

ORIGINAL ARTICLE

Association of periodontitis with radiographic knee osteoarthritis

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Abstract

Background: To examine whether periodontitis is associated with the presence and severity of radiographic knee osteoarthritis (OA).

Methods: Using data from the Korea National Health and Nutrition Examination Survey between 2010 and 2013, participants over the age of 50 were included in this study. Dental examinations and knee radiographs are performed in participants aged ≥ 50 years in this cohort. Periodontitis was defined using the community periodontal index, which was determined by measuring periodontal probing depth. The definition of radiographic knee OA was based on the Kellgren-Lawrence (K-L) grading system, which determined a K-L class ≥ 2 to be radiographic knee OA. The associations between periodontitis and presence and severity of radiographic knee OA were examined using logistic regression analyses.

Results: Among 7969 total participants, 965 men and 2078 women had radiographic knee OA. Periodontitis was observed in 1,185 (39.4%) people among those who had radiographic knee OA. Periodontitis (adjusted odds ratio [aOR] 1.21, 95% confidence interval 1.05 to 1.40) was associated with radiographic knee OA after adjusting for variables including age, sex, body mass index, socioeconomic status, diabetes, and dental status. Participants were more likely to have radiographic knee OA as the severity of periodontitis increased (non-severe periodontitis, aOR 1.14 [0.98 to 1.32]; severe periodontitis, aOR 1.47 [1.17 to 1.85]). Moreover, the presence of periodontitis significantly increased with an increasing K-L class (class 1, aOR 1.30 [1.09 to 1.54]; class 2, aOR 1.32 [1.08 to 1.60]; class 3, aOR 1.39 [1.14 to 1.70]; class 4, aOR 1.45 [1.11 to 1.90]).

Conclusion: Periodontitis is associated with the presence and severity of radiographic knee OA.

KEYWORDS

association, osteoarthritis, periodontitis, risk factors

1 | INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease affecting articular cartilage, subchondral bone, the synovium, and joint capsule through a multifactorial pathophysiology.¹

Degeneration of cartilage is the main pathologic finding of OA; however, inflammation of the synovium (synovitis) is also involved in the pathogenesis of OA.² Synovitis often presents before structural damage of the joints, and the presence of synovitis is associated with OA progression.³



Synovial membrane inflammation is prominent in early OA, which is reflected by the increased presence of mononuclear cells and inflammatory mediators.⁴ Recently, systemic inflammation has been suggested to play a role in OA development and progression.² For example, obesity, as a source of metabolic inflammation, may increase cartilage loss and joint pain by releasing adipokines and proinflammatory cytokines from adipose tissue.⁵

Periodontitis is a chronic inflammatory disease initiated by bacterial infection of the periodontal tissue, but host immune responses are required for full development of the disease.⁶ There are several similarities between periodontitis and OA. Both diseases are mediated by inflammatory cytokines, such as interleukin-1 β (IL-1 β), tumor necrosis factor (TNF), and interleukin-6 (IL-6), and by initial activation of the innate immune system.^{1,7} These inflammatory reactions activate degrading enzymes (e.g., matrix metalloproteinases), which results in the loss of cartilage and alveolar bone in OA and periodontitis, respectively.^{1,7} Moreover, periodontal pathogens were found in knee joint tissues from OA patients who were undergoing knee arthroplasty without a history of joint prosthesis insertion.⁸ The pathogens identified from pre-surgical aspirates were mostly those known to cause periodontal disease. This result suggests that hematogenous spread of periodontal pathogens might contribute to exacerbation of OA.⁸

There is currently no study that evaluates the association between periodontitis and OA. The purpose of our study was to examine whether periodontitis is associated with presence or severity of radiographic knee OA in a nationwide, representative, and non-institutionalized population. We investigated (1) the association between periodontitis and radiographic knee OA and (2) the association between periodontitis and knee OA severity, represented by the Kellgren-Lawrence (K-L) grading system.⁹

