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Dual effect of statin medication on the periodontium

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Abstract

Aim: The aim of this study was to investigate the association between statin medication and periodontal infection in an adult population.

Material and Methods: The study was based on a subpopulation of the Health 2000 Survey, which included dentate non-diabetic, non-rheumatic subjects who did not smoke, aged 40–69 years ($n = 2032$). The main outcome variable was the number of teeth with periodontal pockets of 4 mm or more. Statin medication was categorized in two ways: firstly, subjects with statin medication of some sort ($n = 134$) *versus* those with none, and secondly, subjects taking either simvastatin ($n = 58$), atorvastatin ($n = 38$), some other statin ($n = 38$) or no statin medication. Relative risks (RR) were estimated using negative binomial and Poisson regression models.

Results: We found a weak negative association between statin medication and periodontal infection among subjects with dental plaque or gingival bleeding. Among subjects with no gingival bleeding, statin medication was found to be associated with an increased likelihood of having deepened periodontal pockets.

Conclusion: Statin medication appears to have an effect on the periodontium that is dependent on the inflammatory condition of the periodontium. More evidence is needed to achieve a comprehensive understanding of the effects of statins.

Key words: periodontal infection; statin medication

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Statins, 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors, are widely used medications to prevent cardiovascular events and have been proven to be highly effective. According to conventional thinking, the effectiveness of statins was based on their capability to reduce serum cholesterol levels, primarily low-density lipoprotein cholesterol (LDL cholesterol). However, inflammation is also known to play a role in atherosclerosis (Libby 2002), and it has been suggested that statins also possess anti-inflammatory activity, independent of their lipid-lowering effects (Schönbeck & Libby 2004, Jain & Ridker 2005).

Periodontitis is a continuous inflammatory process, which, if left untreated, may lead to irreversible destruction of periodontal tissues. Statins have been suggested to have a protective effect against periodontal infection, too. A recent study suggested that chronic periodontitis patients taking statin medication had a lower number of pathological periodontal pockets than those without statin medication (Lindy et al. 2008). A novel index, the Periodontal Inflammatory Burden Index, also showed lower figures for periodontitis patients on statin medication than patients without statins (Lindy et al. 2008). It has also been suggested that statin use was associated with decreased tooth loss in chronic periodontitis patients (Cunha-Cruz et al. 2006). In animal models, statins have been suggested to prevent periodontal tissue breakdown (Vaziri et al. 2007) and to have beneficial effects on alveolar bone recovery after ligature-induced alveolar bone resorption (Seto et al. 2008).

Despite the above-mentioned findings, the effects of statins on the periodontium are quite poorly documented. Moreover, unlike in the case of cardiovascular diseases, the mechanisms of how statins have an effect on the periodontium are not well understood. The aim of this study was to examine the association between statin medication and existing periodontal infection in an adult population.

Conflict of interest and source of funding statement

The authors declare that there are no conflicts of interest in this study.
The present study is part of the Health 2000 Survey, organized by the National Institute for Health and Welfare (THL) (former National Public Health Institute (KTL) of Finland) (http://www.terveys2000.fi), and partly supported by the Finnish Dental Society Apollonia and the Finnish Dental Association. The personal grant received from the Finnish Dental Society Apollonia and the Finnish Dental Association is acknowledged by Tuomas Saxlin.

Material and Methods

The Health 2000 Survey was carried out in 2000 and 2001, conducted by the National Institute for Health and Welfare (THL) [former National Public Health Institute (KTL) of Finland]. This survey comprised 8028 subjects aged 30 years or older living in continental Finland. The data for this survey were collected from clinical oral and health examinations, from laboratory analyses, from self-administered questionnaires and by interviews. The study protocol was approved by the ethical committee of the Helsinki University Hospital. Informed consent was obtained from the participants. Additional information about the Health 2000 Survey is available in a published report by Aromaa & Koskinen (2004).

