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Are statins associated with decreased tooth loss in chronic periodontitis?

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Abstract

Aim: To evaluate whether statin use was associated with decreased tooth loss among patients with chronic periodontitis.

Material and Methods: We evaluated administrative health plan data from 1996 to 2002 covering dental and periodontal treatment utilization, dental extractions, and prescription medication fills of 12,631 adults aged 48–64 in 2002. With tooth loss as the outcome, we evaluated a number of different patterns of statin prescription across time in multivariate generalized linear models.

Results: Unadjusted, statin use was associated with increased tooth loss. After adjustment for potential confounders, there was no suggestion of either increased or decreased tooth loss associated with statin use.

Conclusions: Statin use was not associated with either a decreased or an increased risk of tooth loss.

Key words: cohort studies; hydroxymethylglutaryl-CoA reductase inhibitors; periodontal diseases/drug therapy; periodontal diseases; statins; tooth loss

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Chronic periodontitis is a condition characterized by inflammation of the periodontal tissues, leading to tissue destruction, bone resorption, attachment loss, and, in some cases, tooth loss. Matrix metalloproteinases (MMPs) and tumour necrosis factor-α (TNF-α) may play important roles in this process (Birkedal-Hansen 1993, Ryan et al. 1996, Ryan & Golub 2000, Golub et al. 2001, Nishikawa et al. 2002). 5-hydroxymethylglutaryl-CoA reductase inhibitors, commonly known as statins, lower cholesterol levels through inhibition of cholesterol biosynthesis. They reduce the risk of cardiovascular events, as do other drugs that lower serum cholesterol levels, but at least part of their protective cardiovascular effect seems to come from anti-inflammatory properties such as inhibition of MMP-9 and TNF-α (Wong et al. 2001, Koh et al. 2002, Nagashima et al. 2002).

Sub-antimicrobial doses of doxycycline have positive short-term effects on surrogate markers of chronic periodontitis and this is thought to be mediated by inhibition of MMP synthesis (Ryan et al. 1996, Golub et al. 2001). MMP-9 and TNF-α appear to be involved in the tissue destruction of chronic periodontitis (Garlet et al. 2004). Furthermore, statins [with the possible exception of pravastatin (Sugiyama et al. 2000)] are believed to increase bone formation by stimulating the production of bone morphogenetic protein-2 (Mundy et al. 1999, Ohnaka et al. 2001, Garrett & Mundy 2002), which may play an important role in periodontal bone and ligament growth/healing (King & Hughes 2001, Pitaru et al. 2002, Selvig et al. 2002). Hence, it seems possible that statins might be protective not only against cardiovascular disease but also against chronic periodontal disease. We previously conducted an epidemiologic study among over 1,000 chronic periodontitis patients that found some suggestion of a possible protective effect of statin use on tooth loss in later years (Cunha-Cruz et al. 2006). However, this study was limited by modest numbers of subjects and inability to control for smoking status, a common risk factor for both cardiovascular disease and chronic periodontitis (Hujoel et al. 2000, Lavelle 2002). Here, we present findings from

Conflict of interest and source of funding statement

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an observational study of tooth loss among chronic periodontitis patients, utilizing a substantially larger population for which we had data on statin use and smoking status, as well as a variety of other factors.

Methods

Design and data sources

We conducted a retrospective cohort study linking dental utilization data with prescription utilization and medical registry data for 12,631 members of a health maintenance organization (HMO) from 1996 to 2002. The study population consisted of members with medical, dental, and prescription coverage from 1996 to 2002 who had been diagnosed with early, moderate, or advanced chronic periodontal disease by a general dentist or a periodontist between 1999 and 2002. Study eligibility was further limited to persons between the ages of 48 and 64 by the end of 2002; we chose this age group because of the age distributions of chronic periodontitis and statin use, and because dental coverage (and data) were frequently lost during the transition to Medicare at age 65. We used the first 3 years of data to assess baseline utilization of statins, and dental and periodontal treatments.

This study was approved by the institutional review boards of the University of Washington and Kaiser Permanente Northwest.

Outcome – tooth loss

For each individual, tooth loss was determined by the presence of codes in the dental utilization database for simple extraction, additional simple extraction, surgical removal of an erupted tooth, and emergency extraction. A surgical extraction of an impacted tooth was not considered tooth mortality. Self-extraction of teeth or spontaneous tooth loss could not be determined. Tooth loss rates were calculated by dividing the number of teeth lost by the number of person-years of follow-up. The number of tooth-years of follow-up was not calculated because the number of teeth at baseline was not available. We evaluated tooth loss rates in the period from 1, January 1999 through 31, December 2002. Tooth loss during the 3-year baseline period (1996–1998) was not used as an outcome as this might reflect loss of ''hopeless'' teeth, not treatment effects.