2 | MATERIALS AND METHODS

2.1 | Data source and study population

This study was based on data from the Korea National Health and Nutrition Examination Survey (KNHANES) between 2010 and 2013. The KNHANES is a population based, cross-sectional, and representative annual survey that has been conducted by the Korean Center for Disease Control and Prevention since 1998.¹⁰ About 4000 households (including about 10,000 representative participants) are annually selected using a multistage clustered and stratified random sampling method based on the National Census Data. The KNHANES consists of three parts: a health interview, health examination survey, and nutritional survey. The health interview and examination are performed at specially equipped

mobile examination centers, and the nutritional survey is completed by home visits.

A total of 33,552 subjects participated in the KNHANES from 2010 to 2013 (Figure 1). Participants who were over 50 years old and who completed a health interview, examination, and nutritional survey were included in this study. Patients with malignancy ($n = 699$) or patients who did not undergo dental examination and/or knee radiographs ($n = 3969$) were excluded, leaving a total of 7969 subjects. This study was approved by the Institutional Review Board of the Catholic University of Korea, College of Medicine (approval ID: KC17EESI0102). The KNHANES patient data were anonymized and therefore the requirement for informed consent was waived for this study.

2.2 | Classification of radiographic knee OA

Radiographic examination of knee joints was performed as a part of the health examination and was read by two specialized musculoskeletal radiologists. Bilateral anteroposterior and lateral (30° flexion) views of knees were collected using digital radiography (DigiRAD-PG, Sitec Medical, Gimpo, Korea). After the digital images were stored on a hard drive, they were downloaded and graded by two radiologists using the K-L grading system (range 0 to 4).⁹ Patellofemoral and tibiofemoral compartments were all evaluated when grading the knee radiographs. When there was a discrepancy of one class between the two radiologists, the higher class was accepted. If the difference was greater than one class, it was referred to a third radiologist, and the class consistent with the third was accepted. Inter-rater agreement within one class difference was 95.18%, and the Cohen's kappa coefficient was 0.741. Participants were classified to have radiographic knee OA if they had a K-L class ≥ 2 .

2.3 | Definition of periodontitis

A periodontal examination was performed on all study participants using the community periodontal index (CPI) scoring system from the World Health Organization (WHO).¹¹ Teeth were divided into sextants: #1 to 5 (maxillary right posterior), #6 to 11 (maxillary anterior), #12 to 16 (maxillary left posterior), #17 to 21 (mandibular left posterior), #22 to 27 (mandibular anterior), and #28 to 32 (mandibular right posterior). Depth of periodontal pockets was measured from selected index teeth (#2, #3, #8, #14, #15, #18, #19, #24, #30, and #31, in that order) using a CPI (WHO) probe with a 20 g force applied to the pocket. CPI scores for each sextant were determined by CPI scores from index teeth; however, remaining teeth from that sextant were used if the index teeth were absent. Periodontitis was diagnosed if the highest CPI score (range 0 to 4) was 3 (periodontal probing