Our study was based on a subpopulation that included dentate non-diabetic, non-rheumatic subjects who did not smoke and were aged between 40 and 69 years ($n = 2032$). Diabetes was determined on the basis of information obtained from a health interview and health examination. Only subjects who had not been diagnosed with diabetes and had no indications of the disease were included in the study population. Rheumatoid arthritis was determined on the basis of information obtained from the health interview. The question posed was ''Do you have rheumatoid arthritis diagnosed by a physician?'' with the answer options being yes/no. Diabetic and rheumatic subjects were excluded because of the complex association between periodontal infection and these diseases, which would have been difficult to control.

Outcome variables

Clinical oral examinations were performed by five calibrated dentists in a dental chair using a headlamp, mouth mirror and a WHO periodontal probe in line with the WHO instructions. The clinical oral examinations included the assessment of the condition of the periodontium and teeth.

The main outcome variable was existing periodontal infection, measured in two ways: number of teeth with deepened periodontal pockets (4 mm or more) and number of teeth with deep periodontal pockets (6 mm or more). Periodontal pocket depth on probing was measured on four surfaces of each tooth (distobuccal, mid-buccal, mid-oral and mesio-oral), and the deepest pocket depth on each tooth was recorded. Third molars were excluded from the periodontal examination. The percentual agreement for deepened periodontal pockets in the parallel measurements, where field examiners were individually compared with the reference examiner under field circumstances, was 77% ($\kappa = 0.41$) (Vehkalahti et al. 2008, p. 19). Intra-examiner reliability assessments concerning pathologically deepened periodontal pockets produced a κ value of 0.83 (Vehkalahti et al. 2004, p. 29). The distributions of the number of teeth with deepened periodontal pockets are presented in Fig. 1.

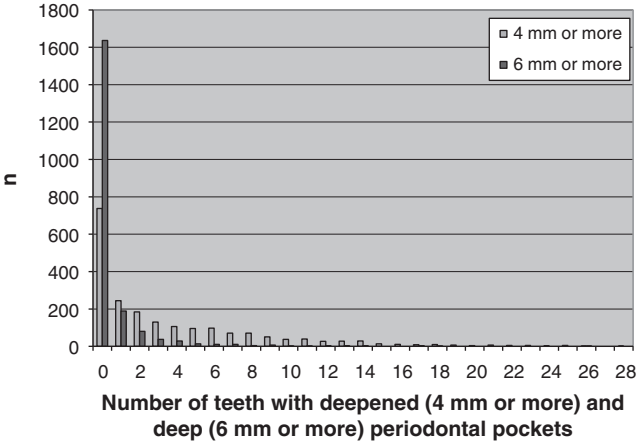

Fig. 1. Number of subjects with teeth with deepened (4 mm or more) and deep (6 mm or more) periodontal pockets.

We also used bleeding on probing as an outcome variable. Bleeding on probing was observed immediately after the measurement of periodontal pockets and the observations were recorded by sextant. The percentual agreement in the parallel measurements between the field examiners and the reference examiner for the presence of gingival bleeding under field circumstances was 66% ($\kappa = 0.36$) (Vehkalahti et al. 2008, p. 19). Intra-examiner reliability assessments of the presence of gingival bleeding produced a κ value of 0.66 (Vehkalahti et al. 2004, p. 29). In the regression analyses, the number of bleeding sextants was used as a continuous variable. In the stratified analyses, gingival bleeding was divided into two categories: subjects with no gingival bleeding *versus* subjects with gingival bleeding in one or more sextants.

Explanatory variables

Information about statin medication was obtained from the health interview. Statin medication was categorized in two ways: firstly, subjects with statin medication of some sort *versus* those with none, and secondly, subjects who use either simvastatin, atorvastatin, some other statin or no statin medication. A total of 134 subjects used statin medication, out of which 58 subjects used simvastatin medication, 38 subjects used atorvastatin medication and 38 subjects used some other statin medication.

