Association Between Statin use and Chronic Periodontitis: A Longitudinal Follow-Up Study using Korean National Health Screening Cohort

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Abstract

Background: Since potential link between statin and the risk of adverse chronic periodontitis (CP) has been raised, we aimed to validate the associations of statin use on the incidence of CP using a nationwide cohort data.

Methods: This longitudinal follow-up study included 169,381 patients who were administered statins matched with an equal number of controls using propensity score from the Korean National Health Insurance Service-Health Screening Cohort database (2002–2015). A Cox proportional hazard model was used to assess the occurrence of CP following statin use after adjusting for multiple covariates.

Results: The occurrence of CP was significantly higher with long-term use (1–3 years, 3–5 years, or >5 years) than with short-term use (≤ 1 year). After adjustment, statin users exhibited a 1.32-fold higher occurrence of CP (95% confidence interval=1.30–1.33) than the matched non-users (incidence: 25.0 and 22.0 per 100 person-years, respectively). Subgroup analyses supported the adverse impact of statins on CP independent of age and sex.

Conclusions: Statin use in individuals aged >40 years, of both sexes, may slightly increase the risk of occurrence of CP, especially with long-term use, warranting a caution regarding the onset of CP as a possible adverse effect of long-term statin use.

Introduction

Statins are the most widely used lipid-lowering agents for treating hypercholesterolemia and cardiovascular disease. They inhibit 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase and statin therapy is generally considered safe and well-tolerated¹. Statins efficiently suppress low-density lipoprotein cholesterol levels and have pleiotropic effects of systemic anti-inflammatory activity including locally atherosclerotic plaques and enhancing antimicrobial and fungicidal activities and bone modulation^{1–4}. Considering these benefits, many studies had suggested that statins have the supplemental clinical benefits of reducing periodontal inflammation and preventing alveolar bone loss in periodontitis^{5,6}; other studies reported contradictory results^{7–10}.

Chronic periodontitis (CP) is a multifactorial infectious inflammatory disease closely related to the host immune system and environmental risk factors¹¹. It is characterized by immune-inflammatory infiltration of the deeper compartments of the periodontium, resulting in destruction of the tooth-supporting tissues such as cementum, periodontal ligament, and alveolar bone and impaired masticatory function, which culminates in tooth loss and negatively impacts quality of daily life^{12,13}. CP is highly prevalent among the elderly, who are often prescribed statins to control cardiovascular disease¹⁴; this highlights the significance of exploring the effects of statins in periodontitis. Orally administered statins were reported to improve healing outcomes and decreased inflammatory activity in experimental periodontitis in rat models and patients with CP undergoing treatment^{2,5,15–18}. Local administration of statins, adjunctive to non-surgical/surgical periodontal treatment, was also effective in preventing alveolar bone loss in clinical and animal studies of periodontitis^{6,19}. Nevertheless, its safety has not been fully elucidated in the short- and long-term with regard to CP.

Risk of unexpected adverse events related to the statin use has been reported in the last two decades, raising safety concerns regarding statin therapy^{4,20}. The mechanism underlying these observations remains unclear. Recent systematic reviews have reported statins to be safe therapeutic agents in improving oral health^{12,21}. Most of the previous clinical and animal studies focused on the relatively short-term effects of statins on the severity of pre-existing periodontitis and had limited sample sizes^{6–8, 15,18}. Research has been scarce on the long-term effects of statin on large cohorts of patients with CP. Alghofaily et al.¹⁶ demonstrated higher healing outcomes in patients with periodontitis on statins for long periods compared with controls; however, the duration of statin intake was not clearly described, and the groups were not age or sex matched. Therefore, longitudinal studies on different populations and with large sample sizes are needed to confirm the relationship between statins and clinical outcomes in CP.

Based on these evidences, we hypothesized that long-term and short-term statin use might have different effects in CP. A longitudinal follow-up study using a nationwide, population-based cohort among Korean adults was carried out to estimate the potential impact of statins on periodontitis-related outcomes depending on the duration of statin intake.