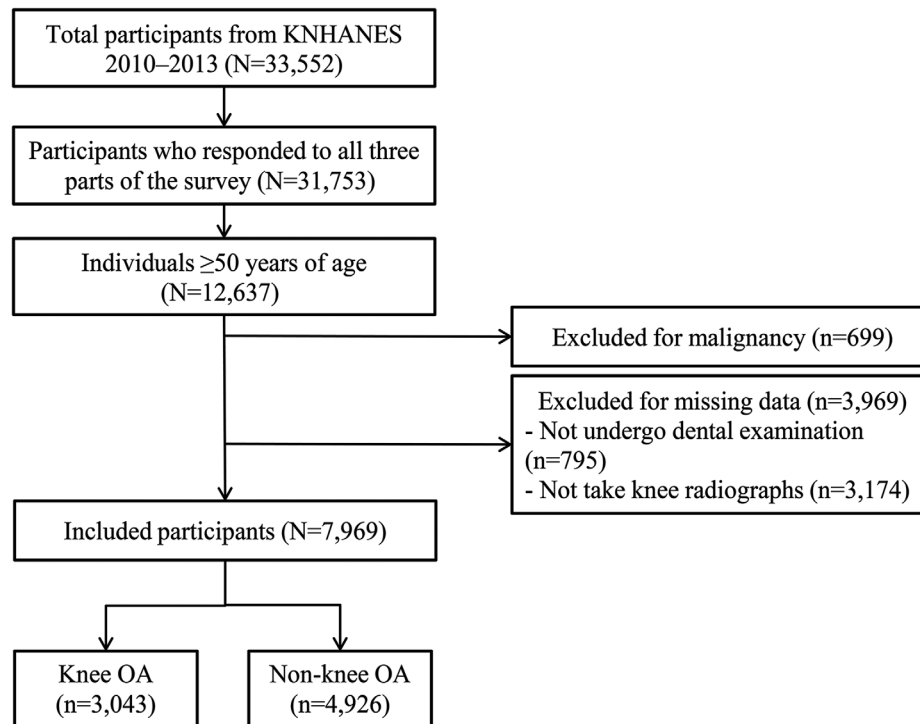


FIGURE 1 Flow chart of the study population

depth of 4 to 5 mm) or 4 (periodontal probing depth ≥ 6 mm). Participants were defined to have severe periodontitis if the CPI score was 4; non-severe periodontitis if the CPI score was 3. Trained dentists performed the periodontal examination, and the mean kappa value for inter-rater reliability of periodontitis was 0.871.

2.4 | Assessment of other variables

Data on age, sex, body mass index (BMI), socioeconomic status (education level and household income), smoking status, alcohol consumption, oral health status, and comorbidity were obtained. Education level was determined by the highest level of education obtained, and the per-capita household income was assessed by the total family income after adjusting for the number of family members. Alcohol consumption, measured in grams per day, was calculated based on the frequency and amount of alcohol consumed. Smoking status was classified into “never smoker” (smoked < 100 cigarettes in their lifetime), “former smoker” (smoked ≥ 100 cigarettes but not currently smoking), and “current smoker” (smoked ≥ 100 cigarettes and currently smoking).¹² Oral health status included the number of dental carries in permanent teeth, presence of a dental prosthesis or implant, and frequency of daily tooth brushing. Diabetes mellitus (DM) was defined to participants who had a fasting glucose level ≥ 126 mg/dL or those who were treating on oral hypoglycemic agents or insulin. Knee pain was determined to be present

if a participant had a knee pain for at least 30 days within 3 months. The intensity of knee pain was assessed using numerical rating scale expressed by a participant who had a knee pain.

2.5 | Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) to reflect the complex sampling design and sampling weights of the KNHANES. Participants’ characteristics were described as the mean (standard error) for continuous variables and as number (percentage) for categorical variables. Differences between radiographic knee OA and controls were examined using the *t*-test and Rao-Scott Chi-Square test for continuous variables and categorical variables, respectively. The association between periodontitis and radiographic knee OA was analyzed using multivariable binary logistic regression adjusting for age, sex, BMI, education level, household income, smoking status, alcohol consumption, oral health status, and comorbidity. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for radiographic knee OA according to presence of periodontitis were reported. Adjusted ORs for radiographic knee OA in relation to severity of periodontitis were also demonstrated by logistic regression analysis. Moreover, association between periodontitis and severity of radiographic knee OA was examined and adjusted ORs for periodontitis in relation to K-L class were shown.

