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Periodontitis as a Risk Factor for Rheumatoid Arthritis: a Matched-Cohort Study

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ABSTRACT

Objective: The intent was to analyse the association of periodontitis with the development of rheumatoid arthritis (RA) using a representative population-based cohort and longitudinal matched-cohort design.

Methods: Participants were 40 years of age or older and had not been diagnosed with RA between 2002 and 2006. Among the participants, those who were newly diagnosed with periodontitis between 2004 and 2006 (excluding cases that had already been diagnosed with periodontitis between 2002 and 2003) were allotted to the periodontitis group. Among the participants, those who had never been diagnosed with periodontitis between 2002 and 2006 formed the control group, matched by sex, age, and household income at a 1:1 ratio. From 2007 to 2018, the 2 groups ($n = 691,506$) were followed to monitor the development of RA. The t-test and χ^2 test compared the general characteristics and health-related variables of both groups. The Kaplan-Meier method with a log-rank test was conducted to compare the incidence of RA in both groups. The hazard ratio (HR) and adjusted hazard ratio (aHR) were calculated using a Cox proportional hazard regression analysis to evaluate the risk of subsequent RA.

Results: Univariate analysis revealed that the periodontitis group was more likely to develop RA than the control group (hazard ratio 1.10), and multivariate analysis also revealed a higher incidence risk of RA (adjusted hazard ratio 1.09) in the periodontitis group.

Conclusions: Our findings demonstrate that periodontitis is associated with an increased risk of developing RA.

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Introduction

Periodontitis is an inflammatory disease that destroys hard and soft tissues surrounding the teeth and is associated with bacterial colonies and biofilms.¹ Several systemic diseases are also related to the action of inflammatory mediators, and periopathogenic bacteria may be the direct or indirect source of these mediators. In this regard, consistent evidence has suggested that periodontitis may affect systemic diseases.^{2,3} In a 2017 literature review of the association between periodontitis and systemic disease,⁴ various systemic diseases such as diabetes, obesity, metabolic syndrome, cognitive impairment, and rheumatoid arthritis (RA) were shown to be associated with periodontitis.

RA is reported to be found in 1% of the world's population,^{5,6} and chronic inflammation associated with RA causes cartilage damage and joint deformation, adversely affecting the quality of life.⁷ Its prevalence increases rapidly with age, affecting 2.2% of individuals age 30 and older, and 5.3% of individuals ages 65 and older. Leaving RA untreated may aggravate health and increase medical costs.⁸

It has been consistently reported that there is an epidemiological link between RA and periodontitis.^{3,9-12} In a case-control study,⁹ a significant correlation between the prevalence of periodontitis and RA was verified, with consideration of confounders, and this correlation was more clearly seen in patients with more severe forms of periodontitis and RA. A study¹⁰ analysing previously published literature in relation to the 2 diseases reported that periodontal treatment helped improve the symptoms of patients with RA. However, a number of studies failed to find any correlation between the 2 diseases,¹³⁻¹⁵ and a previous study¹⁶ reported that tooth loss had a significant

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effect on RA, however, periodontitis had no significant effect on RA.

The authors conducted preliminary studies using the 6th (2013–2015) Korea National Health and Nutrition Examination Survey (KNHANES) and Korea's National Health Insurance Service–National Sample Cohort (NHIS–NSC) to investigate the epidemiological relationship between RA and periodontitis.^{11,12} Both studies were cross-sectional in nature and revealed an association between the prevalence of the 2 diseases. There have been a number of longitudinal studies^{3,17} using population-based databases in Taiwan and the United States, but such studies have not yet been performed in Korea. Therefore, we conducted a longitudinal matched-cohort study to assess the relationship between RA and periodontitis using the nationwide population-based database.

