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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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33 **vi. Abstract and keywords:**

34 Aim:

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

37 Materials and methods:

38 Chart data were collected from 258 patients undergoing post-non-surgical periodontal treatment (mean
39 2.24 visits/year) for 10 - 47.5 (mean 24.2) years. Patients were categorized as: 1) never-smokers, 2)
40 former smokers, 3) current light smokers (<10 cigarettes/day), and 4) current heavy smokers (≥10
41 cigarettes/day).
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48 Results:

49 Of 6,590 teeth present at baseline (mean 25.6 teeth/patient), 264 teeth were lost due to periodontitis,
50 corresponding to 0.03, 0.05, 0.08, and 0.11 TLP annually among never-smokers, former-smokers,
51 current light-smokers, and current heavy-smokers, respectively. A tooth from a current heavy smoker
52 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-
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3 smoker, and a former-smoker, respectively. Both heavy- and light-former-smokers needed washout
4 periods of approximately 15 years to reach the TLP risk level of never-smokers. The TLP risk decreased
5 by 6%/year of smoking cessation.
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8 Conclusions:

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10 It took almost 15 years of smoking cessation for the risk of TLP among former smokers to reach the level
11 of never-smokers. Hence, the 2018 periodontitis grading system should consider the impact of the
12 “wash-out” period on former smokers.
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16 **Keywords:**

17 cigarette smoking, mouth diseases, periodontitis, tooth extraction, validation study
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22 **vii. Clinical Relevance**

23 Scientific rationale for study:

24 Long-term studies are unavailable regarding the dose and effects of smoking cessation on periodontitis-
25 related tooth loss (TLP) during periodontal maintenance therapy.
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28 Principal findings:

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30 Among 258 patients followed for 10 - 47.5 years, a tooth from a former-smoker had 2.6 times greater
31 TLP risk than one from a never-smoker. Within 15 years upon smoking cessation, a tooth in a former
32 heavy smoker (≥ 10 cigarettes/day) had 12 times (OR=12.20; 95% CI: 4.64 - 31.90) -- and in a former light
33 smoker (< 10 cigarettes/day) almost 4 times (OR=3.74; 95%CI: 1.50 - 9.34) -- greater risk of TLP compared
34 to a tooth from a never-smoker. This risk decreased 6%/year after quitting smoking.
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38 Practical implications:

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40 Potential TLP during periodontal maintenance therapy among former-smokers for ≤ 15 years after
41 smoking cessation should be expected by clinicians and be considered in a revised 2018 periodontitis
42 grading system.
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46 **viii. Main text:**

47 **Introduction:**

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49 Periodontal diseases are among the most prevalent diseases in adults (Albandar, 2005; Petersen &
50 Ogawa, 2012). Periodontitis affects around 75% of seniors (Albandar, 2005; Eke et al., 2018) and severe
51 periodontitis is the sixth most prevalent chronic disease in the world (Kassebaum et al., 2014) affecting
52 about 11 - 15% of adults (Dye, 2012; Eke et al., 2018; Kassebaum et al., 2014).
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3 The ultimate goal of periodontal therapy is to preserve the dentition in a state of health and function,
4 with acceptable esthetics. Even though there is no known treatment modality that effectively can cure
5 periodontitis, its precursor, gingivitis, can be prevented and managed by meticulous plaque biofilm
6 control and lifestyle changes to alleviate the effect of modifiable risk factors, such as smoking cessation
7 and prevention or management of hyperglycemia in diabetes (Chapple et al., 2015). When such primary
8 prevention efforts are not successful and destructive periodontitis develops, professional treatment and
9 maintenance management are needed, with the ultimate goal of preventing tooth loss due to
10 periodontitis (TLP) (Chapple et al., 2018; Lang & Bartold, 2018). Even though an abundance of studies
11 report TL, only a subset reported the number of teeth lost specifically due to periodontitis (TLP). In the
12 following, the abbreviation “TLP” is used to denote “tooth loss due to periodontitis” or “teeth lost due
13 to periodontitis,” with similar use of TL for tooth loss (or teeth lost) for any reason.
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23 Oliver (1969) reported TL among 442 patients (two-thirds aged >40 years; n>11,000 teeth) treated in
24 private practice that had received regular periodontal maintenance therapy (PMT). After an average of
25 10.1 years (range: 5 – 17 years) follow-up (FU) and having been seen every 4.6 months for PMT, there
26 were 178 TLP (79.8% of all teeth lost [TL]), amounting to a mean of 0.40 teeth per patient over the 10.1
27 years, equivalent to 0.04 TLP/patient/year. Of note is that 22% of the patients did not lose any teeth
28 with 11% losing only 1 tooth (Oliver, 1969).
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35 Lindhe and Nyman (1984) reported 16 TLP in 7 of 61 patients undergoing PMT over 14 years, averaging
36 0.02 TLP/patient/year. Other studies also reported low annual rates of around 0.1 TLP/patient/year
37 during long-term compliant PMT (Becker et al., 1984; Bostanci & Arpak, 1991; Checchi et al., 2002;
38 Goldman et al., 1986; Hirschfeld & Wasserman, 1978; McFall, 1982; McGuire, 1991; McLeod et al., 1997;
39 Nabers et al., 1988; Wood et al., 1989). Interestingly, none of these early studies addresses the
40 relationship of TLP to tobacco smoking, whereas the following more recent studies specifically report
41 TLP during compliant long-term PMT while considering smoking.
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47 Some studies were conducted in periodontics specialty offices in Spain, Norway, and Italy and reported
48 0.05 TLP/patient/year with current smokers having a 70% statistically significantly increased risk for TLP
49 [Risk Ratio (RR): 1.6; p=0.018] (Martinez-Canut, 2015), 0.036 TLP/pt/year with smokers being 4-fold
50 more likely than non-smokers to have TLP [adjusted odds ratio (aOR)=4.2; 95% CI: 1.4 - 13.8] (Fardal et
51 al., 2004), and 0.008 TLP/pt/year with smokers having almost 50% greater likelihood of TL (OR;1.49)
52 (Carnevale et al., 2007), respectively.
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3 Retrospective studies were performed based on patient charts at dental schools in Canada where a
4 Dalhousie study reported a mean TLP of 0.06/patient/year (Matthews et al., 2001) and one in Manitoba
5 reported a mean TLP of 0.016/patient/year (Fisher et al., 2008). A Japanese multi-site university-based
6 study calculated a mean of 0.040 TLP/patient/year among PMT compliant patients (Hirata et al., 2019).
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8 These 3 studies found smoking to not be associated with TLP.
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13 A German study found smoking to be a significant risk factor for TLP in 142 patients with an initial mean
14 age of 46 years (range 23 - 72 years) that had PMT lasting 10.5 (± 1.6) years, but no estimates of the
15 magnitude of its effect were provided (König et al., 2002). In a Chinese dental school, 94 compliant
16 post-periodontal surgery patients were followed for a mean of 3.8 years (Huang et al., 2016). Current
17 smoking was associated with recurrence of periodontitis, but not with tooth loss, possibly due to the
18 short FU duration and only 5.3% (5/94) being current smokers. A dental school/specialist center in
19 Singapore followed 239 compliant PMT patients (mean age 49.3 years; range 26 – 70 years) for an
20 average of 10.7 years (range: 7.0 - 20.4 years) and reported 0.03 TLP/patient/year (Ng et al., 2011). Even
21 though smoking habits were recorded in detail, smoking was not included in the regression model to
22 identify risk factors due to the participation of only 1 current- and 1 former-smoker. A Swiss dental
23 school study followed 270 PMT patients for a mean of 5.6 (± 3.8) years during which 150 TLP occurred,
24 namely 0.099 TLP/patient/year. Despite 39.6% being current- and 27.8% former-smokers, smoking had
25 no significant role in TL (Tonetti et al., 1998; Tonetti et al., 2000).
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30 Several factors play important roles in pathogenesis and progression of periodontitis (Giannobile et al.,
31 2013) and synergistic effects of two factors simultaneously, such as diabetes/hyperglycemia and
32 smoking, may be greater than the sum of the effects of the individual factors (Ganesan et al., 2017).
33 Such genetic, epigenetic, and behavioral or environmental factors may lead to tooth loss due to
34 hopeless periodontitis, despite standard professional and home care to which a minority, currently
35 estimated to 20 – 25 percent of patients, do not respond adequately and predictably (Giannobile et al.,
36 2013). This situation presents a challenge in assigning the Grade as per the 2018 periodontitis
37 classification (Kornman & Papapanou, 2019) as well as in clinical management, which requires
38 experienced and knowledgeable professional judgement.
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42 Overall, existing literature demonstrates that periodontal treatment with subsequent compliant long-
43 term PMT successfully can maintain a dentition with minimal TLP. While some studies report that
44 cigarette smoking increases the risk for TLP, detailed estimates of such effect by various smoking
45 subcategories are lacking.
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Therefore, the specific goals of our study were to answer the following questions [PICO/PECO elements (Higgins et al., 2019; Miller, 2001; Richardson et al., 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)]