Materials And Methods

Participant Selection

This study was approved by the ethics committee of Hallym University (approval number 2019-10-023) and the requirement for written informed consent was waived by the institutional review board and performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

The present was conducted retrieved from information from the Korean National Health Insurance Service-Health Screening (KNHIS-HS) database, which offers population-based electronic files for research purposes that were deidentified in the identification codes with anonymous information of the Korean population, as previously described²². The diagnostic codes of the KNHIS-HS data follow the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM). From a total of 514,866 individuals with 615,488,428 medical claim codes (from 2002 to 2015), those who first had statin prescriptions for a minimum of 6 months were included in the statin-user group (n = 192,296), while others who had never prescribed statins were included in the control group (n = 322,570). We excluded the statin users from 2002 to 2003 (n = 17,670), as we included pre-existing CP before the index date in the analysis. Further, we excluded patients who did not have total cholesterol records (n = 68), blood pressure records (n = 23), fasting blood glucose records (n = 6), or body mass index (BMI, kg/m²) records (n = 6) from the statin user group.

In the control group, we excluded 1,474 individuals who either died before 2004 or had no records since and 23,650 patients who received a single prescription of statins from 2002 to 2015.

The statin-user group was matched 1:1 with the control group by means of propensity-score matching through logistic regression for age, sex, income, and region of residence. To avoid any selection bias, statin non-users were extracted according to a random number order. The index date of each statin user was defined as the first date of statin prescription. The index date of control group was determined as the index date of their matched

statin users. During the matching process, 128,065 control group and 5,142 statin users were excluded. Finally, 169,381 statin users were matched with 169,381 control group in 1:1 ratio for the study, and then the risk of CP was analyzed as the primary objective.

The statin-user group was subcategorized according to the duration of statin use as: ≤ 1 year ($n = 57,791$), >1 year to ≤ 3 years ($n = 47,117$), >3 years to ≤ 5 years ($n = 29,176$), and >5 years ($n = 35,297$). The risk of CP was analyzed among them as the secondary objective. Figure 1 summarizes the flow illustration of the study population enrollment.

Independent variable (statin prescription)

Statin prescription was considered the independent variable. The date on which statins were first prescribed was defined as the index date, and subsequent statin use data was analyzed. Statin-user group was configured as patients who were prescribed statins for a minimum of 6 months between 2002 and 2015. The patients deemed short-term users as 6 months–1 year prescription, as previously described.²³

Dependent variable (chronic periodontitis)

CP was considered the dependent variable. Diagnosis of CP according to ICD-10 code (K05.3: Chronic periodontitis) and treatment by dentists was analyzed.

Covariates

Participants were classified according to age into 10 groups of 5-year intervals: from 40–44 years to >85 years, according to income into five classes (class 1 [lowest]–class 5 [highest]), according to regions of residence into urban and rural provinces, based on the previous study²⁴. Tobacco smoking, alcohol consumption, and obesity (BMI [body mass index], kg/m^2) were subdivided as described in our previous study²⁴. Dyslipidemia was considered as treatment history with two or more times due to diagnosis with dyslipidemia according to ICD-10 code (E78). Fasting blood glucose level (mg/dL), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and total cholesterol level (mg/dL) were obtained. The number of previous diagnoses of CP before the index date was determined. The Charlson Comorbidity Index (CCI) score was calculated, which is widely applied to quantify disease burden using seventeen comorbidities, as the continuous variable (0 [no comorbidities] to 29 [multiple comorbidities])²⁵.

Statistical Analyses

Differences between study and control groups were adjusted through propensity-score matching calculated by logistic regression with aforementioned four baseline covariates using greedy option of nearest-neighbor matching algorithm²⁶. After matching, balance between groups was evaluated again. Categorical data were summarized with numbers and percentages. Continuous data were depicted as mean and standard deviation. Characteristics between the statin user and control groups were compared using the chi-square test for categorical variables and the independent t-test or one-way analysis of variance (ANOVA) for continuous variables.