Possible confounders and effect modifiers

Age was included in the analyses as a continuous variable. Education was categorized into three categories. Basic education included those who had not graduated from high school and did not have formal vocational qualifications. Intermediate education included those who had graduated from high school. Higher education comprised subjects with a university degree or those who had graduated from polytechnics. Oral health behavioural factors included toothbrushing frequency and dental attendance pattern. Toothbrushing frequency was categorized into three categories as follows: twice a day or more, once daily or less frequently. Dental attendance patterns were categorized as follows: those who regularly had dental check-ups *versus* those who used dental services in a symptom-based manner or had never used them.

The presence of dental plaque was measured using a modified version of the method described by Silness & Löe (1964). The presence of dental plaque was measured from three teeth at one surface each as follows: buccal surface from the most posterior tooth on the upper right side, lingual surface from the most posterior tooth on the lower left side and buccal surface from the left lower canine. The presence of plaque

Table 1. Basic characteristics of the study population; proportions/means and their standard errors (in parentheses) in the total population and in the categories of statin use (no statin medication/statin medication)

	Total ($n = 2032$)	No statin medication ($n = 1898$)	Statin medication ($n = 134$)
Age ($n = 2032$) [mean (SE)]	52.5 (0.2)	52.1 (0.2)	58.4 (0.7)
Gender ($n = 2032$) [% (SE)]			
Males	43.4 (1.1)	42.8 (1.1)	53.0 (4.1)
Females	56.6 (1.1)	57.2 (1.1)	47.0 (4.1)
Educational level ($n = 2032$) [% (SE)]			
Basic	34.6 (1.1)	34.1 (1.1)	41.7 (4.3)
Intermediate	31.7 (1.0)	31.4 (1.0)	36.0 (4.3)
High	33.7 (1.1)	34.5 (1.2)	22.3 (3.7)
Number of teeth, mean ($n = 2032$) (SE)	22.8 (0.2)	23.0 (0.2)	18.9 (0.7)
Number of teeth with periodontal pockets $\geqslant 4$ mm ($n = 2032$) [mean (SE)]	3.7 (0.2)	3.7 (0.2)	3.3 (0.4)
Number of teeth with periodontal pockets $\geqslant 6$ mm ($n = 2032$) [mean (SE)]	0.5 (0.0)	0.5 (0.0)	0.4 (0.1)
Presence of plaque ($n = 2012$) [% (SE)]			
No plaque	42.0 (1.5)	41.7 (1.5)	45.8 (4.3)
Plaque at gingival margins only	48.3 (1.4)	48.6 (1.5)	45.1 (4.4)
Plaque also elsewhere	9.7 (0.7)	9.7 (0.8)	9.1 (2.3)
Gingival bleeding in one or more sextants ($n = 2030$) [% (SE)]			
No	25.8 (1.7)	25.6 (1.8)	29.2 (4.8)
Yes	74.2 (1.7)	74.4 (1.8)	70.8 (4.8)
Number of bleeding sextants, mean (SE) (2030)	2.4 (0.1)	2.4 (0.1)	1.9 (0.2)
Dental attendance pattern ($n = 1970$) [% (SE)]			
Regular check-ups	64.9 (1.4)	65.6 (1.4)	54.7 (4.5)
No regular check-ups	35.1 (1.4)	34.4 (1.4)	45.3 (4.5)
Toothbrushing frequency ($n = 1968$) [% (SE)]			
Twice a day or more often	65.6 (1.2)	65.5 (1.3)	67.2 (4.3)
Once daily	28.9 (1.1)	29.0 (1.1)	27.3 (4.0)
Less frequently	5.5 (0.6)	5.5 (0.6)	5.5 (1.8)
Body mass index, mean (SE) ($n = 2032$)	27.1 (0.1)	27.1 (0.1)	27.4 (0.3)