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 (IRBMED) with study identifier HUM00157260/HUM00160933.

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 et al., 2018) are described elsewhere (Ravida et al., 2019). 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 et al., 2015; Mombelli 2019), patients who underwent at

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3 least one initial, active treatment session of surgical or non-surgical (scaling and root planning)
4 periodontal treatment and subsequently underwent at least one PMT visit per year throughout the
5 entire FU period were included in the study. Data on pertinent patient characteristics, the number of
6 PMT visits per year, and relevant medical history were collected. Radiographic bone loss (BL, % of root
7 length) at baseline (time zero, T0) was measured from periapical radiographs to assess periodontitis
8 stage and grade (Pepelassi et al., 2000). The date of the last PMT visit for which data were available was
9 called T1. Tooth-specific data on clinical parameters, such as periodontal probing depth (PPD), clinical
10 attachment level (CAL) [formerly calculated and recorded in the chart as the difference between PPD
11 and the distance from the free gingival margin (FGM) to the cemento-enamel junction (CEJ)], bleeding
12 on probing (BOP), furcation involvement, presence of restorations and crowns on interproximal
13 surfaces, apical pathology, endodontic root filling, endodontic post, and presence of vertical bone
14 defects were collected at T0 and T1.

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16 Patient charts were searched for tooth loss (TL) by comparing the number of natural teeth present at T0
17 and T1. For each non-third molar tooth that was lost, the date and cause of extraction were recorded.
18 Importantly, the reason for any extraction was always recorded as per school policy. To evaluate the
19 effect of smoking habits on TL, patients were divided at T0 into 4 groups with the current-smokers
20 further allocated to one of two groups by smoking intensity: 1) never-smokers; 2) former-smokers (ex-
21 smokers); 3) low-intensity (light) current-smokers who smoked <10 cigarettes/day; 4) high-intensity
22 (heavy) current-smokers who smoked ≥ 10 cigarettes/day. The number of years since smoking cessation
23 was recorded for patients who were ex-smokers at T0 (Group 2) as well as for patients in Groups 3 and 4
24 who had quit smoking during the FU period. Furthermore, any change in the smoking habits for the
25 other groups were recorded and taken in consideration in the statistical analyses. Any patient with
26 incomplete data for any of the collected information was excluded from the study.

27 **Statistical analysis**

28 Statistical analysis was conducted using SPSS 22 (IBM Corporation, Armonk, NY, USA) and R 3.5.1 (R Core
29 Team. 2018. R: A language and environment for statistical computing. R Foundation for Statistical
30 Computing, Vienna, Austria. URL <http://www.R-project.org/>).

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3 At the patient-level, a simple binary logistic regression model was created to assess the probability of
4 medium - high risk for having TLP (TLP > 1) according to smoking classification. Multiple models were
5 constructed while adjusting for potentially confounding factors (sex, age, number of PMT visits, FU
6 duration, and baseline clinical data).
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11 Based on the number of TLP during the study, participants were categorized as well-maintained (0 - 3
12 TLP), downhill (4 – 9 TLP), and extreme downhill (≥ 10 TLP) (Hirschfeld & Wasserman, 1978), with this
13 index modified to include only TLP, not any TL. At the tooth-level, the outcome TLP (yes/no or $\geq 1/0$)
14 was related to the smoking classification of the patient until the occurrence of the event or at T1 (in case
15 of no change in smoking status) using multi-level logistic regression with generalized estimation
16 equations (GEE). Raw ORs and 95% CIs were calculated and tested for significance of the included
17 variables with the Wald χ^2 test. Again, multiple models were constructed to estimate the need to
18 adjust for potential confounding factors (sex, age, number of PMT visits, FU duration, and baseline
19 clinical data). The goodness of fit of different estimates (for different matrix correlations) was assessed
20 by QIC (Quasilikelihood under the Independence model Criterion) goodness of fit statistic for GEE
21 models.
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31 Upon initial analyses, ex-smokers were further subdivided based on both the former smoking intensity
32 (number of cigarettes smoked per day) and duration of time since cessation in order to study the
33 washout period within former smokers, comparing risk of TLP between categories.
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38 Time-to-event of extraction due to periodontitis was analyzed using survival analysis techniques. In
39 particular, to consider dependence between observations (tooth-level data clustered by patient),
40 univariate and multivariate multilevel Cox regression models with clustering by patient were built to
41 analyze the influence of the smoking condition. The proportional hazard assumption was tested by
42 means of Schoenfeld's tests.
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48 The statistical significance level was set at 5% ($\alpha=0.05$). These calculations are the basis for the
49 subdivision of the group of current smokers by smoking intensity as described earlier with Group 3
50 smoking <10 cigarettes/day (light smokers) and Group 4 smoking ≥ 10 cigarettes/day (heavy smokers).
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Results:

Study population

A total of 258 patients (123 males and 135 females) with a baseline mean age of 46.6 (\pm 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 (\pm 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 ($p=0.008$, 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.

Smoking status was initially determined at T0 (Fig. 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.

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) (Appendix Tables 1). 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 (Appendix Tables 1 and 2) or to former smokers overall (Appendix Table 2).

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; $p<0.001$) upon adjustment for sex. Age, FU

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3 duration, and number of PMT (Appendix Tables 1 and 2) and a statistically significant 9-fold greater risk
4 compared to either former-smokers overall (aOR = 9.07; 95% CI: 2.09 – 39.5; $p < 0.01$) or to current light
5 smokers (aOR = 8.79 (1.49 – 51.8; $p < 0.01$) (Appendix Table 1). A binary logistic regression model showed
6 that whereas sex, age, and number of PMT visits per year were not important confounders, the FU
7 duration was a statistically significant variable.
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11 Based on the number of TLP during the study, more than 9-in-10 (91.9%) of the participants were
12 categorized as well-maintained (0 - 3 TLP), 7.4% as downhill (4 – 9 TLP), and 0.8% as extreme downhill
13 (≥ 10 TLP) (Table 2).
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16 17 18 **Tooth-level results**

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20 At baseline, 6,590 teeth were present in the 258 study participants (mean 25.5 teeth/patient). A total of
21 631 teeth were lost during FU, of which 264 (41.8%) were lost due to periodontitis, amounting to 3.65%
22 (95%CI: 3.22% - 4.09%) of all teeth present at baseline. The proportions of TL by smoking status at T1
23 and reason for TL are illustrated in Figure 2. The mean number of TLP during the study period ranged
24 from 0.03 (± 0.06) TLP/patient/year in never-smokers to 0.11 (± 0.08) TLP/patient/year in heavy-smokers
25 (Table 2). The vast majority of TL between times T0 and T1 occurred in current heavy-smokers, who on
26 average lost almost a quarter (24.0%) of their teeth, with 10.3% being TLP and 13.7% lost due to other
27 reasons (Fig. 2). A dose-response pattern for TLP is seen by smoking status from never-smokers through
28 former- and current light- to current heavy-smokers having lost 2.5%, 4.1%, 5.6%, and 10.3% of their
29 teeth (Fig. 2).
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39 At the tooth-level overall, former-smokers (at the time of the event) had 73% greater odds of TLP
40 compared to never-smokers (aOR = 1.73; 95% CI: 1.08 – 2.75; $p = 0.022$) (Table 3, Appendix Table 3). This
41 risk was substantially greater for teeth in current heavy-smokers whose odds for any TLP were 438
42 percent or 4.4-fold greater than in never-smokers (OR=4.38; 95% CI: 2.67 – 7.21; $p < 0.001$), 2.6-fold
43 greater than in former smokers, and 2.7-fold greater than in current light-smokers (Table 3, Appendix
44 Table 3).
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51 In order to assess differences in tooth survival by smoking status, while taking into consideration the
52 time-to-TLP for each tooth, we built a frailty multilevel Cox regression multivariate model with data
53 clustered for each patient. Results of this analysis revealed no significant difference in risk for TLP
54 between a tooth from never-smokers and former light smokers of < 10 cigarettes/day. In contrast, a
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3 tooth from former heavy smokers of ≥ 10 cigarettes/day (aHR=3.34; 95% CI: 2.08 – 5.37; $p < 0.001$) and
4 current heavy-smokers (aHR=4.69; 95% CI: 2.84 – 7.75; $p < 0.001$) had significantly greater risk of TLP
5 compared to never-smokers during FU (Appendix Table 4).
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8 9 ***Washout period for former smoker***

10 11 12 **Tooth-level results**

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15 Both the intensity of former smoking and the duration of the cessation period significantly influenced
16 the estimated probabilities of TLP during the study period.
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20 The probability of TLP exhibited a dose-dependent response as a tooth from a former heavy smoker
21 (≥ 10 cigarettes/day) was greater than for a tooth from a former light smoker (< 10 cigarettes/day) at all
22 time points. Moreover, the longer the duration since smoking cessation, the lower the probability of TLP
23 becomame for teeth from both light and heavy former-smokers. In fact, the predicted probability of TLP
24 for teeth from heavy and light former-smokers tended to approximate one another as time since
25 smoking cessation increased (Not shown).
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30 Results of binary logistic regression modeling using GEE estimated that each additional year since
31 quitting smoking reduced the risk of TLP by 6% (OR=0.94; 95% CI: 0.89 – 0.99; $p=0.031$) (Table 4).
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33 Furthermore, teeth from former heavy smokers had almost 5 times greater risk of TLP compared to
34 those from former light smokers (OR=4.89; 95% CI: 2.30 - 10.04) (Table 4).
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38 The washout period for former smokers was defined as the duration of time it took for the risk of TLP for
39 a former smoker to approximate the baseline risk of a never smoker. The GEE model at the tooth level
40 showed that the washout period was 15 years for both heavy and light former smokers (Table 5). A
41 tooth in a former light smoker showed almost 4 times greater risk of TLP compared to that from a never-
42 smoker within the first 15 years of smoking cessation (OR=3.74; 95%CI: 1.50 - 9.34). Within the same
43 timeframe, a tooth in a former heavy smoker had 12 times greater risk of TLP compared to that from a
44 never-smoker (OR=12.20; 95% CI: 4.64 - 31.90). However, the TLP risk was not statistically significantly
45 different for neither light nor heavy former-smokers relative to never-smokers after 15 years cessation
46 (Table 5). A tooth from a never-smoker had 2.5% risk for TLP during the study period. This was the
47 reference probability ($p=0.025$) of TLP at T1 because 103 teeth were lost to periodontitis among the
48 4,088 teeth originally present in never-smokers at T0, so $p=103/4,088=0.025$.
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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 1 current and 1 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).