To analyze the hazard ratio (HR), with 95% confidence interval (CI), for CP (primary objective) between statin user and control groups, a stratified Cox proportional hazard model was applied; crude and adjusted models (adjusted for fasting blood glucose, alcohol consumption, obesity, dyslipidemia history, total cholesterol, smoking, SBP, DBP, the number of preexisting CP, and CCI scores) were calculated. The analysis was stratified according to age, sex, areas of residence, and income. For the further subgroup analyses, participants were subdivided according to age (<60 and ≥ 60 years old) and sex (men and women) and both the crude and adjusted models were analyzed.

To analyze the HR, with 95% CI, for CP among the duration of statin use (secondary objective), an unstratified cox proportional hazard method was performed. In this analysis, crude model 1 (adjusted for fasting blood glucose, CCI scores, obesity, smoking, total cholesterol, alcohol consumption, SBP, and DBP), and model 2 (dyslipidemia history and the number of previous CP diagnoses added to model 1) were calculated.

Statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-tailed $P < 0.05$ indicates statistical significance.

Results

Baseline characteristics

The study comprised 169,381 patients with history of statin use and those equivalent numbers of matched controls were retrieved from the database. The average duration from January 1, 2002 to CP diagnosis was 454,036 person-years in the statin user group and 484,893 person-years in the control group. Age, region of residence, sex, and income were evenly matched between the two groups ($P = 1.000$; Table 1). Development of new CP during the study period was higher in the statin user group (66.9% [113,349 of 169,381]) than in the control group (62.9% [106,562 of 169,381]) ($P < 0.001$). Compared with the controls, statin users were more likely to have dyslipidemia, obesity, smoking habit, comorbidities, frequent alcohol consumption (≥ 1 /week), and higher total cholesterol or fasting glucose level, or hypertension ($P < 0.001$).

Table 1
General characteristics of participants between statin and control groups

Characteristics	Total participants		
	Statin	Statin non-user	<i>P</i> -value
Age (years old, n, %)			1.000
40-44	1,646 (1.0)	1,646 (1.0)	
45-49	13,335 (7.9)	13,335 (7.9)	
50-54	33,627 (19.9)	33,627 (19.9)	
55-59	34,815 (20.6)	34,815 (20.6)	
60-64	30,282 (17.9)	30,282 (17.9)	
65-69	24,429 (14.4)	24,429 (14.4)	
70-74	16,780 (9.9)	16,780 (9.9)	
75-79	9,485 (5.6)	9,485 (5.6)	
80-84	4,005 (2.4)	4,005 (2.4)	
85+	977 (0.6)	977 (0.6)	
Sex (n, %)			1.000
Males	82,117 (48.5)	82,117 (48.5)	
Females	87,264 (51.5)	87,264 (51.5)	
Income (n, %)			1.000
1 (lowest)	27,596 (16.3)	27,596 (16.3)	
2	22,433 (13.2)	22,433 (13.2)	
3	26,619 (15.7)	26,619 (15.7)	
4	35,917 (21.2)	35,917 (21.2)	
5 (highest)	56,816 (33.5)	56,816 (33.5)	
Region of residence (n, %)			1.000
Urban	74,748 (44.1)	74,748 (44.1)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.

* Chi-square test. Significance at $P < 0.05$

† Independent *t* test. Significance at $P < 0.05$

‡ Obesity (BMI, body mass index, kg/m²) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

Characteristics	Total participants		
Rural	94,633 (55.9)	94,633 (55.9)	
Total cholesterol (mg/dL, mean, SD)	225.6 (40.2)	191.7 (32.5)	<0.001†
SBP (mmHg, mean, SD)	130.0 (17.3)	125.5 (16.7)	<0.001†
DBP (mmHg, mean, SD)	80.2 (11.0)	77.8 (10.7)	<0.001†
Fasting blood glucose (mg/dL, mean, SD)	106.9(36.5)	97.4 (24.8)	<0.001†
Obesity (n, %)‡			<0.001*
Underweight	2,115 (1.3)	5,494 (3.2)	
Normal	47,435 (28.0)	67,007 (39.6)	
Overweight	47,704 (28.2)	45,855 (27.1)	
Obese I	64,908 (38.3)	47,238 (27.9)	
Obese II	7,219 (4.3)	3,787 (2.2)	
Smoking status (n, %)			<0.001*
Nonsmoker	120,170 (71.0)	123,188 (72.7)	
Past smoker	21,082 (12.5)	18,789 (11.1)	
Current smoker	28,129 (16.6)	27,404 (16.2)	
Alcohol consumption (n, %)			<0.001*
< 1 time a week	114,307 (67.5)	117,201 (69.2)	
≥ 1 time a week	55,074 (32.5)	52,180 (30.8)	
CCI score (score, n, %)			<0.001*
0	104,801 (61.9)	125,212 (73.9)	
1	29,556 (17.5)	19,495 (11.5)	
2	15,741 (9.3)	11,156 (6.6)	
3	8,625 (5.1)	5,355 (3.2)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.