**TABLE 1** Characteristics of study participants according to the presence of radiographic knee OA

Variable	Overall (n = 7969)			Men (n = 3390)			Women (n = 4579)		
	non-OA (n = 4926)	OA (n = 3043)	P value	non-OA (n = 2425)	OA (n = 965)	P value	non-OA (n = 2501)	OA (n = 2078)	P value
Age, years	59.7 (0.2)	66.9 (0.2)	<0.001	59.8 (0.2)	65.5 (0.4)	<0.001	59.6 (0.2)	67.5 (0.3)	<0.001
Female sex	2501 (46.3)	2078 (67.1)	<0.001						
Education level									
<High School	2684 (53.6)	2283 (73.9)	<0.001	1076 (43.4)	544 (55)	<0.001	1608 (65.3)	1739 (83.2)	<0.001
≥High School	2228 (46.4)	747 (26.1)		1344 (56.6)	419 (45)		884 (34.7)	328 (16.8)	
Per-capita household income ^a									
Quartile 1 or 2	2369 (49.4)	1551 (52.3)	0.054	1179 (49.9)	479 (50)	0.957	1190 (48.8)	1072 (53.5)	0.008
Quartile 3 or 4	2503 (50.6)	1459 (47.7)		1220 (50.1)	477 (50)		1283 (51.2)	982 (46.5)	
BMI, kg/m ²	23.8 (0.1)	24.9 (0.1)	<0.001	23.8 (0.1)	24.5 (0.1)	<0.001	23.8 (0.1)	25 (0.1)	<0.001
BMI ≥25	1482 (31.1)	1321 (44.5)	<0.001	753 (32.4)	376 (41.1)	<0.001	729 (29.5)	945 (46.1)	<0.001
Smoking status									
Never smokers	2752 (52.1)	2136 (68.8)	<0.001	422 (17.6)	207 (19.7)	0.055	2330 (91.9)	1929 (93.1)	0.282
Former smokers	1262 (25.9)	551 (18.4)		1190 (45.6)	489 (48.7)		72 (3.2)	62 (3.3)	
Current smokers	885 (22)	334 (12.9)		797 (36.8)	266 (31.6)		88 (4.9)	68 (3.6)	
Alcohol consumption ^b , g/day	5.6 (0.2)	3.6 (0.2)	<0.001	9.3 (0.3)	9 (0.5)	0.663	1.3 (0.1)	0.9 (0.1)	0.001
Oral health status									
Periodontitis ^c	1802 (37.4)	1185 (39.4)	0.185	1075 (44.7)	439 (46.5)	0.489	727 (28.8)	746 (35.9)	<0.001
Dental caries in permanent teeth	0.6 (0)	0.7 (0)	0.048	0.7 (0)	0.9 (0.1)	0.029	0.5 (0)	0.6 (0.1)	0.073
Dental prosthesis	3020 (58.6)	2264 (72.8)	<0.001	1514 (58.8)	696 (69.5)	<0.001	1506 (58.4)	1568 (74.5)	<0.001
Dental implant	630 (11.9)	338 (11.3)	0.471	329 (12.6)	112 (12.2)	0.781	301 (11.1)	226 (10.8)	0.822
Tooth brushing									
≥2/day	4066 (81.8)	2309 (76.1)	<0.001	1853 (76.7)	662 (70.4)	0.002	2213 (87.6)	1647 (78.8)	<0.001
<2/day	860 (18.2)	734 (23.9)		572 (23.3)	303 (29.6)		288 (12.4)	431 (21.2)	
Comorbidity									
DM									
Normal or IFG	3842 (83.8)	2106 (79.5)	<0.001	1812 (80.5)	662 (77.9)	0.176	2030 (87.7)	1444 (80.3)	<0.001
DM	731 (16.2)	553 (20.5)		453 (19.5)	199 (22.1)		278 (12.3)	354 (19.7)	
Presence of knee pain	671 (13.2)	1111 (35.6)	<0.001	207 (8.6)	206 (20.2)	<0.001	464 (18.5)	905 (43.1)	<0.001

Data are reported as the mean (standard error) for continuous variables and as number (percentage) for categorical variables.

^aLower income included quartiles 1 and 2, and higher income included quartiles 3 and 4.

^bAlcohol consumption (g/day) was calculated based on the frequency and amount of alcohol consumed.