Key independent variable – statin use

Our key independent variable was statin use. For each participant, the utilization of statins was determined based on prescriptions of simvastatin, lovastatin, pravastatin sodium, atorvastatin calcium, and fluvastatin sodium during the period 1996 through 2002. The number of days supplied in each prescription was added for each calendar year, and carry-overs from 1 year to the next of up to 180 days were allowed as the HMO's policies allowed, in some cases, for dispensing up to 180 days of medication at one time. We evaluated six different representations of statin use to look for both short-term and long-term effects: (1) ''regular'', ''intermittent'', or no statin use during the first 3 years: at least one statin prescription filled during each (''regular'') or one to two but not each (''intermittent'') of the first 3 years after the initial periodontal exam; (2) duration of statin use during the first 3-year period, represented as the number of months of statins dispensed during the first 3 years after the initial periodontal exam; (3) ''regular'', ''intermittent'', or no statin use during three consecutive years; (4) duration of statin use over 3 consecutive years, represented as the number of months of statins dispensed; (5) any statin use during 1 year: at least one statin prescription filled during a year; and (6) duration of statin use in a 1-year period, represented as the number of months of statins dispensed. Statin use during the first 3-year period (representations 1 and 2) did not vary over time and it was used to predict tooth loss rates in the fourth and subsequent years. Definitions 1, 3, and 5 yielded categorical variables, with reference groups of no statin prescriptions filled in the period being evaluated. Representations three to six were used as time-dependent covariates to predict tooth loss rates in each subsequent year beginning in the fourth year of each participant's years in the study.

Other independent variables

In addition to information about statin prescription fills, we utilized administrative data about age, gender, diabetes status (yes/no, based on the HMO's diabetes registry), smoking status as reported to clinic personnel (never, past, infrequent, or frequent smoker; we used the worst recorded smoking status during 1994–2002), periodontal status, dental care utilization, and prescription medication fills for non-steroidal anti-inflammatory drugs (NSAIDS).

Periodontal disease status was assessed between 1999 and 2002 by general dentists or periodontists using a standardized classification similar to the American Academy of Periodontology classification (Wiebe & Putnins 2000). Patients were classified as having (1) a healthy periodontium or gingivitis in the absence of bone loss or clinical attachment loss; (2) early periodontitis if they had bone loss involving up to 30% of the tooth root, clinical attachment loss, periodontal pockets of 4–6 mm, or grade I furcation involvement; (3) moderate periodontitis if they had localized bone loss or generalized horizontal bone loss involving between 30% and 50% of the tooth root, clinical attachment loss, periodontal pockets of 5–7 mm, and furcation involvement grade greater than I; (4) advanced periodontitis if they had severe bone loss greater than 50% of the tooth root, possible immediate tooth loss, and periodontal pockets 7+ mm; and (5) edentulous if no teeth were present. We considered the first recorded periodontal status during the study as an indicator of the initial periodontal condition of a participant. Only persons having their first recorded periodontal disease status during 1999–2002 of early, moderate, or advanced periodontitis were included in the study.

Assessment of dental care utilization was based on analysis of American Dental Association Codes on Dental Procedures and Nomenclature (CDT) from administrative claims data. Subjects were classified according to: (1) use of dental preventive services (above the median users of dental preventive procedures during the first 3-year period: yes/no); (2) use of caries treatments (above the median users of restorative and endodontic procedures during the first 3-year period: yes/no); and (3) use of periodontal treatment (time-dependent covariate for use in the previous 3 years: none, intermittent, or regular). For each participant and in each year of the study, we analysed NSAID prescription fills recorded in the prescription database. We excluded once daily aspirin from this tabulation as this would not approach anti-inflammatory levels. Annual number of days of NSAID fills in the previous year was represented as a time-dependent covariate in our models. Also, as use of many

NSAIDs is very poorly captured in pharmacy data due to low cost and over-the-counter availability, we evaluated models excluding all NSAID (including aspirin) use; the results were not appreciably different and are not presented.