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 et al., 2007). Another study among men (Veterans Administration) also found that TL due to any cause decreased over time after smoking cessation (Krall et al., 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 et al., 1997). Women who quit showed no difference due to their low number (n=14). During the study

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3 that lasted 18 (± 7) years, male quitters ($n=167/N=813$) lost more teeth on average
4 [0.223($\pm n/a$)/participant/year] than non-smokers [0.133($\pm n/a$)/participant/year] and had 70% greater
5 risk for incident TL (RR=1.7; 95% CI: 1.5 - 1.8) compared to non-smokers ($n=529$) (Krall et al., 1997).
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8 These results, as well as the results of the present study, demonstrate that former smokers have a
9 residually elevated risk for TL compared to non-smokers for a substantial duration of time immediately
10 after quitting.
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13 14 15 ***Years long wash-out period after smoking cessation***

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17 When taking into consideration the broad range of detrimental effects and physiological mechanisms
18 that are at play, it is understandable that it takes a long time to revert to healthy tissues in former
19 smokers after smoking cessation. The oral epithelium and its cover of saliva together represent a barrier
20 to protect the underlying tissues. However, this protection is likely compromised in smokers due to the
21 desiccation and toxic effects of tobacco and its smoke, which facilitates the transfer of bacteria and their
22 toxins into the bloodstream where they are disseminated throughout the body and contribute to
23 chronic systemic inflammation (Borgnakke, 2019).
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26 In smokers, changes in the oral microbiota that favor anaerobic species occur (Beghini et al., 2019), so
27 the subgingival biofilm in smokers displays less species diversity than non-smokers (Bizzarro et al.,
28 2013). Moreover, interactions occur between periodontal clinical manifestations and bacterial antibody
29 profiles and are mediated by antibody responses (Nagarajan et al., 2017). Both host genetic factors
30 (Zhang et al., 2020) and epigenetic modifications (non-DNA encoded changes in gene expression caused
31 by environmental and other factors) play important roles in the pathogenesis of periodontitis (Larsson
32 et al., 2015; Martins et al., 2016). Neutrophil function is also altered in smokers (Armitage, 2020).
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35 However, the specific cellular and molecular mechanisms that may contribute towards the washout
36 period in former smokers are still largely unknown. Overall, we found that both current and former
37 heavy smokers had more TLP than current and former light smokers. However, we did not identify any
38 past study that provided such detailed reporting of TLP by intensity of current and former smoking
39 habits in a compliant population with long-term PMT. Hence, we cannot make any direct comparisons
40 regarding the impact of smoking on TLP by smoking intensity.
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51 52 ***2018 periodontitis case definitions***

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3 The 2017 World Workshop aligned and updated the periodontitis classification to the current
4 understanding of periodontal diseases. Among the five major recommendations of the 2017 World
5 Workshop Consensus pertaining to future research, is the use of existing databases to validate and
6 refine the newly introduced classification system (Papapanou et al., 2018). In a previous study, our
7 group *validated* the capability of the staging and grading system to predict future TLP (Ravida et al.,
8 2019). In the present study, we advocate for the *refinement* of the new classification when allocating
9 former smokers a periodontitis grade (Tonetti et al., 2018). Firstly, our finding of great differences
10 between light and heavy former smokers is a factor that we believe should be incorporated. That is, the
11 category former smokers should be divided into two subgroups, distinguishing between heavy (≥ 10
12 cigarettes/day) and light (< 10 cigarettes/day) former-smokers. Secondly, instead of considering a patient
13 a non-smoker once he/she quits smoking, our findings suggest that the periodontitis grade for a former
14 smoker should be changed only after a sufficient wash-out period has passed and not immediately upon
15 smoking cessation.

26 **Strengths**

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28 To the best of our knowledge, this study is one of the largest studies of its kind, as the 258 participants
29 underwent compliant PMT for an unusually extended FU period [mean 24.2 (± 6.7) years] ranging from
30 10 to 47 years with the participants undergoing a mean of 2.24 PMT visits/year. Due to the high number
31 of patients available, we could exclude those with less than 10 years of PMT. Furthermore, Ravida and
32 team (2019) are the first to allocate each patient to one of the 2018 clinical periodontitis case definitions
33 (Tonetti et al., 2018) and explore the effects of smoking on tooth loss caused by periodontitis while
34 applying the 2018 smoking history categories (Ravida et al., 2019). Historically, smoking was not
35 generally recognized as an important risk factor for progression of periodontitis until the 1990s. The US
36 Surgeon General's report on oral health of 2000 was the first such report to mention smoking as an
37 evidence-based risk factor for periodontitis (U.S. Department of Health and Human Services, 2000). To
38 avoid the confounding influence of diabetes on TLP and heterogeneity in reported glycemic
39 measurements (HbA1c vs. blood glucose), patients with diabetes were not included. It is known that the
40 additive effects of putative risk factors (such as smoking, diabetes, and the presence of interleukin-1
41 polymorphisms) increase the risk for tooth loss over the long-term (Giannobile et al., 2013). Also, while
42 diabetes/hyperglycemia and smoking influence the subgingival microbiome in different ways, their
43 synergistic effect is greater than that which would be expected from the added effects of those two
44 individual factors (Ganesan et al., 2017).

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 years 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 (Ramseier et al., 2019; Mombelli, 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 (*versus* 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.

