risk for tooth loss over the long-term (Giannobile et al., 2013). Also, while diabetes/hyperglycaemia and smoking influence the subgingival microbiome in different ways, their synergistic effect is greater than that which would be expected from the added effects of those two individual factors (Ganesan et al., 2017).

4.5 | Limitations

Inherent in retrospective studies are several potential biases, as the data were originally recorded by individuals other than those conducting this study, and for other purposes. Therefore, charting, diagnoses and various treatments may not have been recorded consistently due to differing levels of provider clinical experience.

The present study set the limit of 10 or more years of regular FU as a criterion for inclusion. Since we had a large patient pool, we wanted to avoid the shortfall of prior studies that did not follow the patients long enough. Inadvertently, this attempt to improve the validity of the study may have introduced an unintentional bias by selectively excluding patients who either died or lost their entire dentition due to rapid periodontitis progression before the 10-year mark. However, our finding showed that only 0.8% of patients were categorized as "extreme downhill" (≥ 10 TLP) and 7.4% as downhill (4–9 TLP) (Table 2), with a mean of 25.5 (± 0.3) teeth present at baseline and a narrow range of 25.2–25.8 teeth (Table 2). In any case, this ≥ 10 years PMT threshold ensured that the primary objective of our study was not compromised. Previous studies have shown that smoking washout requires significant time, well beyond 10 years (Dietrich et al., 2007). With the role of maintenance in periodontal health being pivotal (Mombelli, 2019; Ramseier et al., 2019), we considered a criterion indicating true long-term compliance to be obligatory.

Our study was conducted using data from patients treated at a dental school by a variety of operators, such as undergraduate and graduate dental students, students of dental hygiene and their instructors, some of whom would have been general dentists and others periodontists, all of whom bring their own biases. This could for example lead to different subjective criteria for the need for extractions, which hinges on a variety of factors that are not all related solely to the periodontal health status of the tooth, such as economic considerations and overall treatment plans. The inclusion of data from many years could also lead to some systematic bias caused by changing views on the possibility of salvaging a tooth (vs.

extraction and replacement by an implant) and periodontal practice protocols for PMT over time. Moreover, the clinical judgement of the clinician may play a role and may also change over time as well as differ between operators. Additionally, the attitude, motivation and financial circumstances of each patient also influence the decision to extract a tooth "for periodontal reasons." The importance of this study in terms of identifying a washout period for former smokers as well as demonstrating a dose-dependent response in former smokers cannot be ignored. That said, only intervention studies are capable of demonstrating such impact.

5 | CONCLUSION

Current and former smokers lost significantly more teeth due to periodontitis than never smokers after active non-surgical periodontal treatment and long-term PMT. In addition, we identified a dose-response pattern, namely that former heavy smokers had more TLP than former light smokers. Importantly, even though it took about 15 years of smoking cessation for the risk of TLP among former smokers to reach that of never smokers, there was a clear difference in the magnitude of TLP between former heavy and light smokers.

Consequently, we propose that these findings should further be explored in other studies and, if validated, subsequently be incorporated in the 2018 periodontal disease classification (Tonetti et al., 2018) that currently does not include a "former smoker" category. Furthermore, if considered, it should also distinguish between heavy and light former smokers.

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CONFLICT OF INTEREST

All authors declared they have no conflict of interest related to this report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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