Statistical methods

We used generalized linear models with a negative binomial distribution to relate the number of teeth lost in any given year to the main exposure variables, controlling for the number of person-years and the other covariates. Inferences were based on robust standard error estimates with an independent correlation structure to account for the correlation between the outcomes for participants with more than one tooth extraction. Statistical analyses were conducted with SAS software, version 8.2 (proc genmod). All reported p values are based on two-sided tests.

Results

Table 1 shows the characteristics of our study population and their use of statins during the initial 3 years of observation. Overall, 6.9% of our study population had some statin use during the initial 3-year period. Statin use differed significantly among different groups according to all the covariates except for use of dental preventive services. As would be expected based on cardiovascular disease risk, statin use was substantially higher with increasing age, male gender, diabetes, and current or former tobacco use. Statin users were also more likely to use antibiotics and NSAIDS. During the study period, 68% of the patients lost no teeth, 18% lost one tooth, 7% lost two teeth, and 8% lost three or more teeth.

Table 1. Characteristics of the study population and statin use in the baseline observation period

	Number of subjects (percentage of population) ($n = 12{,}631$)	Statin use (%)*		
		regular ($n = 415$)	intermittent ($n = 451$)	none ($n = 11{,}765$)
Age group (years)				
45–48	3571 (28%)	1	2	97
49–51	2893 (23%)	2	2	95
52–55	3056 (24%)	4	4	92
55–61	3111 (25%)	6	6	88
Gender				
Female	6471 (51%)	2	3	95
Male	6160 (49%)	4	4	91
Diabetes				
No	11005 (87%)	2	3	95
Yes	1626 (13%)	9	9	82
High use of dental preventive treatment				
No	6522 (52%)	3	3	93
Yes	6109 (48%)	3	4	93
High use of caries treatment				
No	6248 (49%)	3	3	94
Yes	6383 (51%)	4	4	93
Periodontal treatment				
No	10,864 (86%)	3	3	93
Intermittent	809 (6%)	4	5	90
Regular	958 (8%)	4	5	92
Periodontal status				
Mild	10,036 (79%)	3	3	94
Moderate	2366 (19%)	4	5	91
Advanced	229 (2%)	4	5	91
Anti-inflammatory use				
No	5719 (45%)	3	3	94
Yes	6912 (55%)	4	4	92
Antibiotics use				
No	3643 (29%)	3	2	95
Yes	8988 (71%)	4	4	92
Smoking†				
Missing	367 (3%)	1	1	98
No	6366 (50%)	2	3	95
Former	3290 (26%)	5	5	91
Yes	2608 (21%)	4	4	91

*Differences in statin use during the first 3-year period were statistically significant for all characteristics of participants (χ^2 test, $p < 0.001$), except for high dental preventive treatment (χ^2 test, $p > 0.05$).

†Information on smoking status was not available for 367 participants.

As shown in Table 2, before adjustment, all of our representations of statin use were associated with a significantly increased risk of tooth loss. Controlling for our covariates reduced the rate ratios towards unity. After adjustment for diabetes and smoking status, only one representation of statin use remained (marginally) significantly greater than unity. However, even in our full models, no evidence appeared suggesting a protective effect of statin use – none of the adjusted rate ratios were substantially, let alone significantly, less than one.

We hypothesized that a statin effect, if there was one, might be different among people who were still smoking *versus* those who had stopped smoking or those who had never smoked. However, as shown in Table 3, stratified analyses according to smoking status did not suggest a protective effect for any of these groups. Furthermore, analyses restricted to a sub-sample of participants for whom we had annual smoking status with smoking status as a time-dependent covariate again yielded no suggestion of any protective effect of statin use.

We also considered the possibility that statins might only be effective in persons with the most severe disease or, conversely, that they could only help before substantial tooth loss occurs. However, as shown in Table 4, analyses restricted to persons assessed as having moderate to severe periodontal disease and to those with only mild disease also failed to suggest any benefit, as did multinomial models looking at loss of either one to three teeth or more than three teeth, relative to no tooth loss (data not shown).