^cPeriodontitis was defined based on the community periodontal index (periodontal probing depth ≥4 mm).

3 | RESULTS

3.1 | Characteristics of study participants based on sex and the presence of radiographic knee OA

Both male and female participants with radiographic knee OA were older and had a higher BMI than those without radiographic knee OA (all $P < 0.05$, Table 1). Participants with knee OA were of a lower socioeconomic status than those without knee OA, as represented by lower education levels in both

male and female knee OA patients and by lower household incomes in female knee OA patients (all $P < 0.05$). Smoking status was not significantly different between those with and without knee OA in both sexes ($P > 0.05$). Female knee OA patients consumed less alcohol than women without knee OA ($P = 0.001$). Knee pain was more common in those with radiographic knee OA than in those without radiographic knee OA (all $P < 0.05$). Among the participants who had knee pain, mean numerical rating scale (standard error) was 6.6 (0.1) and 5.5 (0.1) in those with and without radiographic knee OA, respectively.

TABLE 2 Association between periodontitis and radiographic knee OA

Variable	Age- and sex-adjusted		Multivariable-adjusted ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
No periodontitis	Reference		Reference	
Periodontitis	1.26 (1.10 to 1.45)	<0.001	1.21 (1.05 to 1.40)	0.008

^aAdjusting for age, sex, BMI, education level, household income, smoking, alcohol consumption, dental prosthesis or implant, dental caries, frequency of tooth brushing, and DM.

TABLE 3 Association between severity of periodontitis and radiographic knee OA

Variable	Age- and sex-adjusted		Multivariable-adjusted ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
No periodontitis	Reference		Reference	
Non-severe periodontitis ^b	1.18 (1.02 to 1.36)	0.027	1.14 (0.98 to 1.32)	0.093
Severe periodontitis ^c	1.53 (1.24 to 1.89)	<0.001	1.47 (1.17 to 1.85)	0.001

^aAdjusting for age, sex, BMI, education level, household income, smoking, alcohol consumption, dental prosthesis or implant, dental caries, frequency of tooth brushing, and DM.

^bPeriodontal probing depth of 4 to 5 mm.

^cPeriodontal probing depth \geq 6 mm.

Periodontitis was more common in those with radiographic knee OA than in those without radiographic knee OA, but this difference was significant only in women ($P < 0.001$). Dental caries in permanent teeth were more common in those with radiographic knee OA than in those without radiographic knee OA, but the difference was statistically significant in men ($P = 0.029$). Dental prostheses were more common in the radiographic knee OA group than in controls (all $P < 0.05$). Tooth brushing was less frequent in participants with knee OA than in those without knee OA (all $P < 0.05$). Female knee OA patients were more likely to have DM than women without knee OA ($P < 0.001$).

3.2 | Association between periodontitis and presence of radiographic knee OA

Age- and sex-adjusted model (OR 1.26, 95% CI [1.10 to 1.45], $P < 0.001$) and multivariable-adjusted model (OR 1.21, 95% CI [1.05 to 1.40], $P = 0.008$) revealed that participants with periodontitis were more likely to have radiographic knee OA compared with those without periodontitis (Table 2). Periodontitis was significantly associated with radiographic knee OA after controlling for age, sex, BMI, education level, household income, smoking status, alcohol consumption, dental prosthesis or implant, dental caries, frequency of tooth brushing, and DM. Sex-stratified analysis was also performed to examine the association between periodontitis and radiographic knee OA in both sexes (see supplementary Table 1 in online *Journal of Periodontology*). Men with periodontitis showed increasing trend for radiographic knee OA, but without statistical significance (age-adjusted OR 1.15, 95% CI [0.94 to 1.41], $P = 0.186$; multivariable-adjusted OR 1.17, 95% CI [0.93 to 1.46], $P = 0.177$). Periodontitis

was significantly associated with radiographic knee OA in women (age-adjusted OR 1.35, 95% CI [1.18 to 1.62], $P < 0.001$; multivariable-adjusted OR 1.24, 95% CI [1.04 to 1.47], $P = 0.016$).

