



## Scientific Research Report

# Association Between the Extent of Periodontal Inflammation and the Severity of Rheumatoid Arthritis in Japanese Patients With Rheumatoid Arthritis

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## ABSTRACT

**Objective:** Periodontal inflammation can affect the progression of rheumatoid arthritis (RA), and RA drugs may influence the periodontal condition of patients with RA. We examined whether the association between periodontal inflammation and the severity of RA is influenced by RA medication.

**Methods:** This cross-sectional study recruited 98 Japanese patients with RA from an orthopaedic clinic. We assessed the severity of RA using the Steinbrocker class and stage. The periodontal inflamed surface area (PISA) was used as an indicator of periodontal status. We obtained data on RA medications from medical records. We examined the associations among periodontal tissue inflammation, RA medications, and RA severity using multinomial logistic regression analyses.

**Results:** In univariate multinomial logistic regression analyses, no significant association between PISA score and RA severity was observed. There was no significant association between PISA score and RA severity in multivariate analyses not including variables about RA drugs as independent variables. However, in multivariate analyses adjusted for RA drugs and other confounding variables, patients with a PISA >550 mm<sup>2</sup> had significantly higher odds ratios (ORs) for Steinbrocker class III-IV and stage III-IV (OR, 20.24; 95% confidence interval [CI], 1.78-229.85 and OR, 12.42; 95% CI, 1.79-86.49, respectively) compared to patients with PISA score ≤550 mm<sup>2</sup>.

**Conclusion:** The extent of periodontal inflammation is associated with the severity of RA independent of RA medications.

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## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by joint swelling and pain.<sup>1</sup> In Japan, about 1 million people (approximately 1.0% of the population) suffer from RA.<sup>2</sup> Periodontitis is a prevalent chronic inflammatory disease of periodontal tissue that increases the risk of tooth loss<sup>3</sup> and has been reported to be related to various systemic diseases, including diabetes, cardiovascular disease, and stroke.<sup>4-6</sup>

Periodontitis is related to the onset and progression of RA.<sup>7</sup> Patients with RA and periodontitis had greater RA disease activity than those without periodontitis.<sup>8</sup> Among patients with arthralgia but not RA, those with periodontitis had a higher risk of developing RA than those without periodontitis.<sup>9</sup> Thus, inflammation of periodontal tissue may affect the onset and progression of RA. Studies of the relationship between RA and periodontitis have used various measures to evaluate the condition of the periodontal tissue, such as the periodontitis scale of the Centers for Disease Control and Prevention (CDC) and the American Academy of Periodontology (AAP),<sup>10</sup> the number of sites with a probing pocket depth (PPD) ≥4 mm, and the clinical attachment level (CAL) ≥4 mm.<sup>11</sup>

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Given that periodontitis is a type of inflammation affecting periodontal tissue, local periodontal inflammation might influence RA. Thus, the relationship between the degree of periodontal tissue inflammation and RA must be investigated. The periodontal inflamed surface area (PISA) is used to evaluate the extent of local periodontal inflammation.<sup>12</sup> Investigation of the relationship between the PISA score and severity of RA will provide insight into the relationship between periodontitis and RA.

Most patients with RA take 1 or more RA medications to prevent disease progression and achieve remission of symptoms.<sup>13</sup> Typical RA medications include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), methotrexate (MTX), and biologic disease-modifying antirheumatic drugs (bDMARDs). The periodontal condition of patients with RA improved after taking bDMARDs,<sup>14,15</sup> suggesting that RA drugs may influence the periodontal condition of patients with RA. However, little information is available about the effects of periodontal inflammation and RA medication on the severity of RA.

This study was performed to investigate the relationship between periodontal inflammation assessed by the PISA score and the severity of RA in Japanese adults. In addition, we investigated the impact of RA medications on the association between the PISA score and the severity of RA.