was categorized into three categories as follows: no visible plaque, visible plaque at gingival margins only or visible plaque also elsewhere. The highest value was recorded. The percentual agreement in the parallel measurements between the field examiners and the reference examiner for the presence of dental plaque under field circumstances was 58% ($\kappa = 0.36$) (Vehkalahti et al. 2008, p. 19). Intra-examiner reliability assessments of the presence of dental plaque produced a κ value of 0.79 (Vehkalahti et al. 2004, p. 29). Body weight was assessed by using body mass index (BMI), which is a measure of body weight in relation to height (kg/m^2). Information on weight and height was collected from the health examination, or alternatively, when this was not possible, from the health interview and questionnaires. BMI was included in the analyses as a continuous variable. The basic characteristics of the study population according to statin medication are presented in Table 1.

Statistical methods

Because of the skewed distribution of the outcome variables among the total population, especially the number of teeth with periodontal pockets of 6 mm deep or deeper, we estimated relative risks (RR) and 95% confidence intervals (95% CI) using negative binomial and Poisson regression models. In addition, we performed analyses where we excluded subjects with no teeth with pathologically deepened periodontal pockets (extent of infection among subjects with teeth with deepened periodontal pockets). The number of teeth (as a continuous variable) was treated as the offset variable in the regression models. The selection of covariates was based on current knowledge of the potential risk factors of periodontal infection. We studied the possible interaction by adding the interaction terms (product terms for statin medication and the other covariates one by one) in the regression model.

A stratified two-stage cluster sampling design was used in the survey. Weighting of the sample was based on post-stratification according to gender, age and region. The data analyses were performed using Stata 8.0 (negative binomial regression) and the SUDAAN statistical package 10.0 (Poisson regression) to take into account the two-stage cluster sampling design.

Results

Among the total study population, statin medication was weakly negatively associated with the number of teeth with deepened periodontal pockets (4 mm or more; RR 0.9, 95% CI 0.7–1.2) and the number of bleeding sextants (RR 0.8, 95% CI 0.7–1.0) after adjusting for confounding factors such as gender, age, education, dental attendance pattern, toothbrushing frequency, presence of dental plaque and BMI. The negative association of statin medication with the number of teeth with deep periodontal pockets (6 mm or more) was stronger than with the number of teeth with deepened (4 mm or more) periodontal pockets, but did not reach statistical significance at a 0.05 level (Table 2). Simvastatin medication was found to be most strongly negatively associated with the number of teeth with deepened and deep periodontal pockets (Table 2).

We found an interaction between statin medication and the presence of dental plaque [statistically significant product term for the number of teeth with deepened periodontal pockets (4 mm or more) ($p = 0.004$)]. We therefore stratified the data according to the presence of plaque. We found that the negative association between statin medication and the number of teeth with deepened (4 mm or more) and deep (6 mm or more) periodontal pockets was stronger among subjects with plaque, whereas a weak and statistically insignificant (at 0.05 level) positive

Table 2. Association between statin medication and the number of teeth with deepened periodontal pockets. Unadjusted and adjusted* relative risks (RR) with 95% confidence intervals (CI)