Methods

Participants

This study was conducted using the National Health Insurance Service-Customized Research Database (NHIS-CRDB) of Korea. In Korea, health insurance enrolment is mandated by law, and more than 99% of the population is enrolled in the NHIS. These individuals' demographic and medical records are stored in the NHIS database. NHIS conducts a health checkup every year or 2, collects health-related behaviour information through a self-reported questionnaire, and acquires physical measurements (height, weight, blood pressure, etc.), blood tests, and urine tests. Information on test results is also included in the NHIS-CRDB, making it valuable research data on health-related topics. We conducted this study with approval from the institutional review board of Shinhan University (IRB No. SHIRB-201904-HR-092-02) and in full accordance with the World Medical Association Declaration of Helsinki. The requirement for written consent was waived by institutional review board because the study used the NHIS database, which contains only anonymised secondary data.

This study used a longitudinal matched-cohort design. Patients 40 years of age or older (as of 2006) who were newly diagnosed with periodontitis between 2004 and 2006 were selected as the periodontitis group, and those who had been diagnosed with periodontitis between 2002 and 2003 were excluded. Patients with periodontitis were defined as those having received periodontitis treatment (U1010; Subgingival curettage, U1051–1052; Periodontal flap surgery, U1060; Root conditioning, U1071–1072; Bone graft for alveolar bone defects, U1081–1083; Guided tissue regeneration) under the corresponding disease codes K052, K053, K054, or K056. For the control group, 1:1 matching with the periodontitis group was performed based on sex, age, and household income among the participants who had no history of periodontitis treatment between 2002 and 2006. For both the periodontitis group and the control group, those who were diagnosed with RA between 2002 and 2006, died before 2018, and did not receive any health examination between 2004 and 2006 were excluded.

Variables

For 12 years, from January 2007 to the last day of 2018, we observed whether RA (diagnostic code: M05, M06, M08) developed in the periodontitis and control groups. As possible confounders that can affect the 2 diseases, information such as sex, age, and household income was collected based on 2006 NHIS records. In addition, smoking status, alcohol consumption, body mass index (BMI), systolic blood pressure, fasting serum glucose level, and total cholesterol were collected from the most recent records of the health examination results between 2004 and 2006. Participants' household income was classified into quartiles based on the health insurance premiums paid (low, medium-low, medium-high, high). Smoking was classified into 'No,' 'former smoker,' and 'Yes.' Current alcohol consumption status was classified into 'Yes' and 'No,' and age, systolic blood pressure, fasting serum glucose level, total cholesterol, and BMI were analysed as continuous variables.

Data analysis

A *t*-test and χ^2 test were performed to compare the general characteristics and health-related variables of the periodontitis and control groups. The Kaplan-Meier method with a log-rank test was performed to estimate and compare the cumulative incidence of RA in the control and periodontitis groups. A Cox proportional hazard regression analysis was performed to determine the hazard ratio (HR) of RA based on the presence of periodontitis. Using a multivariate analysis incorporating all variables used in this study, the adjusted hazard ratio (aHR) was calculated. Subgroup analysis was conducted after stratifying the participants by sex. The proportional hazards assumption was evaluated graphically by analysis with log-log plots. All statistical analyses and plotting graphs were performed using the SAS statistical program (version 9.2, SAS Institute), and the statistical significance level was set to 0.05.

Results

The study included a total of 691,506 individuals, with 345,753 patients in the periodontitis group and 345,753 participants in the control groups. There was no difference in sex, age, or household income between the periodontitis and control groups, confirming that the 1:1 matching was appropriately performed (Table 1). The mean age of the study participants was 51.4 ± 8.2 years, and the proportion of males was 56.8%.

Examination of the characteristics of participants according to the development of RA (Table 2) revealed that women accounted for 60.6% of those who developed RA, and 39.4% of these were men ($P < .001$). The mean age of participants with RA was 52.8 ± 8.3 years, which was higher than that of participants without RA (51.1 ± 8.2 years) ($P < .001$).

The 12-year follow-up results of RA development in each group are shown in Table 3. RA developed in 53,332 patients (15.4%) in the control group and 58,113 (16.8%) in the periodontitis group. The 12-year cumulative incidence of RA was calculated to be 1412 per 100,000 persons in the control group

Table 1 – Characteristics of the study participants at baseline.