Next, participants with periodontitis were classified into non-severe or severe periodontitis to examine whether increasing severity of periodontitis is associated with radiographic knee OA. Participants with severe periodontitis were more likely to have radiographic knee OA (Table 3). Adjusted OR values for radiographic knee OA increased with severity of periodontitis (non-severe periodontitis: OR 1.14, 95% CI [0.98 to 1.32], $P = 0.093$; severe periodontitis: OR 1.47, 95% CI [1.17 to 1.85], $P = 0.001$ from multivariable-adjusted model). The increasing risk of radiographic knee OA in relation to severity of periodontitis was also significant in a subgroup analysis for men (see supplementary Table 2 in online *Journal of Periodontology*).

3.3 | Association between periodontitis and severity of radiographic knee OA

Periodontitis was significantly associated with severity of radiographic knee OA from age- and sex-adjusted model and multivariable-adjusted model (Table 4). Adjusted ORs for periodontitis increased along with an increasing severity of radiographic knee OA (K-L class 1: OR 1.30, 95% CI [1.09 to 1.54], $P = 0.002$; K-L class 2: OR 1.32, 95% CI [1.08 to 1.60], $P = 0.006$; K-L class 3: OR 1.39, 95% CI [1.14 to 1.70], $P = 0.001$; K-L class 4: OR 1.45, 95% CI [1.11 to 1.90], $P = 0.005$ from multivariable-adjusted model). Female participants showed the significant association between periodontitis and severity of radiographic knee OA; however, the association was weak in male participants

**TABLE 4** Association between periodontitis and severity of knee OA based on the Kellgren-Lawrence (K-L) grading system

Variable	Age- and sex-adjusted		Multivariable-adjusted ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
K-L class 0	Reference		Reference	
K-L class 1	1.28 (1.09 to 1.50)	0.002	1.30 (1.09 to 1.54)	0.002
K-L class 2	1.34 (1.12 to 1.61)	0.001	1.32 (1.08 to 1.60)	0.006
K-L class 3	1.45 (1.20 to 1.76)	<0.001	1.39 (1.14 to 1.70)	0.001
K-L class 4	1.48 (1.16 to 1.90)	0.001	1.45 (1.11 to 1.90)	0.005

^aAdjusting for age, sex, BMI, education level, household income, smoking, alcohol consumption, dental prosthesis or implant, dental caries, frequency of tooth brushing, and DM.

(see supplementary Table 3 in online *Journal of Periodontology*).

Three hundred and twenty-one peoples were edentulous (no natural teeth) from 3043 OA participants and 243 peoples were edentulous from 4926 non-OA participants. Multiple logistic regression analysis with the edentulous as the dependent variable and K-L class as the independent variable was performed to determine the association between edentulous and severity of knee OA (see supplementary Table 4 in online *Journal of Periodontology*). In contrast to the association between periodontitis and severity of knee OA, there was no association between edentulism and severity of knee OA.

4 | DISCUSSION

Our nationwide, cross-sectional study revealed that individuals with periodontitis were more likely to have radiographic knee OA compared with those without periodontitis. Increasing severity of periodontitis showed increased risk of radiographic knee OA. The association between periodontitis and radiographic knee OA was maintained after adjustment for potential confounders. Although the association may be bidirectional and underlying mechanism is not understood, we found the association between periodontitis and OA in a general population-based study design. Notably, increasing severity of knee OA, represented by K-L class, was associated with periodontitis, whereas the severity of knee OA was not associated with being edentulous. Edentulism is frequently found in progressed periodontitis, but there are also other contributors to edentulism. The association of knee OA with periodontitis, not with edentulism, underscores the role of periodontitis in knee OA.