	Teeth with periodontal pockets ⩾4 mm		Teeth with periodontal pockets ⩾6 mm	
	unadjusted RR (95% CI)	adjusted RR (95% CI)	unadjusted RR (95% CI)	adjusted RR (95% CI)
	Total population ($n = 1949$)†			
Statin medication				
No	1.0	1.0	1.0	1.0
Yes	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.9 (0.5–1.5)	0.7 (0.4–1.1)
	Subjects with the number of teeth with periodontal pockets >0 ($n = 1248$)‡			
Statin medication				
No	1.0	1.0	1.0	1.0
Yes	1.0 (0.8–1.2)	0.9 (0.7–1.1)	0.8 (0.5–1.3)	0.6 (0.3–1.0)
	Total population ($n = 1949$)†			
Statin medication				
No statin	1.0	1.0	1.0	1.0
Simvastatin	1.0 (0.7–1.4)	0.8 (0.6–1.2)	0.6 (0.3–1.3)	0.4 (0.2–1.0)
Atorvastatin	1.1 (0.8–1.6)	1.1 (0.7–1.6)	0.7 (0.3–1.8)	0.8 (0.3–1.8)
Other statin	1.0 (0.6–1.6)	0.8 (0.5–1.3)	1.5 (0.6–3.9)	1.1 (0.5–2.4)
	Subjects with the number of teeth with periodontal pockets >0 ($n = 1248$)‡			
Statin medication				
No statin	1.0	1.0	1.0	1.0
Simvastatin	1.0 (0.8–1.3)	0.9 (0.7–1.1)	0.7 (0.3–1.5)	0.4 (0.2–0.9)
Atorvastatin	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.7 (0.3–1.7)	0.6 (0.2–1.4)
Other statin	1.0 (0.7–1.5)	0.9 (0.6–1.3)	1.1 (0.5–2.4)	0.9 (0.4–2.1)

*Adjusted for gender, age (continuous variable), education, presence of dental plaque, dental attendance pattern, toothbrushing frequency, body mass index (continuous variable) and number of teeth (offset variable).
†Negative binomial regression models used.
‡Poisson regression models used.

association was found among subjects with no plaque; statin medication was found to be associated with an increased likelihood of having teeth with deepened and deep periodontal pockets (Table 3).

Based on the findings of the stratification according to dental plaque, we also stratified the data according to the presence of gingival bleeding. In these analyses, the association between statin medication and the number of teeth with deepened (4 mm or more) and deep (6 mm or more) periodontal pockets followed a pattern similar to the one for stratification according to dental plaque. Among subjects with gingival bleeding in one or more sextants, a negative association was found between statin medication and the number of teeth with deepened (RR 0.9, 95% CI 0.7–1.1) and deep (RR 0.6, 95% CI 0.3–1.1) periodontal pockets. Among subjects with no gingival bleeding, statin medication was associated with an increased likelihood of having teeth with deepened (RR 1.7, 95% CI 1.0–2.8) and deep (RR 3.1, 95% CI 1.1–9.0) periodontal pockets (Table 4).

The results of the analyses where the association between statin use and the extent of periodontal infection was studied (subjects with no teeth with deepened periodontal pockets excluded) followed a pattern similar to the one for the total population (Tables 2–4).

Discussion

The results of this study showed that among the total study population, statin medication was weakly negatively associated with the presence and extent of periodontal infection. In stratified analyses, this beneficial effect was seen only in subjects with dental plaque or gingival bleeding. Among subjects with no gingival bleeding, and also to a lesser extent among subjects with no dental plaque, statin medication was associated with an increased likelihood of having teeth with deepened periodontal pockets.

Some recent studies have suggested that statins have protective effects against periodontal infection. For example, a study by Lindy et al. (2008) showed that statin use was associated with fewer numbers of pathologically deepened periodontal pockets compared with subjects not taking statin medication among chronic periodontitis patients. Statin use was also suggested to be associated with decreased tooth loss among subjects with chronic periodontitis (Cunha-Cruz et al. 2006). Our results partly concurred with these results because our results also suggested that statin medication may have some beneficial effects when subjects have aetiological load (dental plaque) or a sign of periodontal infection (gingival bleeding).

Anti-inflammatory effects of statins

Tissue destruction in periodontal disease results from the interaction of the host's immune responses with microorganisms in dental plaque. Statins have been suggested to have several anti-inflammatory qualities, which may also be important in the case of periodontal infection. For example, it has been demonstrated that statins are able to inhibit leucocyte function antigen-1 (LFA-1)–intercellular adhesion molecule-1 interaction in vitro by binding to LFA-1 (Weitz-Schmidt et al. 2001). This binding inhibition might prevent leucocyte adhesion and extravasation to sites of inflammation and antigen presentation. In addition, Weitz-Schmidt et al. found that inhibition of LFA-1 resulted in impaired T-cell costimulation.