Characteristic	Periodontitis	Control	P*
Total	345,753 (50.0)	345,753 (50.0)	
Sex, N (%)			
Male	196,341 (56.8)	196,341 (56.8)	1.000
Female	149,412 (43.2)	149,412 (43.2)	
Age, y, mean (SD)	51.4 (8.2)	51.4 (8.2)	1.000
Household income, N (%)			
Low	52,532 (15.2)	52,532 (15.2)	1.000
Medium-low	53,424 (15.5)	53,424 (15.5)	
Medium-high	84,465 (24.4)	84,465 (24.4)	
High	155,332 (44.9)	155,332 (44.9)	
Smoking status, N (%)			
No	228,907 (66.2)	234,588 (67.9)	<.001
Former smoker	39,788 (11.5)	35,083 (10.2)	
Yes	77,058 (22.3)	76,082 (22.0)	
Alcohol consumption, N (%)			
No	246,028 (71.2)	244,879 (70.8)	.002
Yes	99,725 (28.8)	100,874 (29.2)	
Body mass index, kg/m ² , mean (SD)	24.1 (3.0)	24.0 (3.1)	<.001
Systolic blood pressure, mmHg, mean (SD)	124.2 (16.3)	124.8 (16.6)	<.001
Fasting serum glucose, mg/dL, mean (SD)	97.7 (27.2)	96.3 (24.6)	<.001
Total cholesterol, mg/dL, mean (SD)	198.8 (44.0)	198.5 (40.2)	.003

SD = standard deviation.

* P values were calculated by a χ^2 test or independent t-test.

and 1546 in the periodontitis group. In other words, the RA incidence rate per 100,000 person-years was higher in the periodontitis group than in the control, corresponding to 128.8 and 117.6, respectively. In addition, the incidence of RA was higher in women than in men in both the control and periodontitis groups.

The Cox proportional hazard regression analysis results are shown in Table 4 and the Figure. In the univariate analysis, the periodontitis group was shown to be more likely to develop RA than the control group (HR, 1.10; $P < .001$), and the multivariate analysis incorporating all variables used in this study also showed that the periodontitis group was at a higher risk of developing RA (aHR, 1.09; $P < .001$). In the multivariate analysis, women were found to be at a higher risk of

developing RA (aHR, 2.09; $P < .001$), and older individuals were more likely to develop RA (aHR, 1.02; $P < .001$). The risk of RA was lowest when household income was 'high' (aHR, 0.94; $P < .001$), and the incidence of RA was highest in the case of former smokers (aHR, 1.06; $p < 0.001$). In addition, the risk of developing RA was higher in those that drank alcohol than in nondrinkers (aHR, 1.06; $P < .001$), and the higher the BMI, the higher the risk of RA (aHR, 1.01; $P < .001$). Systolic blood pressure, fasting serum glucose level, and total cholesterol levels revealed an aHR close to 1.00. In the subgroup multivariate analysis (Table 5), the incidence of RA was higher in the periodontitis group than in the control group in both men and women, and the aHR value was higher for men than for women (1.13 and 1.07, respectively; $P < .001$).

Table 2 – Characteristics of the study participants according to occurrence of rheumatoid arthritis over the course of 12 years.

Characteristic	Occurrence of rheumatoid arthritis		P*
	Yes	No	
Total	111,445 (16.1)	580,061 (83.9)	
Sex, N (%)			
Male	43,930 (39.4)	348,752 (60.1)	<.001
Female	67,515 (60.6)	231,309 (39.9)	
Age, y, mean (SD)	52.8 (8.3)	51.1 (8.2)	<.001
Household income, N (%)			
Low	19,113 (17.2)	85,951 (14.8)	<.001
Medium-low	18,406 (16.5)	88,442 (15.3)	
Medium-high	27,131 (24.3)	141,799 (24.5)	
High	46,795 (42.0)	263,869 (45.5)	
Smoking status, N (%)			
No	85,514 (76.7)	377,981 (65.2)	<.001
Former smoker	9338 (8.4)	65,533 (11.3)	
Yes	16,593 (14.9)	136,547 (23.5)	
Alcohol consumption, N (%)			
No	86,129 (77.3)	404,778 (69.8)	<.001
Yes	25,316 (22.7)	175,283 (30.2)	
Body mass index, kg/m ² , mean (SD)	24.2 (2.9)	24.0 (3.0)	<.001
Systolic blood pressure, mm Hg, mean (SD)	123.8 (16.6)	124.6 (16.4)	<.001
Fasting serum glucose, mg/dL, mean (SD)	96.3 (24.7)	97.1 (26.1)	<.001
Total cholesterol, mg/dL, mean (SD)	199.3 (44.8)	198.6 (41.6)	<.001

SD = standard deviation.