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 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.

ix. References:


- Albandar, J. M. (2005). Epidemiology and risk factors of periodontal diseases. *Dental Clinics of North America*, 49(3), 517-532, v-vi. doi:10.1016/j.cden.2005.03.003
- Armitage, G. C. (2020). A brief history of periodontics in the United States of America: Pioneers and thought-leaders of the past, and current challenges. *Periodontology 2000*, 82(1), 12-25. doi:10.1111/prd.12303
- Becker, W., Berg, L., & Becker, B. E. (1984). The long term evaluation of periodontal treatment and maintenance in 95 patients. *The International Journal of Periodontics & Restorative Dentistry*, 4(2), 54-71.
- Beghini, F., Renson, A., Zolnik, C. P., Geistlinger, L., Usyk, M., Moody, T. U., . . . Waldron, L. (2019). Tobacco exposure associated with oral microbiota oxygen utilization in the New York City Health and Nutrition Examination Study. *Annals of Epidemiology*, 34, 18-25:e13. doi:10.1016/j.annepidem.2019.03.005
- Bizzarro, S., Loos, B. G., Laine, M. L., Crielaard, W., & Zaura, E. (2013). Subgingival microbiome in smokers and non-smokers in periodontitis: an exploratory study using traditional targeted techniques and a next-generation sequencing. *Journal of Clinical Periodontology*, 40(5), 483-492. doi:10.1111/jcpe.12087
- Borgnakke, W. S. (2019). Ch 3. The traveling oral microbiome. In M. Glick (Ed.), *The oral-systemic health connection: A guide to patient care*. 2nd ed. (pp 38-85). Chicago, IL: Quintessence.

- 1
2
3 Bostanci, H. S., & Arpak, M. N. (1991). Long-term evaluation of surgical periodontal treatment with and
4 without maintenance care. *The Journal of Nihon University School of Dentistry*, *33*(3), 152-159.
5 doi:10.2334/josnusd1959.33.152
6
7
8 Carnevale, G., Cairo, F., & Tonetti, M. S. (2007). Long-term effects of supportive therapy in periodontal
9 patients treated with fibre retention osseous resective surgery. II: Tooth extractions during
10 active and supportive therapy. *Journal of Clinical Periodontology*, *34*(4), 342-348.
11 doi:10.1111/j.1600-051X.2007.01052.x
12
13
14
15 Chapple, I. L., Van der Weijden, F., Doerfer, C., Herrera, D., Shapira, L., Polak, D., . . . Graziani, F. (2015).
16 Primary prevention of periodontitis: managing gingivitis. *Journal of Clinical Periodontology*,
17 *42*(Suppl 16):S71-S76. doi:10.1111/jcpe.12366
18
19
20 Chapple, I. L., Mealey, B. L., Van Dyke, T. E., Bartold, P. M., Dommisch, H., Eickholz, P., . . . Yoshie, H.
21 (2018). Periodontal health and gingival diseases and conditions on an intact and a reduced
22 periodontium: Consensus report of Workgroup 1 of the 2017 World Workshop on the
23 Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Clinical*
24 *Periodontology*, *45*(Suppl 20):S68-S77. doi:10.1111/jcpe.12940
25
26
27
28 Checchi, L., Montevecchi, M., Gatto, M. R., & Trombelli, L. (2002). Retrospective study of tooth loss in 92
29 treated periodontal patients. *Journal of Clinical Periodontology*, *29*(7), 651-656.
30 doi:10.1034/j.1600-051x.2002.290710.x
31
32
33
34 Dietrich, T., Garcia, R. I., de Pablo, P., Schulze, P. C., & Hoffmann, K. (2007). The effects of cigarette
35 smoking on C-reactive protein concentrations in men and women and its modification by
36 exogenous oral hormones in women. *European Journal of Cardiovascular Prevention and*
37 *Rehabilitation*, *14*(5), 694-700. doi:10.1097/HJR.0b013e328270b913
38
39
40 Dye, B. A. (2012). Global periodontal disease epidemiology. *Periodontology 2000*, *58*(1), 10-25.
41 doi:10.1111/j.1600-0757.2011.00413.x
42
43
44 Eke, P. I., Thornton-Evans, G. O., Wei, L., Borgnakke, W. S., Dye, B. A., & Genco, R. J. (2018). Periodontitis
45 in US Adults: National Health and Nutrition Examination Survey 2009-2014. *Journal of the*
46 *American Dental Association*, *149*(7), 576-588 e576. doi:10.1016/j.adaj.2018.04.023
47
48
49 Fardal, O., Johannessen, A. C., & Linden, G. J. (2004). Tooth loss during maintenance following
50 periodontal treatment in a periodontal practice in Norway. *Journal of Clinical Periodontology*,
51 *31*(7), 550-555. doi:10.1111/j.1600-051X.2004.00519.x
52
53
54
55
56
57
58

- 1
2
3 Farooqi, O. A., Wehler, C. J., Gibson, G., Jurasic, M. M., & Jones, J. A. (2015). Appropriate recall interval
4 for periodontal maintenance: A systematic review. *The Journal of Evidence-Based Dental
5 Practice, 15*(4), 171-181. doi:10.1016/j.jebdp.2015.10.001
6
7
8 Fisher, S., Kells, L., Picard, J. P., Gelskey, S. C., Singer, D. L., Lix, L., & Scott, D. A. (2008). Progression of
9 periodontal disease in a maintenance population of smokers and non-smokers: a 3-year
10 longitudinal study. *Journal of Periodontology, 79*(3), 461-468. doi:10.1902/jop.2008.070296
11
12
13 Ganesan, S. M., Joshi, V., Fellows, M., Dabdoub, S. M., Nagaraja, H. N., O'Donnell, B., . . . Kumar, P. S.
14 (2017). A tale of two risks: smoking, diabetes and the subgingival microbiome. *International
15 Society for Microbial Ecology (ISME) Journal, 11*(9), 2075-2089. doi:10.1038/ismej.2017.73
16
17
18 Giannobile, W. V., Braun, T. M., Caplis, A. K., Doucette-Stamm, L., Duff, G. W., & Kornman, K. S. (2013).
19 Patient stratification for preventive care in dentistry. *Journal of Dental Research, 92*(8), 694-701.
20 doi:10.1177/0022034513492336
21
22
23 Goldman, M. J., Ross, I. F., & Goteiner, D. (1986). Effect of periodontal therapy on patients maintained
24 for 15 years or longer; a retrospective study. *Journal of Periodontology, 57*(6), 347-353.
25 doi:10.1902/jop.1986.57.6.347
26
27
28 Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., . . . (Eds). (2019). *Cochrane
29 Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019) (2 ed.)*.
30 Chichester, UK: John Wiley & Sons. URL: <https://training.cochrane.org/handbook/current>
31
32
33 Hirata, T., Fuchida, S., Yamamoto, T., Kudo, C., & Minabe, M. (2019). Predictive factors for tooth loss
34 during supportive periodontal therapy in patients with severe periodontitis: a Japanese
35 multicenter study. *BioMed Central Oral Health, 19*(1), 19. doi:10.1186/s12903-019-0712-x
36
37
38 Hirschfeld, L., & Wasserman, B. (1978). A long-term survey of tooth loss in 600 treated periodontal
39 patients. *Journal of Periodontology, 49*(5), 225-237. doi:10.1902/jop.1978.49.5.225
40
41
42 Huang, K. C., Lai, C. H., Huang, C. F., & Lu, H. K. (2016). A comprehensive periodontal treatment project:
43 the periodontal status, compliance rates, and risk factors. *Journal of Dental Sciences, 11*(2), 182-
44 188. doi:10.1016/j.jds.2015.07.006
45
46
47 Kassebaum, N. J., Bernabe, E., Dahiya, M., Bhandari, B., Murray, C. J., & Marcenes, W. (2014). Global
48 burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *Journal
49 of Dental Research, 93*(11), 1045-1053. doi:10.1177/0022034514552491
50
51
52 König, J., Plagmann, H. C., Ruhling, A., & Kocher, T. (2002). Tooth loss and pocket probing depths in
53 compliant periodontally treated patients: a retrospective analysis. *Journal of Clinical
54 Periodontology, 29*(12), 1092-1100. doi:10.1034/j.1600-051x.2002.291208.x
55
56
57
58