Statins have also been suggested to repress T-cell functions. Major histocompability complex class II (MHC-II) molecules are directly involved in the activation of T-lymphocytes and in the control of the immune response through

Table 3. Association between statin medication (no/yes) and the number of teeth with deepened periodontal pockets, stratified according to the presence of dental plaque. Adjusted* relative risks (RR) with 95% confidence intervals (CI)

	No plaque		Plaque in gingival margins		Plaque also elsewhere	
	RR	95% CI	RR	95% CI	RR	95% CI
Teeth with periodontal pockets ⩾4 mm						
	Total population†					
	$n = 821$		$n = 944$		$n = 184$	
Statin medication						
No	1.0		1.0		1.0	
Yes	1.2	0.8–1.8	0.6	0.5–0.9	0.8	0.5–1.2
	Subjects with the number of teeth with periodontal pockets >0‡					
	$n = 430$		$n = 666$		$n = 152$	
Statin medication						
No	1.0		1.0		1.0	
Yes	1.2	0.9–1.7	0.7	0.6–0.9	0.8	0.6–1.1
Teeth with periodontal pockets⩾6 mm						
	Total population†					
	$n = 821$		$n = 944$		$n = 184$	
Statin medication						
No	1.0		1.0		1.0	
Yes	1.2	0.6–2.2	0.3	0.1–0.8	0.1	0.0–0.5
	Subjects with the number of teeth with periodontal pockets >0‡					
	$n = 430$		$n = 666$		$n = 152$	
Statin medication						
No	1.0		1.0		1.0	
Yes	1.5	0.8–2.8	0.3	0.1–0.6	0.1	0.0–0.4

*Adjusted for gender, age (continuous variable), education, dental attendance pattern, toothbrushing frequency, body mass index (continuous variable) and number of teeth (offset variable).
†Negative binomial regression models used.
‡Poisson regression models used.

antigen presentation. Kwak et al. (2000) found that statins act in vitro as direct inhibitors of MHC-II expression inducted by interferon γ. They also found that repression of MHC-II was highly specific for the inducible form of MHC-II and concerned neither constitutive expression of MHC-II, like for example in B-lympho cytes, nor MHC class I expression. They suggested that the effect is due to the inhibition of inducible promoter IV of a class II transactivator.

It has also been proposed that statins decrease the production of many pro-inflammatory cytokines. Sakoda et al. (2006) studied the effect of simvastatin on a human epithelial cell line KB and found that simvastatin in vitro down-regulated interleukin-1α-induced interleukin-6 (IL-6) and IL-8 production in epithelial cells in a dose-dependent manner. Ikeda & Shimada (1999) found that statins were associated with decreased IL-6 production in vitro, whereas Rosenson et al. (1999) found that pravastatin was associated with decreased blood concentrations of tumour necrosis factor α and IL-6 among hypercholesterolaemic patients.

Matrix metalloproteinases (MMP) are considered to be one of the main proteinases involved in periodontal tissue destruction, as they degrade extracellular matrix molecules. Statins have been found to decrease secretion of MMP-1, MMP-2, MMP-3 and MMP-9 in vitro (Luan et al. 2003). Also, reduced levels of C-reactive protein have been suggested to be associated with statin medication (Ridker et al. 1999).

Statins as immunomodulators in periodontal tissues?

An interesting finding in this study was that among subjects with no dental plaque or no gingival bleeding, statin medication was associated with an increased likelihood of having teeth with deepened periodontal pockets. One interpretation for this result is that statins may dampen the fierce immune response in a situation where the aetiological load of dental plaque is substantial, thus protecting against periodontal tissue destruction, possibly via some of the above-mentioned anti-inflammatory mechanisms. However, in situations where the magnitude of the aetiological load is small (no visible plaque) and the visible inflammation is minimal (no gingival bleeding), this dampening of immune responses may lead to disruption of the immune homeostasis in periodontal tissues, which could predispose to periodontal tissue breakdown.