Periodontitis presents with local inflammatory reactions, but these reactions may have systemic effects on the onset and progression of knee OA. A similar phenomenon is observed in the relationship between adipose tissue and OA. Obesity influences OA not only by increasing weight loads on the knee joints, but also by adipose tissue working as a source of inflammation.¹³ Body composition represented as fat mass, rather than body weight, is more important and closely related

to knee OA.^{14–16} Adipose tissue releases adipokines, which enhance catabolic factors and lead to the synovial inflammation and structural damage of OA.^{17–20}

The association between periodontitis and OA severity is also supported by the finding that local and systemic inflammatory markers are well correlated with OA progression. A prospective study found that increased serum IL-6 levels can predict the presence of radiographic knee OA.²¹ Another study reported that serum IL-6 and TNF- α levels were associated with radiographic knee OA and cartilage loss of the knee joints.²² Additionally, plasma interleukin-1 receptor antagonist (IL-1Ra) levels can predict joint space narrowing in knee OA.²³ Baseline and increasing levels of IL-6 and TNF- α in synovial fluid were also related to the progression of radiographic knee OA.²⁴ Periodontitis originates from the formation of a dysbiotic biofilm that results in host inflammatory responses through the expression of inflammatory cytokines, CXCL8, and MMP-8.²⁵ The present study suggested that inflammatory reactions occurring in periodontal tissue may be associated with the development and progression of knee OA.

Oral pathogens from periodontitis influence development and progression of arthritis through several virulence factors. Major contribution of *Porphyromonas gingivalis* (Pg) to rheumatoid arthritis (RA) is induced by citrullination.²⁶ Lipopolysaccharide, gingipain, and fimbriae from Pg contribute to chronic mucosal inflammation and subsequent arthritis.^{27,28} Mechanisms of oral pathogens against inflammatory reaction are complex and could be explained by other than citrullination. In addition, mouth and synovium are distant organs but are linked systemically. Oral pathogens might spread to joints: same bacterial DNA was found in periodontal tissue and synovial fluid of RA and OA patients.²⁹ This bacterial inoculation may contribute to joint inflammation and damage through a chain reaction.

There might be other unmeasured or unknown factors explaining the relationship between periodontitis and radiographic knee OA. For example, patients with knee OA may have some factors that can lead to poor oral hygiene, thus predisposing to periodontitis. In the present study, patients with knee OA presented less frequent tooth brushing, low

socioeconomic status, and more prevalent diabetes. We controlled these confounders in the analysis to examine the association between periodontitis and radiographic knee OA. However, other comorbidities and habits that we did not discover may exist.

Our results revealed a significant association between periodontitis and radiographic knee OA in women, whereas the association was relatively weak in men. This sex difference might be related to lower risk threshold for knee OA in women. Women are at a greater risk of suffering from more common and severe knee OA.^{30,31} On the other hand, periodontitis is less common in women than in men.³² The difference in prevalence of periodontitis or knee OA may be one reason for different degrees of association between periodontitis and knee OA in men and women.

There are some limitations to the present study. First, a causal relationship between periodontitis and knee OA cannot be determined by our cross-sectional study. Second, as the study included only an Asian population, the results may not be generalizable to other races. Third, the KNHANES used CPI to determine periodontitis.^{33,34} Probing depth is widely measured in clinical practice because of its cost- and time-effectiveness; however, the prevalence of periodontitis may be underestimated or overestimated without measuring clinical attachment loss.³⁴ CPI was developed to assess treatment needs, rather than to evaluate the prevalence of periodontitis.³⁵

The strength of the present study is that we explored the positive relationship between periodontitis and radiographic knee OA using non-institutionalized data covering a whole nation, which provides an excellent representation of the general population. Knee x-ray examinations and dental examinations were generally performed in person 50 years of age or older.

5 | CONCLUSION

Periodontitis was associated with presence of radiographic knee OA. The severity of radiographic knee OA, represented by K-L grading system, was also associated with periodontitis. Further research will be required to confirm the detailed mechanisms which can explain the association between periodontitis and development and progression of knee OA.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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