- 1
2
3 Kornman, K. S., & Papapanou, P. N. (2019). Clinical application of the new classification of periodontal
4 diseases: ground rules, clarifications and "gray zones". *Journal of Periodontology*, *91*(3), 352-
5 360, doi:10.1002/JPER.19-0557
6
7
8 Krall, E. A., Dawson-Hughes, B., Garvey, A. J., & Garcia, R. I. (1997). Smoking, smoking cessation, and
9 tooth loss. *Journal of Dental Research*, *76*(10), 1653-1659. doi:10.1177/00220345970760100601
10
11 Krall, E. A., Dietrich, T., Nunn, M. E., & Garcia, R. I. (2006). Risk of tooth loss after cigarette smoking
12 cessation. *Preventing Chronic Disease*, *3*(4), A115. URL:
13 https://www.cdc.gov/pcd/issues/2006/oct/pdf/05_0243.pdf
14
15
16
17 Lang, N. P., & Bartold, P. M. (2018). Periodontal health. *Journal of Clinical Periodontology*, *45*(Suppl 20),
18 S9-S16. doi:10.1111/jcpe.12936
19
20 Larsson, L., Castilho, R. M., & Giannobile, W. V. (2015). Epigenetics and its role in periodontal diseases: a
21 state-of-the-art review. *Journal of Periodontology*, *86*(4), 556-568. doi:10.1902/jop.2014.140559
22
23 Lindhe, J., & Nyman, S. (1984). Long-term maintenance of patients treated for advanced periodontal
24 disease. *Journal of Clinical Periodontology*, *11*(8), 504-514. doi:10.1111/j.1600-
25 051x.1984.tb00902.x
26
27
28 Martinez-Canut, P. (2015). Predictors of tooth loss due to periodontal disease in patients following long-
29 term periodontal maintenance. *Journal of Clinical Periodontology*, *42*(12), 1115-1125.
30 doi:10.1111/jcpe.12475
31
32
33 Martins, M. D., Jiao, Y., Larsson, L., Almeida, L. O., Garaicoa-Pazmino, C., Le, J. M., . . . Castilho, R. M.
34 (2016). Epigenetic modifications of histones in periodontal disease. *Journal of Dental Research*,
35 *95*(2), 215-222. doi:10.1177/0022034515611876
36
37
38 Matthews, D. C., Smith, C. G., & Hanscom, S. L. (2001). Tooth loss in periodontal patients. *Journal of the*
39 *Canadian Dental Association*, *67*(4), 207-210. URL: [http://www.cda-
41 adc.ca.proxy.lib.umich.edu/jcda/vol-67/issue-4/207.html](http://www.cda-
40 adc.ca.proxy.lib.umich.edu/jcda/vol-67/issue-4/207.html)
42
43
44 McFall, W. T., Jr. (1982). Tooth loss in 100 treated patients with periodontal disease; a long-term study.
45 *Journal of Periodontology*, *53*(9), 539-549. doi:10.1902/jop.1982.53.9.539
46
47 McGuire, M. K. (1991). Prognosis versus actual outcome: a long-term survey of 100 treated periodontal
48 patients under maintenance care. *Journal of Periodontology*, *62*(1), 51-58.
49 doi:10.1902/jop.1991.62.1.51
50
51
52 McLeod, D. E., Lainson, P. A., & Spivey, J. D. (1997). The effectiveness of periodontal treatment as
53 measured by tooth loss. *Journal of the American Dental Association*, *128*(3), 316-324.
54 doi:10.14219/jada.archive.1997.0195
55
56
57

- 1
2
3 Miller, S. A., & Forrest, J. L. . (2001). Enhancing your practice through evidence-based decision making:
4 PICO, learning how to ask good questions. *The Journal of Evidence-Based Dental Practice*, *1*(2),
5 136-141. doi: 10.1016/s1532-3382(01)70024-3.
6
7
8 Mombelli, A. (2019). Maintenance therapy for teeth and implants. *Periodontology 2000*, *79*(1), 190-199.
9 doi:10.1111/prd.12255
10
11 Nabers, C. L., Stalker, W. H., Esparza, D., Naylor, B., & Canales, S. (1988). Tooth loss in 1535 treated
12 periodontal patients. *Journal of Periodontology*, *59*(5), 297-300. doi:10.1902/jop.1988.59.5.297
13
14 Nagarajan, R., Miller, C. S., Dawson, D., 3rd, Al-Sabbagh, M., & Ebersole, J. L. (2017). Cross-talk between
15 clinical and host-response parameters of periodontitis in smokers. *Journal of Periodontal*
16 *Research*, *52*(3), 342-352. doi:10.1111/jre.12397
17
18
19 Ng, M. C., Ong, M. M., Lim, L. P., Koh, C. G., & Chan, Y. H. (2011). Tooth loss in compliant and non-
20 compliant periodontally treated patients: 7 years after active periodontal therapy. *Journal of*
21 *Clinical Periodontology*, *38*(5), 499-508. doi:10.1111/j.1600-051X.2011.01708.x
22
23
24 Oliver, R. C. (1969). Tooth loss with and without periodontal therapy. *Periodontal Abstracts*, *17*(1), 8-9.
25 doi: n/a. URL: n/a.
26
27
28 Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., . . . Tonetti, M. S. (2018).
29 Periodontitis: Consensus report of Workgroup 2 of the 2017 World Workshop on the
30 Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of*
31 *Periodontology*, *89*(Suppl 1), S173-S182. doi:10.1002/JPER.17-0721
32
33
34 Pepelassi, E. A., Tsiklakis, K., & Diamanti-Kipiotti, A. (2000). Radiographic detection and assessment of the
35 periodontal endosseous defects. *Journal of Clinical Periodontology*, *27*(4), 224-230.
36 doi:10.1034/j.1600-051x.2000.027004224.x
37
38
39 Petersen, P. E., & Ogawa, H. (2012). The global burden of periodontal disease: towards integration with
40 chronic disease prevention and control. *Periodontology 2000*, *60*(1), 15-39. doi:10.1111/j.1600-
41 0757.2011.00425.x
42
43
44 Ramseier, C. A., Nydegger, M., Walter, C., Fischer, G., Sculean, A., Lang, N. P., & Salvi, G. E. (2019). Time
45 between recall visits and residual probing depths predict long-term stability in patients enrolled
46 in supportive periodontal therapy. *Journal of Clinical Periodontology*, *46*(2), 218-230.
47 doi:10.1111/jcpe.13041
48
49
50
51 Ravida, A., Qazi, M., Troiano, G., Saleh, M. H. A., Greenwell, H., Kornman, K., & Wang, H. L. (2019). Using
52 periodontal staging and grading system as a prognostic factor for future tooth loss: a long-term
53
54
55
56
57
58
59
60