* P values were calculated by a χ^2 test or independent t-test.

Table 3 – Incidence rate of rheumatoid arthritis.

	RA cases N (%)	Total person-years	RA incidence rate per 100,000 person-years		
			12-year cumulative incidence	Incidence rate	95% CI
Control					
Total (n = 345,753)	53,332 (15.4)	3777,896	1412	117.6	1399.8-1423.6
Male (n = 196,341)	20,608 (10.5)	2203,129	935	77.9	922.8-948.2
Female (n = 149,412)	32,724 (21.9)	1574,767	2078	173.2	2055.9-2100.4
Periodontitis					
Total (n = 345,753)	58,113 (16.8)	3759,561	1546	128.8	1533.3-1558.3
Male (n = 196,341)	23,322 (11.9)	2197,920	1061	88.4	1047.6-1074.7
Female (n = 149,412)	34,791 (23.3)	1561,641	2228	185.7	2204.8-2251.1

CI = confidence interval; RA = rheumatoid arthritis.

Table 4 – Covariates associated with rheumatoid arthritis.

Characteristic		Univariate analysis			Multivariate analysis		
		HR	95% CI	P*	aHR	95% CI	P*
Periodontitis, control = 1	Yes	1.10	1.08-1.11	<.001	1.09	1.08-1.11	<.001
Sex, male = 1	Female	2.16	2.13-2.19	<.001	2.09	2.05-2.12	<.001
Age, y		1.02	1.02-1.02	<.001	1.02	1.02-1.02	<.001
Household income, low = 1	Medium-low	0.94	0.92-0.96	<.001	1.01	0.98-1.03	.655
	Medium-high	0.87	0.86-0.89	<.001	0.97	0.96-0.99	.005
	High	0.81	0.80-0.83	<.001	0.94	0.92-0.95	<.001
Smoking status, no = 1	Former	0.65	0.64-0.67	<.001	1.06	1.03-1.08	<.001
	Yes	0.56	0.55-0.57	<.001	0.93	0.91-0.95	<.001
Alcohol consumption, no = 1	Yes	0.70	0.69-0.71	<.001	1.06	1.04-1.08	<.001
Body mass index, kg/m ²		1.01	1.01-1.01	<.001	1.01	1.01-1.01	<.001
Systolic blood pressure, mm Hg		1.00	1.00-1.00	<.001	1.00	1.00-1.00	<.001
Fasting serum glucose, mg/dL		1.00	1.00-1.00	<.001	1.00	1.00-1.00	.005
Total cholesterol, mg/dL		1.00	1.00-1.00	<.001	1.00	1.00-1.00	.012

aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio.

* P values were calculated by a Cox proportional hazard regression analysis.