Discussion

Our findings do not provide any support for the hypothesis that statin use can ameliorate the course of chronic periodontal disease. Given the evidence for the role of inflammatory mediators in chronic periodontal disease (Birkedal-Hansen 1993, Ryan et al. 1996, Ryan &

Table 2. Effects of other factors on the association of statin use with the risk of tooth loss

	number of person-years	number of teeth lost	Incidence rate ratio (95% CI) unadjusted	adjusted for age and gender	+ dental preventive, caries and periodontal treatments	+ antibiotic and anti-inflammatory use	+ diabetes	+ smoking status	+ periodontal disease severity
Stain use during the first 3 years									
None	47,019	6233							
Intermittent	1789	410	1.75 (1.35–2.27)	1.66 (1.29–2.14)	1.57 (1.22–2.02)	1.57 (1.21–2.04)	1.48 (1.13–1.95)	1.37 (1.03–1.81)	1.29 (1.01–1.65)
Regular	1660	266	1.22 (0.92–1.62)	1.15 (0.87–1.52)	1.14 (0.86–1.51)	1.11 (0.82–1.49)	1.05 (0.77–1.42)	0.95 (0.70–1.29)	0.94 (0.71–1.24)
Months of statin use in the first 3 years			1.009 (1.001–1.017)	1.007 (0.999–1.015)	1.007 (0.998–1.015)	1.006 (0.997–1.014)	1.003 (0.994–1.012)	1.000 (0.991–1.009)	0.999 (0.991–1.007)
Stain use during the previous 3 years									
None	45,557	6018							
Intermittent	2347	438	1.43 (1.11–1.84)	1.34 (1.06–1.71)	1.28 (1.01–1.64)	1.25 (0.98–1.61)	1.19 (0.91–1.55)	1.00 (0.79–1.26)	1.01 (0.80–1.26)
Regular	2564	453	1.35 (1.08–1.68)	1.28 (1.03–1.58)	1.27 (1.02–1.58)	1.26 (1.00–1.59)	1.19 (0.93–1.52)	1.12 (0.87–1.45)	1.11 (0.88–1.39)
Months of statin use in the previous 3 years			1.011 (1.004–1.018)	1.009 (1.002–1.015)	1.009 (1.002–1.015)	1.008 (1.001–1.015)	1.006 (0.999–1.013)	1.003 (0.996–1.011)	1.003 (0.996–1.010)
Any stain use during 1 year									
No	45,880	6117							
Yes	4588	792	1.31 (1.09–1.56)	1.23 (1.04–1.46)	1.21 (1.02–1.44)	1.19 (0.99–1.42)	1.11 (0.92–1.35)	1.01 (0.83–1.22)	1.02 (0.86–1.22)
Months of statin use in the previous year			1.029 (1.011–1.047)	1.023 (1.005–1.040)	1.022 (1.005–1.040)	1.021 (1.003–1.039)	1.015 (0.996–1.034)	1.006 (0.987–1.025)	1.007 (0.990–1.025)

Golub 2000, Golub et al. 2001, Nishikawa et al. 2002, Tatakis & Kumar 2005) and the anti-inflammatory properties of statins (Sukhova et al. 2002, Undas et al. 2002, Weitz-Schmidt 2002), such an effect would be biologically plausible and potentially of clinical importance. Our previous epidemiologic study involving a different, smaller cohort did not find strong evidence supporting this hypothesis but did find some suggestion of a beneficial effect (Cunha-Cruz et al. 2006).

The present study has a number of significant strengths. The longitudinal design with data spanning 7 years allowed us to look for associations of both short- and long-term statin use with tooth loss. The presence of dental care and prescription drug claims, plus periodontal disease status assessments, in our data are additional, significant strengths of our study and could be duplicated in few other settings. Relative to our previous study, this study has involved a substantially larger cohort and, importantly, was able to control for smoking status.

Our study is subject to a number of limitations. First, as an observational study, it is potentially subject to bias from uncontrolled confounding. Periodontal disease and cardiovascular disease have several common risk factors and statin use cannot be considered a random event. However, we were able to control for what we believe are likely to be the two main potential confounders: tobacco use and diabetes. Our findings demonstrate that smoking status, in particular, is a critically important factor and our ability to control for this appears to have eliminated the modest suggestion of a possible protective effect of statins in our previous study (Cunha-Cruz et al. 2006). We cannot think of any unmeasured factors that, if controlled for, seem likely to uncover a significant relationship between statin use and tooth loss. Second, we did not have a measure of number of teeth at risk, only when someone became edentulous. In our previous study (Cunha-Cruz et al. 2006), statin users had fewer teeth at baseline than statin non-users. Lack of information about baseline number of teeth at risk and number of tooth-years could, therefore, have biased our findings towards the null hypothesis. However, our analyses did control for clustering of tooth loss events within individuals. Third, we did not assess all