retrospective study. *Journal of Periodontology*. First published online September 9, 2019. 

doi:10.1002/JPER.19-0390

Richardson, W. S., Wilson, M. C., Nishikawa, J., & Hayward, R. S. (1995). The well-built clinical question: a key to evidence-based decisions. *American College of Physicians (ACP) Journal Club*, 123(3), A12-A13. doi: n/a. URL: n/a.

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: framework and proposal of a new classification and case definition. a) *Journal of Periodontology*, 89(Suppl 1), S159-S172. doi:10.1002/jper.18-0006; b) *Journal of Clinical Periodontology*, 45(Suppl 20), S149-S161. doi:10.1111/jcpe.12945

Tonetti, M. S., Muller-Campanile, V., & Lang, N. P. (1998). Changes in the prevalence of residual pockets and tooth loss in treated periodontal patients during a supportive maintenance care program. *Journal of Clinical Periodontology*, 25(12), 1008-1016. doi:10.1111/j.1600-051x.1998.tb02406.x

Tonetti, M. S., Steffen, P., Muller-Campanile, V., Suvan, J., & Lang, N. P. (2000). Initial extractions and tooth loss during supportive care in a periodontal population seeking comprehensive care. *Journal of Clinical Periodontology*, 27(11), 824-831. doi:10.1034/j.1600-051x.2000.027011824.x

U.S. Department of Health and Human Services. (2000). Oral health in America: a report of the Surgeon General. 332 pp. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health. URL: <https://www.nidcr.nih.gov/sites/default/files/2017-10/hck1ocv.%40www.surgeon.fullrpt.pdf>.

Wood, W. R., Greco, G. W., & McFall, W. T., Jr. (1989). Tooth loss in patients with moderate periodontitis after treatment and long-term maintenance care. *Journal of Periodontology*, 60(9), 516-520. doi:10.1902/jop.1989.60.9.516

World Medical Association. (1975). Declaration of Helsinki: recommendations guiding medical doctors in biomedical research involving human subjects; adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and as revised by the 29th World Medical Assembly, Tokyo, Japan, October 1975. 4 pp. URL: <https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct1975.pdf>.

World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Journal of the American Medical Association*, 310(20), 2191-2194. doi:10.1001/jama.2013.281053

Zhang, S., Yu, N., & Arce, R. M. (2020). Periodontal inflammation: integrating genes and dysbiosis. *Periodontology 2000*, 82(1), 129-142. doi:10.1111/prd.12267

x. Tables:

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

Characteristics	Total N (%) 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 \geq 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 (\pm 11.8)	46.7 (\pm 12.2)	49.5 (\pm 10.0)	43.1 (\pm 11.6)	45.1 (\pm 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*	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 (\pm 81.1)	292.1 (\pm 81.6)	273.8 (\pm 70.4)	291.4 (\pm 79.0)	315.3 (\pm 97.1)
# PMT Visits/Year	2.24 (\pm 0.68)	2.23 (\pm 0.68)	2.28 (\pm 0.60)	2.19 (\pm 0.62)	2.26 (\pm 0.95)
# teeth Present	25.5 (\pm 3.0)	25.8 (\pm 2.7)	25.2 (\pm 3.6)	25.3 (\pm 2.8)	25.3 (\pm 3.4)

*2017 periodontitis classification (Tonetti et al., 2018).

or N or n, number; cig, cigarettes; PMT, periodontal maintenance therapy; SD, standard deviation

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)				
	Total N (%) or Mean (\pm SD)	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 \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*	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*	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)

*(Hirschfeld and Wasserman 1978)

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

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)* (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)
Current Smokers	Never Smokers	1			
	Former Smokers	1.73 (1.08 – 2.75) [†]	1		
	Light Smokers <10 cig/day	1.89 (0.91 – 3.94)	1.05 (0.54 – 2.07)	1	
	Heavy Smokers ≥ 10 cig/day	4.38 (2.67 – 7.21)	2.56 (1.55 – 4.22)	2.74 (1.26 – 5.94)	1

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

aOR, adjusted odds ratio; cig, cigarettes; CI, confidence interval.

bolded font, statistically significant at $p < 0.05$.

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).

Characteristics	Odds* Ratio (OR)	95% Confidence Interval
Former-smoking intensity		
Light Smokers <10 cig/day	1	
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 x Duration	1.03	0.94 – 1.14

#, number; cig, cigarettes; T0, baseline; T1, last follow-up visit.

bolded font, statistically significant at $p < 0.05$.

*Binary logistic regression model using GEE without adjustment.

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)	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*				
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

*2017 periodontitis classification (Tonetti et al. 2018).

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

bolded font, statistically significant at p<0.05

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3 **xi. Figure legends:**
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5 Fig. 1. Patient-level distribution of the study population by smoking habits at baseline (T0) and at the
6 last periodontal maintenance therapy visit (T1) (Panel A). Final smoking habits at T1 (Panel B)
7 (N=258).