* Chi-square test. Significance at $P < 0.05$

† Independent t test. Significance at $P < 0.05$

‡ Obesity (BMI, body mass index, kg/m^2) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

Characteristics	Total participants		
≥ 4	10,658 (6.3)	8.163 (4.8)	
Dyslipidemia (n, %)	134,151 (79.2)	18,848 (11.1)	<0.001*
The number of periodontitis before index date (mean, SD)	2.7 (4.5)	2.4 (4.2)	<0.001†
Periodontitis (n, %)	113,349 (66.9)	106,562 (62.9)	<0.001*
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.			
* Chi-square test. Significance at $P < 0.05$			
† Independent t test. Significance at $P < 0.05$			
‡ Obesity (BMI, body mass index, kg/m^2) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).			

Characteristics of statin users according to the duration of use

Participants in the statin user group aged between 50 to 70 years were than other age groups ($P < 0.001$) (Table 2). Women tended to use statins for a longer durations than men ($P < 0.001$). Long-term statin users (>5 years) tended to have higher income, were more likely to be from an urban region, obese (BMI 25–30), non-smokers, or consumed less alcohol (less than once a week), and had more comorbidities than short-term users (≤ 1 year) ($P < 0.001$). Blood pressure, fasting blood glucose level, and total cholesterol level were the highest among those who used statins for >5 years (all $P < 0.001$). The rate of pre-existing periodontitis decreased with increased duration of statin use ($P < 0.001$), while the incidence of dyslipidemia and subsequent CP tended to increase with an increase in duration (1–3 years, 3–5 years, or >5 years) compared to short-term duration (≤ 1 year) (each $P < 0.001$).

Table 2
General characteristics of participants in statin user according to the periods of the statin-use

Characteristics	The periods of the statin-use				<i>P</i> -value
	≤ 1 y (n = 57,791)	1-3 y (n = 47,117)	3-5y (n = 29,176)	> 5 y (n = 35,297)	
Age (years old, n, %)					<0.001*
40-44	509 (0.9)	375 (0.8)	246 (0.8)	516 (1.5)	
45-49	3,941 (6.8)	3,235 (6.9)	2,420 (8.3)	3,739 (10.6)	
50-54	11,886 (20.6)	9,501 (20.2)	5,847 (20.0)	6,393 (18.1)	
55-59	12,342 (21.4)	9,817 (20.8)	5,754 (19.7)	6,902 (19.6)	
60-64	10,087 (17.5)	8,429 (17.9)	5,228 (17.9)	6,538 (18.5)	
65-69	7,480 (12.9)	6,756 (14.3)	4,416 (15.1)	5,777 (16.4)	
70-74	5,421 (9.4)	4,719 (10.0)	3,052 (10.5)	3,588 (10.2)	
75-79	3,594 (6.2)	2,773 (5.9)	1,632 (5.6)	1,486 (4.2)	
80-84	1,959 (3.4)	1,213 (2.6)	498 (1.7)	335 (1.0)	
85+	572 (1.0)	299 (0.6)	83 (0.3)	23 (0.1)	
Sex (n, %)					<0.001*
Males	29,296 (50.7)	22,765 (48.3)	13,467 (46.2)	16,589 (47.0)	
Females	28,495 (49.3)	24,352 (51.7)	15,709 (53.8)	18,708 (53.0)	
Income (n, %)					<0.001*

SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.