Table 3. Statin use, smoking status, and the risk of tooth loss

	Adjusted rate ratio (95% CI)			
	restricted to non-smokers	restricted to former-smokers	restricted to smokers	adjusted for annual smoking status
Statin use in the first 3 years*				
Intermittent	1.21 (0.77–1.91)	1.37 (0.87–2.16)	1.30 (0.90–1.88)	1.27 (0.96–1.67)
Regular	0.82 (0.54–1.24)	0.95 (0.54–1.66)	1.04 (0.71–1.51)	1.00 (0.72–1.39)
Months of statin use in the first 3 years	0.994 (0.981–1.006)	1.000 (0.985–1.015)	1.003 (0.991–1.015)	1.000 (0.991–1.009)
Statin use during the previous 3 years*				
Intermittent	0.90 (0.66–1.24)	0.77 (0.49–1.22)	1.33 (0.92–1.92)	1.16 (0.87–1.54)
Regular	1.11 (0.76–1.61)	1.19 (0.78–1.83)	0.99 (0.74–1.33)	1.04 (0.79–1.36)
Months of statin use during the previous 3 years	1.001 (0.990–1.013)	1.004 (0.991–1.017)	1.004 (0.994–1.013)	1.003 (0.995–1.011)
Any statin use in the previous year	0.93 (0.70–1.25)	1.01 (0.72–1.41)	1.13 (0.86–1.47)	1.05 (0.85–1.31)
Months of statin use in the previous year	1.000 (0.972–1.030)	1.006 (0.974–1.040)	1.013 (0.988–1.039)	1.008 (0.987–1.029)

*Reference category is no use.

Table 4. Statin use, periodontal disease status, and the risk of tooth loss

	Adjusted rate ratio (95% CI)	
	restricted to persons with mild periodontal disease	restricted to persons with moderate to severe periodontal disease
Statin use in the first 3 years†		
Intermittent	1.22 (0.90–1.66)	1.40 (0.93–2.11)
Regular	0.75 (0.55–1.01)	1.33 (0.86–2.06)
Months of statin use in the first 3 years	0.993 (0.984–1.001)	1.010 (0.997–1.023)
Statin use in the previous 3 years†		
Intermittent	0.99 (0.75–1.30)	1.05 (0.72–1.54)
Regular	0.93 (0.71–1.22)	1.45* (1.01–2.07)
Months of statin use in the previous 3 years	0.998 (0.991–1.006)	1.011 (0.999–1.022)
Any statin use in the previous year	0.92 (0.74–1.13)	1.18 (0.89–1.57)
Months of statin use in the previous year	0.997 (0.977–1.018)	1.022 (0.994–1.051)

*$p = 0.04$.
†Reference category is no use.

possible relationships between statin use and tooth loss. For example, too few people in our sample used high-dose statins continuously over a substantial number of years to allow evaluation of whether, among regular statins users, high-dose therapy might have had a protective effect not seen among statin users overall. As chronic periodontitis is typically a chronic, slowly progressive condition, the small number of continuous, long-term users prevented us from evaluating the potential effects of use over many years. Fourth, we treated all statins as being equivalent and could have missed an effect limited to a specific statin. However, beyond a dose/potency–response relationship, there is no reason to suspect that there would be such a selective relationship. Fifth, it is possible that statins affect intermediate periodontal outcomes such as attachment and bone levels. As we did not have access to probing charts, the effects of statins on intermediate periodontal outcomes could not be assessed. Given the lack of effect on tooth loss, the evaluation of intermediate outcomes would be unlikely to alter clinical decision making about the utility of long-term statin therapy for periodontal disease. Finally, we did not have data on statin use by persons without periodontal disease. Thus, we cannot assess whether statin use might be associated with a lower risk of developing clinical periodontal disease, even if it does not appear to affect the course of established disease.

In summary, despite the theoretical reasons why statins might well ameliorate the course of periodontal disease, we found no evidence that statin use decreases tooth loss. We believe that the suggestions in our previous epidemiologic study of a possible beneficial effect likely resulted from our inability to control for smoking status in those analyses. It would take a large-scale, long-term, randomized, controlled trial to provide more definitive evidence about the possible relationship between statin use and the course of periodontal disease. Given our findings, we do not believe such a trial is justified.

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Clinical Relevance

Scientific rationale for the study: Statins have pleiotropic effects, including inhibition of inflammatory mediators that appear to play a role in chronic periodontitis, and might ameliorate the course of periodontal disease.

Principal findings: This study found no evidence to suggest that, as used in usual medical practice, statins reduce a clinically important outcome of chronic periodontitis: tooth loss.

Practical implications: Statins do not appear to represent a useful new treatment for periodontal disease.