8 [Footnotes:]
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10 cig/d, cigarettes per day; N or n, number of patients; T0, baseline; T1, last study visit
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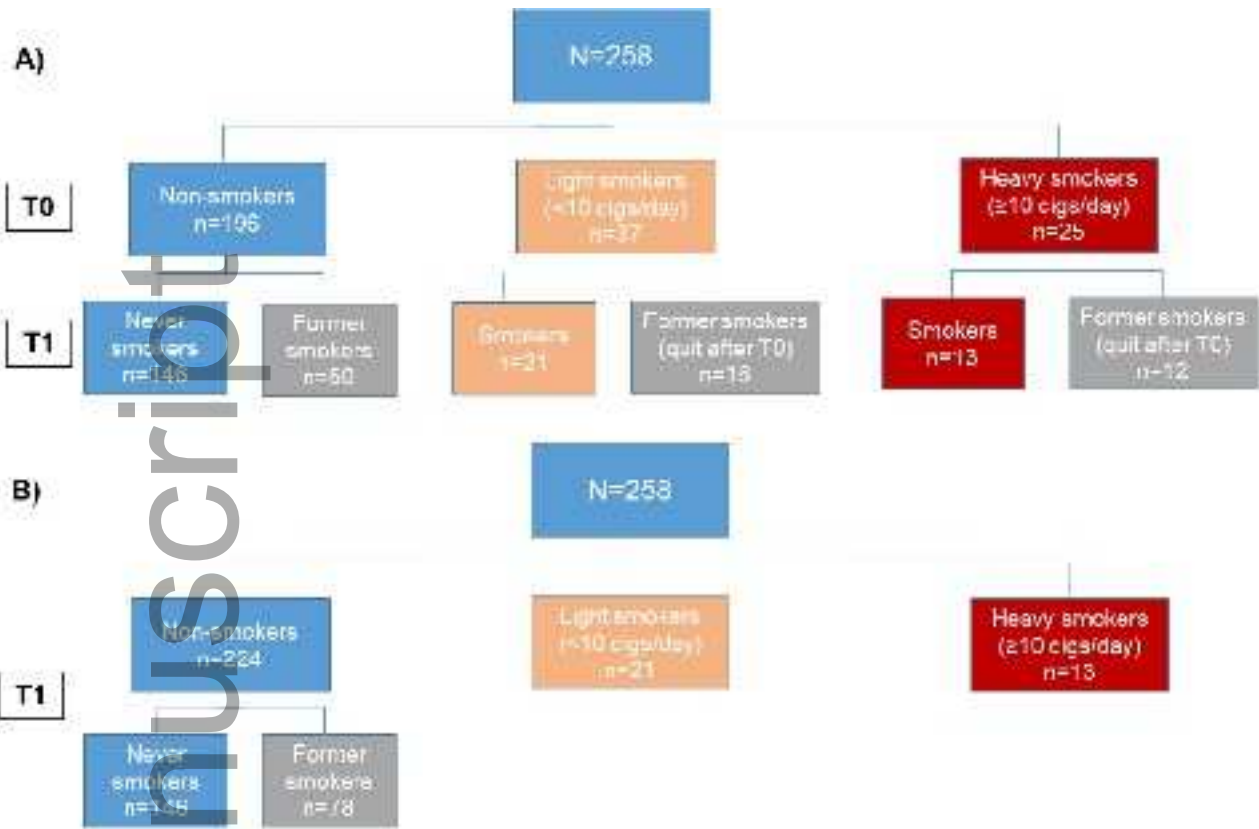
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15 Fig. 2. Tooth-level distribution of tooth loss (TL) during the follow-up period by reason for tooth loss
16 and smoking status at the last periodontal maintenance therapy (PMT) visit (T1) (N=6,590).

17 [Footnotes:]
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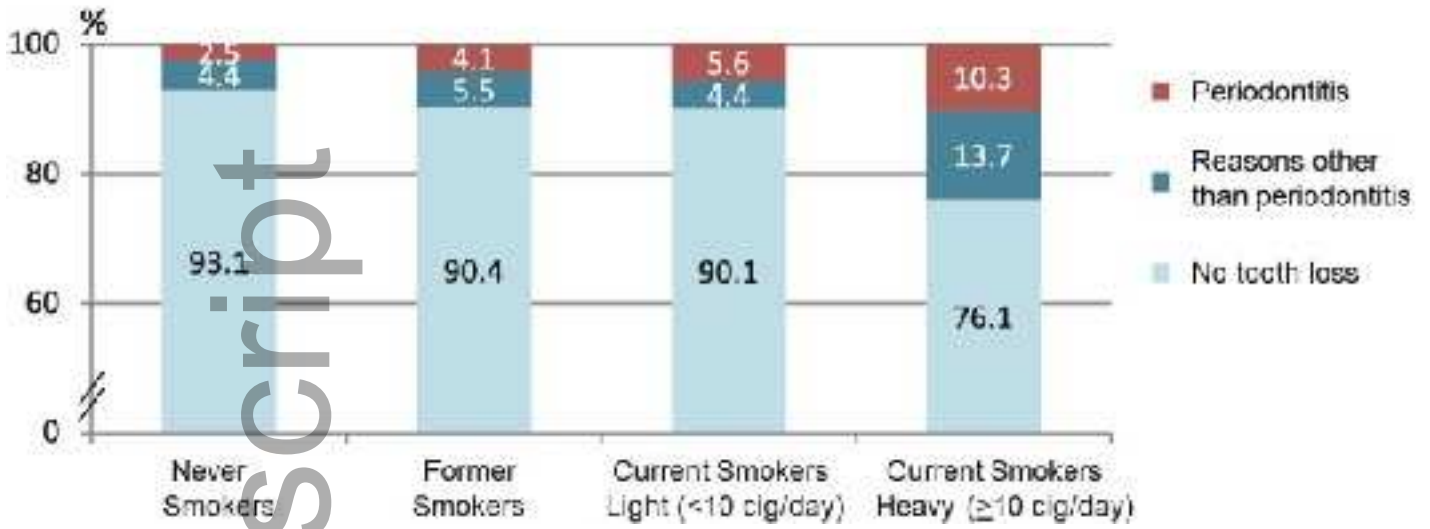
19 cig, cigarettes
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25 **xiii. Appendices:**

26 [Please note: One separate Appendix file containing four tables is submitted as Supplementary
27 Materials.]
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