* Chi-square test. Significance at $P < 0.05$

†One-way analysis of variance (ANOVA). Significance at $P < 0.05$

‡ Obesity (BMI, body mass index, kg/m²) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

Characteristics	The periods of the statin-use				
1 (lowest)	9,621 (16.7)	7,721 (16.4)	4,766 (16.3)	5,488 (15.6)	
2	8,061 (14.0)	6,328 (13.4)	3,722 (12.8)	4,322 (12.2)	
3	9,284 (16.1)	7,509 (15.9)	4,521 (15.5)	5,305 (15.0)	
4	12,344 (21.4)	10,001 (21.2)	6,144 (21.1)	7,428 (21.0)	
5 (highest)	18,481 (32.0)	15,558 (33.0)	10,023 (34.4)	12,754 (36.1)	
Region of residence (n, %)					<0.001*
Urban	24,068 (41.7)	20,359 (43.2)	13,248 (45.4)	17,073 (48.4)	
Rural	33,723 (58.4)	26,758 (56.8)	15,928 (54.6)	18,224 (51.6)	
Total cholesterol (mg/dL, mean, SD)	223.1 (39.7)	224.8 (39.6)	227.4 (39.8)	229.3 (41.6)	<0.001†
SBP (mmHg, mean, SD)	128.1 (16.9)	129.5 (17.0)	130.8 (17.3)	132.9 (17.8)	<0.001†
DBP (mmHg, mean, SD)	79.2 (10.7)	79.9 (10.8)	80.7 (11.1)	82.0 (11.4)	<0.001†
Fasting blood glucose (mg/dL, mean, SD)	104.3 (33.1)	107.1 (36.1)	108.1 (37.0)	110.0 (41.5)	<0.001†
Obesity (n, %)‡					<0.001*
Underweight	984 (1.7)	584 (1.2)	289 (1.0)	258 (0.7)	
Normal	18,126 (31.4)	13,404 (28.5)	7,640 (26.2)	8,265 (23.4)	
Overweight	16,270 (28.2)	13,361 (28.4)	8,202 (28.1)	9,871 (28.0)	
Obese I	20,474 (35.4)	17,791 (37.8)	11,651 (39.9)	14,992 (42.5)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.

* Chi-square test. Significance at $P < 0.05$

†One-way analysis of variance (ANOVA). Significance at $P < 0.05$

‡ Obesity (BMI, body mass index, kg/m^2) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

Characteristics	The periods of the statin-use				
Obese II	1,937 (3.4)	1,977 (4.2)	1,394 (4.8)	1,911 (5.4)	
Smoking status (n, %)					<0.001*
Nonsmoker	39,842 (68.9)	32,980 (70.0)	21,064 (72.2)	26,284 (74.5)	
Past smoker	8,098 (14.0)	6,335 (13.5)	3,461 (11.9)	3,188 (9.0)	
Current smoker	9,851 (17.1)	7,802 (16.6)	4,651 (15.9)	5,825 (16.5)	
Alcohol consumption (n, %)					<0.001*
< 1 time a week	34,566 (59.8)	31,649 (67.2)	21,010 (72.0)	27,082 (76.7)	
≥ 1 time a week	23,225 (40.2)	15,468 (32.8)	8,166 (28.0)	8,215 (23.3)	
CCI score (score, n, %)					<0.001*
0	37,693 (65.2)	29,712 (63.1)	17,578 (60.3)	19,818 (56.2)	
1	8,906 (15.4)	7,944 (16.9)	5,437 (18.6)	7,269 (20.6)	
2	4,685 (8.1)	4,249 (9.0)	2,855 (9.8)	3,952 (11.2)	
3	2,671 (4.6)	2,321 (4.9)	1,517 (5.2)	2,116 (6.0)	
≥ 4	3,836 (6.6)	2,891 (6.1)	1,789 (6.1)	2,142 (6.1)	
Dyslipidemia (n, %)	42,186 (73.0)	38,089 (80.8)	24,189 (82.9)	29,687 (84.1)	<0.001*
Periodontitis before index date (number, mean, SD)	3.2 (5.1)	3.1 (5.0)	2.4 (3.9)	1.6 (2.8)	<0.001†
Periodontitis (n, %)	32,892 (56.9)	30,812 (65.4)	21,342 (73.2)	28,303 (80.2)	<0.001*
SBP, systolic blood pressure; DBP, diastolic blood pressure; CCI, Charlson comorbidity index; SD, standard deviation.					
* Chi-square test. Significance at $P < 0.05$					
†One-way analysis of variance (ANOVA). Significance at $P < 0.05$					
‡ Obesity (BMI, body mass index, kg/m ²) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).					