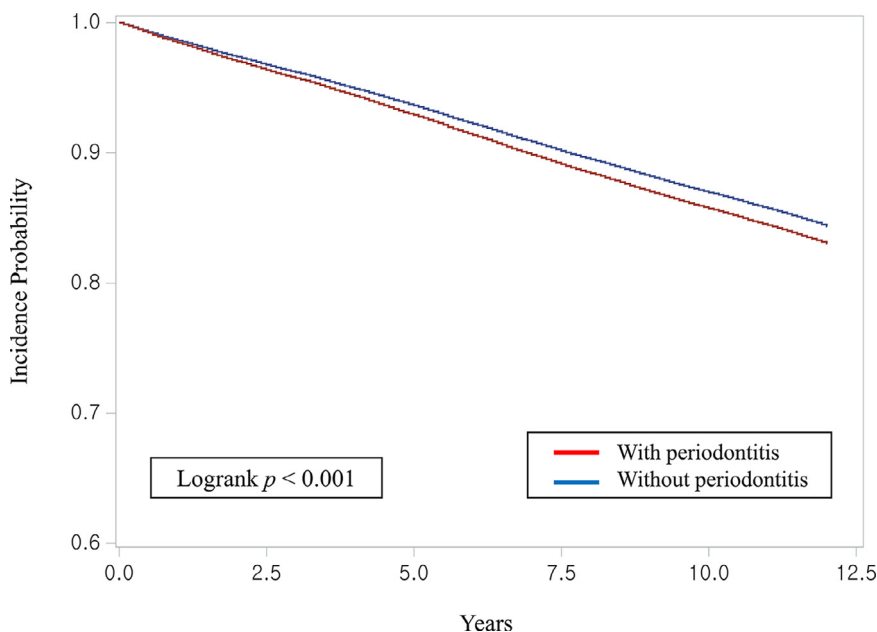


Figure – Kaplan-Meier curve showing the cumulative incidence of rheumatoid arthritis with and without periodontitis.

Table 5 – HRs (95% CIs) for rheumatoid arthritis by sex.

Characteristic		Male (n = 392,682)				Female (n = 298,824)			
		Univariate HR (95% CI)	P*	Multivariate aHR (95% CI)	P*	Univariate HR (95% CI)	P*	Multivariate aHR (95% CI)	P*
Periodontitis, control = 1	Yes	1.13 (1.11-1.16)	<.001	1.13 (1.11-1.15)	<.001	1.07 (1.06-1.09)	<.001	1.07 (1.06-1.09)	<.001
Age, y		1.03 (1.03-1.03)	<.001	1.03 (1.03-1.03)	<.001	1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001
Household income, low = 1	Medium-low	0.99 (0.96-1.03)	.732	1.04 (1.01-1.08)	.023	1.01 (0.98-1.03)	.495	1.00 (0.98-1.03)	.976
	Medium-high	0.93 (0.90-0.96)	<.001	1.01 (0.98-1.04)	.577	1.00 (0.97-1.02)	.787	0.98 (0.96-1.00)	.095
	High	0.90 (0.88-0.93)	<.001	0.97 (0.94-1.00)	.022	0.96 (0.94-0.98)	<.001	0.95 (0.93-0.97)	<.001
Smoking status, no = 1	Former	1.04 (1.01-1.07)	.003	1.07 (1.05-1.10)	<.001	0.98 (0.91-1.06)	.627	0.98 (0.91-1.06)	.616
	Yes	0.87 (0.85-0.89)	<.001	0.94 (0.92-0.96)	<.001	1.12 (1.07-1.18)	<.001	1.09 (1.04-1.15)	<.001
Alcohol consumption, no = 1	Yes	1.00 (0.98-1.01)	.595	1.04 (1.02-1.06)	<.001	1.05 (1.03-1.08)	<.001	1.08 (1.05-1.11)	<.001
Body mass index, kg/m ²		1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001	1.01 (1.01-1.01)	<.001
Systolic blood pressure, mm Hg		1.00 (1.00-1.00)	.002	1.00 (1.00-1.00)	<.001	1.00 (1.00-1.00)	.043	1.00 (1.00-1.00)	<.001
Fasting serum glucose, mg/dL		1.00 (1.00-1.00)	.041	1.00 (1.00-1.00)	.123	1.00 (1.00-1.00)	.350	1.00 (1.00-1.00)	.026
Total cholesterol, mg/dL		1.00 (1.00-1.00)	.483	1.00 (1.00-1.00)	.896	1.00 (1.00-1.00)	<.001	1.00 (1.00-1.00)	.864

aHR =adjusted hazard ratio; CI = confidence interval; HR = hazard ratio.

* P values were calculated by a Cox proportional hazard regression analysis.