In addition to the direct anti-inflammatory effects, some of the beneficial effects of statins could be mediated through lowered oxidized LDL cholesterol, which has been suggested to have pro-inflammatory properties (Matsuura et al. 2006). This could be a complementary/alternative explanation, especially because elevated levels of serum lipids have, in some studies, been found to associate with periodontal infection (Lösche et al. 2000, Noack et al. 2000, Nibali et al. 2007). However, this interpretation is not supported by the findings in our previous study using these Health 2000 data, in which we found that serum LDL cholesterol did not seem to associate with the number of teeth with deepened periodontal pockets (Saxlin et al. 2008).

From the medications investigated in this study, simvastatin was found to be most strongly negatively associated with periodontal infection. However, the number of subjects using different statins was fairly small, meaning that no definite conclusions on their effect can be made. Therefore, no detailed analyses on the effect of different statins were carried out.

Validity issues

The presence of deepened periodontal pockets is a standardized method to assess periodontal infection and it is widely used in research, in screening and in clinical work. Probing depths of 4 and 6 mm were used as cut-off values, which are commonly used boundary values for pathologically deepened periodontal pockets. We measured the presence and the extent of periodontal infection in this study in terms of the number of teeth with deepened periodontal pockets, which produced count data. This in turn means that we could use negative binomial or Poisson regression models, which yield risk estimates, i.e. RR, which can be interpreted in a probabilistic manner.

This study population had a relatively large number of subjects with no teeth with pathologically deepened periodontal

Table 4. Association between statin medication (no/yes) and the number of teeth with deepened periodontal pockets, stratified according to the presence of gingival bleeding. Adjusted* relative risks (RR) with 95% confidence intervals (CI)

	Among subjects with no gingival bleeding in any sextants		Among subjects with gingival bleeding in one or more sextants	
	RR	95% CI	RR	95% CI
Teeth with periodontal pockets ⩾4 mm				
	Total population†			
	$n = 494$		$n = 1453$	
Statin medication				
No	1.0		1.0	
Yes	1.7	1.0–2.8	0.9	0.7–1.1
	Subjects with the number of teeth with periodontal pockets >0‡			
	$n = 175$		$n = 1071$	
Statin medication				
No	1.0		1.0	
Yes	1.7	1.2–2.5	0.8	0.7–1.0
Teeth with periodontal pockets ⩾6 mm				
	Total population†			
	$n = 494$		$n = 1453$	
Statin medication				
No	1.0		1.0	
Yes	3.1	1.1–9.0	0.6	0.3–1.1
	Subjects with the number of teeth with periodontal pockets >0‡			
	$n = 175$		$n = 1071$	
Statin medication				
No	1.0		1.0	
Yes	3.5	1.6–7.6	0.5	0.3–0.9

*Adjusted for gender, age (continuous variable), education, presence of dental plaque, dental attendance pattern, toothbrushing frequency, body mass index (continuous variable) and number of teeth (offset variable).

†Negative binomial regression models used.

‡Poisson regression models used.

pockets (periodontally healthy subjects). This excessive number of zeros caused overdispersion, which meant that Poisson regression models did not fit properly. Therefore, we estimated RRs among the total population using negative binomial regression models. When the estimates of negative binomial regression models were compared with the estimates of Poisson regression models, it could be noted that the difference in the estimates, if any, did not exceed 0.1 in most cases (data not shown).

We also performed analyses using Poisson regression models where we excluded subjects with no teeth with deepened periodontal pockets. This sort of exclusion reduces overdispersion and is one suggested method to handle a situation where overdispersion is apparent (Lewsey et al. 2000). There was no essential difference in the results of the analyses of the total population and the subpopulation where periodontally healthy subjects were excluded, which increases the credibility of the results obtained in the main analyses.