Association between statin use and CP

Influence of statin use on the occurrence of new CP analyzed and it compared with the control group (Table 3). A higher incidence of new CP was found among statin users than the controls during the follow-up period (25.0% vs. 22.0% per 100 person-years, $P<0.001$). Cox regression analysis revealed that patients who used statin had an elevated likelihood of developing new CP compared to the control group after adjusting for demographic data and medical comorbidities, including pre-existing CP, history of dyslipidemia, total cholesterol, and fasting blood glucose (HR 1.32; 95% CI 1.30–1.33; $P<0.001$).

Table 3

Hazard ratio (95% confidence interval) for CP in the statin-user and control groups with subgroup analyses according to age and sex

Characteristics	CP/Total (n)	FU (Person-year)	IR	Hazard ratios for CP			
				Crude†	P-value	Adjusted‡	P-value
Total participants (n = 338,762)							
Statin-user	113,349/169,381	454,036	25.0	1.12 (1.11-1.13)	<0.001*	1.32 (1.30-1.33)	<0.001*
Control	106,562/169,381	484,893	22.0	1		1	
Age < 60 years old (n = 166,846)							
Statin-user	60,305/83,423	230,533	26.2	1.11 (1.10-1.12)	<0.001*	1.38 (1.36-1.41)	<0.001*
Control	57,625/83,423	248,067	23.2	1		1	
Age ≥ 60 years old (n = 171,916)							
Statin-user	53,044/85,958	223,503	23.7	1.13 (1.12-1.14)	<0.001*	1.27 (1.25-1.29)	<0.001*
Control	48,937/85,958	236,826	20.7	1		1	
Males (n = 164,234)							
Statin-user	55,755/82,117	195,398	28.5	1.13 (1.11-1.14)	<0.001*	1.29 (1.26-1.31)	<0.001*
Control	52,477/82,117	210,721	26.5	1		1	
Females (n = 174,528)							
Statin-user	57,594/87,264	258,638	22.3	1.11 (1.10-1.13)	<0.001*	1.35 (1.33-1.38)	<0.001*
Control	54,085/87,264	274,172	19.7	1		1	
Abbreviations: CP, chronic periodontitis; FU, Follow-up duration; IR, Incidence rate per 100 person-years.							
* Stratified Cox proportional hazard model, Significance at $P < 0.05$							
† Models were stratified by age, sex, income, and region of residence.							
‡ Adjusted for dyslipidemia history, total cholesterol, systolic blood pressure, diastolic blood pressure, fasting blood glucose, obesity, smoking, alcohol consumption, the number of previous CP, and CCI scores.							

The incidence of CP during the study period was higher in statin users than in control group in all age and sex subgroups. In subgroup analyses, statin use was consistently associated with a high likelihood of having subsequent CP among those aged either <60 years or ≥60 years ([HR 1.38; 95% CI 1.36–1.41; $P<0.001$] and [HR 1.27; 95% CI 1.25–1.29; $P<0.001$], respectively) and among both men and women ([HR 1.29; 95% CI 1.26–1.31; $P<0.001$] and [HR 1.35; 95% CI 1.33–1.38; $P<0.001$], respectively).

Association between duration of statin use and CP

The participants with either 1–3 years, 3–5 years, or >5 years of statin use demonstrated higher HR for CP compared with patients who used statin for ≤1 year (1.08 [95% CI 1.07–1.10, $P<0.001$]; 1.08 [95% CI 1.06–1.09, $P<0.001$]; 1.04 [95% CI 1.02–1.06, $P<0.001$], respectively) (Table 4). However, the HRs were slightly reduced in the group with >5 years of statin use compared to durations of 3–5 years or 1–3 years (P for trend = 0.002).