Discussion

We sought to assess the relationship between periodontitis and RA using NHIS-CRDB data of Korean patients between 2002 and 2018. Monitoring RA incidence for 12 years revealed that the incidence of RA was 16.8% in the periodontitis group compared with 15.4% in the control group. In the Cox proportional hazards model, the periodontitis group showed a higher probability of RA development compared to the control group (HR, 1.10), and even when controlling for all the confounders used in this study, the periodontitis group was shown to have a higher risk of developing RA (aHR, 1.09). This was consistent with a previously published cross-sectional study¹² in which patients with periodontitis were more likely to have RA (odds ratio 1.07) as compared to those without periodontitis. A longitudinal study³ using the Taiwanese National Health Insurance Research Database on periodontitis and RA development also reported a higher risk of RA in the periodontitis group compared with the group without periodontitis (HR, 1.91). In a study conducted in the United States,¹⁷ female patients with a history of periodontitis were more likely to develop RA than those without (relative risk 1.18), but the results were not statistically significant. In contrast, our subgroup analysis revealed that the risk of developing RA was significantly higher in female patients with periodontitis. However, this previous study is different from the present study in terms of its methods. Indeed, the previous study only enrolled women participants, and periodontitis history was determined using periodontal surgery and tooth loss as proxies, which may have led to the discrepancies between the previous study and ours.

As shown, periodontitis can be a risk factor for RA because of the similar aetiology between the 2 diseases.⁶ RA is regarded as an autoimmune disease, and periodontitis is classified as an inflammatory disease. Although the pathogenesis is not exactly the same, they have a similar aetiology on the cellular and molecular levels including: (i) increased infiltration of immune and inflammatory cells, such as monocytes, T lymphocytes, B lymphocytes, and neutrophils;¹⁸ (ii) an imbalance between pro-inflammatory and anti-inflammatory

cytokines release;¹⁹ and (iii) shared genetic risk markers, such as polymorphic HLA-DRB1 locus or single nuclear polymorphisms in cytokine genes, including the interleukin-6 gene.²⁰ A study²¹ reported that the subgingival microbiota of patients with recently developed RA is similar to that of patients who have had RA for a long time and healthy participants with relatively severe periodontitis. Because periodontitis and RA have similar aetiology on the cellular and molecular levels, the treatment of 1 disease can affect the prognosis of the other.²²

In this study, RA was more likely to develop in women and in older individuals, consistent with the results of a previous study.¹² In contrast, in the case of former smokers, alcohol consumption was more likely to be associated with RA development, which is different from the results of a previous study^{12,23} that showed a higher incidence of RA in non-smokers and nondrinkers, but similar to the findings of Li et al.²⁴ In addition, the higher the BMI, the higher the risk of developing RA, consistent with the findings of Kim et al.²⁵ However, the risk of RA was lowest when household income was 'high,' which was different from the results of previous studies.^{12,25} Another report noted that patients with recently developed RA have a high incidence of periodontitis, regardless of their age and smoking history.²¹ As can be seen from these studies, health-related behaviours, such as alcohol consumption and smoking, vary across studies, and follow-up research is warranted to clarify the relationship.

To obtain information on items such as smoking status, alcohol consumption, blood pressure, blood glucose level, total cholesterol, and BMI, which are potential confounding factors between the 2 diseases, the participants in this study were limited to individuals who had received a health examination, despite the possibility of incurring a selection bias. In addition, because the data used in this study consist of the medical records from medical institutions, this study is also limited in that those who did not visit the medical institution could not participate in the study. Although RA and periodontitis are both influenced by genetic factors, it is difficult to include genetic factors as confounders in this study because the NHIS-CRDB data used are limited to the variables

investigated. Therefore, it is necessary to use caution when generalising the results of this study. Because we used claims data, information on the clinical characteristics of periodontitis, such as onset, severity, and distribution, were not available. Despite these limitations, however, this study is significant in that the relationship between periodontitis and the development of RA was deduced by conducting a longitudinal cohort analysis of NHIS-CRDB data, a data set representative of the Korean population, based on accurate specialist-delivered diagnoses. In addition, age, sex, and household income are known to have a strong effect on RA and periodontitis incidence, and there is a clear limitation when controlling for the role of these confounders by a statistical model alone. This being said, the use of the matching method to establish the control group in this study enhances the credibility of the findings.

Conclusion

In conclusion, this study analysed 17 years of medical records from 691,506 patients, thereby confirming that periodontitis could be a risk factor for RA. Further efforts to identify mediators shared by the 2 diseases are warranted to further clarify the relationship between these 2 diseases.

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Conflict of interest

None disclosed.

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