The distribution of the number of bleeding sextants did not follow the Poisson distribution completely. Therefore, we performed complementary analyses using a cumulative logit model to assess the effect of this deviation from Poisson distribution (data not shown). These results were in accordance with the results obtained of the Poisson regression models.

We studied the possible interaction by adding the interaction terms (product terms for statin medication and the other covariates one by one) in the regression model. In theory, there is always a risk of finding spurious interactions if the number of such tests is large. However, in this study, the number of interaction tests totalled seven, meaning that in the case of no association, the probability of obtaining a statistically significant interaction between statin medication and dental plaque is low. Our interpretation that the effect of statin medication on periodontium is dependent on the presence of dental plaque is supported by the fact that the p-value for the interaction between statin medication and dental plaque was low ($p = 0.004$). It could be noted that because gingival bleeding is a sign of periodontal infection, we did not consider gingival bleeding as a potential confounder and therefore the interaction between statin medication and the presence of gingival bleeding was not tested.

The strengths of this study include the restriction of the study population to non-smokers, because smoking is known to be a strong risk factor for periodontitis and can therefore prevent detection of weaker determinants. Moreover, it has been suggested that adjusting for smoking may otherwise be insufficient (Hujoel et al. 2002). In this study, restriction to non-smokers is also important because smoking is known to reduce gingival bleeding (Bergström & Preber 1994), which was used as one of the outcome variables and as a variable for stratification. Restricting the study population to non-rheumatic subjects is also an advantage because rheumatic patients often have other medications, such as immunomodulatory and anti-inflammatory medications, whose effect would have been difficult to take into account in the analyses. However, we cannot totally exclude the possibility that unreported smoking or undiagnosed diseases could have some effect on the association between statin medication and periodontal infection.

This study had a cross-sectional design, which is considered to be a limitation. It prevents us from making any definite conclusions about the temporal sequence between expected cause and effect. We also acknowledge that the presence of dental plaque and gingival bleeding are crude markers of aetiological load and inflammation in gingival tissues, respectively, and are also subject to biases in registration. It is, however, noteworthy that despite this crudeness, the associations between statin medication and the number of teeth with pathologically deepened periodontal pockets, especially in stratified analyses, were fairly strong.

Concluding remarks

Our assumption was that statin medication has beneficial effects on the periodontium, as has been suggested in earlier studies. In line with this assumption, statin medication was weakly negatively

associated with periodontal infection in this low-risk adult population of non-diabetic and non-rheumatic subjects who did not smoke. An interesting and important finding was that among subjects with no dental plaque or no gingival bleeding, statin medication was associated with an increased likelihood of having pathologically deepened periodontal pockets.

The results of this study suggested that statins have an effect on the periodontium that is dependent on the inflammatory condition of the periodontium. This has not been suggested previously. We acknowledge that these findings may be due to chance, not at least due to the low number of individuals who had statin medication, and must therefore be interpreted with caution. We also acknowledge that these results may be affected by various forms of biases, such as errors in measurements of clinical parameters, insufficient or incorrect information about medications or confounding by extraneous factors. Altogether, the results of this study call for further studies to replicate and verify these findings and to attain a comprehensive understanding of the effects of statins.

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Clinical Relevance

Scientific rationale for the study: Statins have been suggested to have anti-inflammatory effects, independent of their lipid-lowering effects. Some recent studies have suggested that statin medication may also have beneficial effects on the periodontium.

Principal findings: Among subjects with dental plaque or gingival bleeding, statin medication was found to be weakly and negatively associated with periodontal infection. Among subjects with no gingival bleeding, statin medication was associated with an increased likelihood of having teeth with deepened periodontal pockets.

Practical implications: Statins may also have therapeutic effects due to their anti-inflammatory potential, but more studies are needed to replicate and verify these effects of statins.