Table 4
Hazard ratio (95% confidence interval) for CP according to the periods of statin-use (n = 169,381)

Periods of statin-use	CP/Total (n)	FU (Person-year)	IR	Hazard ratios for CP					
				Crude	P -value	Model 1†	P -value	Model 2‡	P -value
P for trend					<0.001*		<0.001*		0.002*
> 5 y	28,303/35,297	129,503	21.9	0.94 (0.92-0.95)	<0.001*	0.96 (0.95-0.98)	<0.001*	1.04 (1.02-1.06)	<0.001*
3–5 y	21,342/29,176	86,144	24.8	1.01 (0.99-1.03)	0.310	1.03 (1.01-1.05)	0.003*	1.08 (1.06-1.09)	<0.001*
1-3 y	30,812/47,117	113,073	27.2	1.06 (1.04-1.07)	<0.001*	1.07 (1.05-1.09)	<0.001*	1.08 (1.07-1.10)	<0.001*
≤ 1 y (Ref)	32,892/57,791	125,316	26.2	1		1		1	
Abbreviations: FU, Follow-up duration; IR, Incidence rate per 100 person-years; CCI, Charlson comorbidity index; CP, chronic periodontitis.									
* Un-stratified Cox proportional hazard model, Significance at $P < 0.05$									
† A model 1 was adjusted for total cholesterol, systolic blood pressure, diastolic blood pressure, fasting blood glucose, obesity, smoking, alcohol consumption, and CCI scores.									
‡ A model 2 was adjusted for model 1 plus dyslipidemia history and the number of previous CP.									

Discussion

Using a nationwide and large-scale cohort data, this longitudinal follow-up study demonstrated that both men and women aged over 40 years who use statins have an increased likelihood of newly occurring CP compared with matched controls. Among long-term statin users, pre-existing periodontitis was low while newly occurring periodontitis was high. The relation between statin use and increased likelihood of CP occurrence remained significant even after adjustment for confounders, indicating that statin use was independently involved in an increased tendency to develop CP.

Large-scale nationwide studies are scarce on the relationship between statin use and CP risk based on duration of use. Among the 338,762 participants aged ≥ 40 years, those receiving statin exhibited a 1.32-fold higher chance for developing CP (95% CI 1.30–1.33) than matched control participants (incidence: 25.0% and 22.0% per 100 person-years, respectively). Although the magnitude of risk is low, statin use may slightly increase the risk of developing CP. Long-term statin users (1–3 years, 3–5 years, or >5 years) had a higher risk for CP than short-term users (≤ 1 year). Pre-existing periodontitis decreased in long-term statin users compared to short-term users, implying that statins may likely be effective in decreasing pre-existing periodontitis but adversely effects newly occurring periodontitis. Decrease in pre-existing CP during the 5-year period is partly in line with results from a prospective double-blind, randomized study among 83 participants conducted in USA, which demonstrated that 12 week-therapy of statin markedly reduced periodontitis⁵. The trend of reduction in periodontitis was perceived in first 28 days after initiation of statin intake⁵. An epidemiologic study reported that the use of any statin is associated with a 48% decrease in CP-related tooth loss in the initial three years, which may suggest that statins possess anti-inflammatory and bone modulating features during the first several years that may positively influence pre-existing CP¹⁷.

Conversely, literature is still scarce to support our findings on increased risk of CP occurrence due to statin therapy among long-term users. The accuracy of the present data is supported by the similar clinical characteristics of statin users with respect to obesity, smoking, increased comorbidities, alcohol drinking, or dyslipidemia, and high total cholesterol, blood pressure, or fasting glucose level, as reported in previous studies^{1,4,5,16,20}. This may be because most of the previous studies focused on the relatively short-term effects of statins on the inflammatory parameters of pre-existing periodontitis. In a previous study², it was mentioned that subsequent 15 periodontitis among 29 patients with hyperlipidemia treated with statins were observed during a statin intake period of 3 to 132 months; though the observed duration ranged widely, compared to other studies relatively long-term use of statins was studied. Notably, a preliminary study identified that a high percentage of oral symptoms are associated with statin use, and these symptoms markedly improved after suspension of the treatment⁹, raising the possibility of diverse statin-induced oral adverse effects.

Myopathy, rhabdomyolysis, diabetes, and cancers have been reported as adverse effects of statins^{4,27–29}. An association between statin-induced adverse events and statin therapy is infrequent^{4,27–29}. Clinical trials of pravastatin therapy for hypercholesterolemia with a 15-year follow-up reported a greater incidence of prostate cancer in these patients¹, which indicates that adverse effects may become evident after a long time such as a decade or more. Likewise, incidence of CP related to statin use might have been underestimated because of the short periods of previous studies. Our findings may be of importance with respect to the safety of the long-term use of statins in the development of periodontitis. Therefore, patients who are prescribed statin therapy needs to be informed of the increased risk of diseases, including CP.

The mechanism underlying the association between statin use and increased risk of CP remains unclear. Statins have cholesterol-independent or pleiotropic effects attributable to several mechanisms vital to cellular functions via the post-transcriptional modification of mevalonate intermediates in multiple tissues, including the periodontium^{1–4, 20,21,30}. In fact, the systemic administration of statins have potential effects in the periodontium, and it has been reported that their concentration in gingival crevicular fluid is 10- to 100-fold higher than in the serum, with an anti-inflammatory effect that influences the level of IL-1 β in the gingiva. As statins also possess immunomodulatory and antimicrobial properties³¹, their long-term effects might include a shift in the microbial balance between pathogenic and nonpathogenic species in oral cavity which has over 700 microorganisms; this deteriorates periodontal homeostasis and immune response of the host^{13,32}. Interactions between the polymicrobial synergistic and dysbiotic action, host response, and modifying factors may determine the defense against CP or its progression¹³. Individuals with defective neutrophil recruitment or neutrophil adhesion deficiencies reportedly have increased susceptibility to periodontitis^{33,34}. The range of drug action observed in statin therapy seems to be greater than expected and the precise predictions of adverse events are not possible until those events occur³².

The strengths of this study are its large, representative, nationwide population-based data and analysis that was fully adjusted for socioeconomic status, potential risk factors, and comorbidities related to CP or statin use (e.g., fasting blood glucose, total cholesterol, obesity, alcohol, smoking, and blood pressure). To the best of our knowledge, a nationwide follow-up epidemiologic study on the association between long-term statin intake and CP risk has not previously attempted. As the KNHIS-HS data encompass information from every hospital and clinic across the entire nation without exception, full medical histories could be obtained during the follow-up period.

There are limitations to our study. Statin users had been treated with different statins. No information pertaining to the severity of periodontitis, measurements such as probing depth and clinical attachment loss at interproximal sites that could help diagnose CP, type, dosage, and frequency of statins, family history and genetic data of related systemic diseases were available in the health insurance database; however, the possibility of missing data was not taken into consideration.

In summary, our nationwide cohort study indicates that both men and women aged over 40 years taking statins may have a slightly increased likelihood of subsequent CP onset, especially if used long term, which warrants potential cautions regarding the onset of CP as a possible adverse effect of long-term statin use.

Data Availability

Releasing of the data by the researcher is not allowed legally. All data are available from the database of National Health Insurance Sharing Service (NHISS) <https://nhiss.nhis.or.kr/> NHISS allows access to all of this data for the any researcher who promises to follow the research ethics at some cost. If you want to access the data of this article, you can download it from the website after promising to follow the research ethics.

Declarations

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Author contributions

HGC: conceptualization, funding acquisition, project administration, writing-review & editing; MJK: investigation, funding acquisition, writing-original draft, review& editing; J-HK: formal analysis, supervision; JHK: formal analysis, methodology; S-HB: methodology, software; SHK and H-RP: supervision; NYK: validation. All authors contributed to the article and approved the submitted version

Competing interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

Figure 1

A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 169,381 of the statin-user group were matched with 169,381 of the control group for age, sex, income, and region of residence. Statin-user group was subclassified according to the periods of statin-use as follows: ≤ 1 year (n = 57,791), > 1 year & ≤ 3 years (n = 47,117), > 3 years & ≤ 5 years (n = 29,176), and > 5 years (n = 35,297). Abbreviations: BMI, body mass index