## Methods

### Study population

This cross-sectional study examined different themes pertaining to patients we previously reported on; the methods for evaluating RA and oral health are based on that study.<sup>16</sup> The diagnosis of RA was made by a rheumatologist in a private orthopaedic clinic based on the 1987 revised criteria of the American Rheumatism Association.<sup>17</sup> (1) morning stiffness in and around joints lasting for  $\geq 1$  h before maximal improvement; (2) soft tissue swelling of 3 or more joint areas; (3) swelling of the proximal interphalangeal, metacarpophalangeal, or wrist joints; (4) symmetric swelling; (5) rheumatoid nodules; (6) the presence of rheumatoid factor (RF); and (7) radiographic erosion or periarticular osteopenia in the hand or wrist joints. Criteria 1-4 must have been present for  $\geq 6$  weeks to be eligible for inclusion. RA was defined as the presence of 4 or more criteria. This study included only patients aged  $\geq 18$  years. Edentulous and pregnant patients were excluded. This study was approved by the Ethics Committee of the School of Dentistry of Aichi Gakuin University (approval number 405) and conducted in full accordance with the Declaration of Helsinki. All of the patients provided written informed consent. A total of 98 Japanese adults with RA (mean age,  $62.7 \pm 14.3$  years) were recruited from an orthopaedic clinic in Aichi Prefecture, Japan between April 2015 and March 2016.

### Assessment of clinical rheumatological parameters

The methods for assessing RA were based on our previous paper.<sup>16</sup> The Steinbrocker functional classification was applied by a single physician, who was trained in physical function assessment, to categorise the extent of physical disability from

class I to IV as follows: (1) complete functional capacity with the ability to carry out all usual duties without handicap; (2) functional capacity adequate to conduct normal activities despite handicap, discomfort or limited mobility in 1 or more joints; (3) functional capacity adequate to perform only a few or none of the duties of one's usual occupation or of self-care; and (4) largely or wholly incapacitated, with the patient bedridden or confined to a wheelchair, permitting little or no self-care.<sup>18</sup> The Steinbrocker stage classification was applied by a single physician to categorise the extent of joint disability from stage I to IV, as follows: I. early: (1) no destructive changes radiographically; (2) radiographic evidence of osteoporosis may be present; II. moderate: (1) roentgenological evidence of osteoporosis, with or without slight subchondral bone destruction; slight cartilage destruction may be present; (2) no joint deformities, although limitation of joint mobility may be present; (3) adjacent muscle atrophy; (4) extra-articular soft tissue lesions, such as nodules and tenosynovitis, may be present; III, severe: (1) roentgenological evidence of cartilage and bone destruction, in addition to osteoporosis; (2) joint deformity, such as subluxation, ulnar deviation, or hyperextension, without fibrous or bony ankylosis; (3) extensive muscle atrophy; (4) extra-articular soft tissue lesions, such as nodules and tenosynovitis, may be present; and IV, terminal: (1) fibrous or bony ankylosis in addition to the criteria of stage III.<sup>18</sup> We obtained data on the duration of RA treatments and RA drugs taken by patients from medical records and divided them into 5 categories: NSAIDs, corticosteroids, DMARDs, MTX, and bDMARDs. We confirmed the duration of current RA drug use.

### Oral examination

The methods used for evaluating oral health were based on our previous paper.<sup>16</sup> Patients' oral health status was examined by a single dentist at the orthopaedic clinic using a portable chair under adequate artificial light; the dentist was blinded to the subjects' rheumatoid data. The number of teeth was counted. As parameters of periodontal health status, PPD and bleeding on probing (BOP) were assessed at 6 points (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) around all teeth using a periodontal probe (CPUNC 15; Hu-Friedy). PPD was recorded to the nearest millimetre, and every observation close to 0.5 mm was rounded to the lowest whole number. BOP was classified dichotomously as the presence or absence of bleeding at 30 seconds after probing. Periodontal examiner reliability was verified by the intraexaminer calibration of 4 volunteers; the percentage of agreement ( $\pm 1$  mm) for PPD ranged from 81.0% to 98.8%, and the  $\kappa$  value ranged from 0.69 to 0.98. PISA, calculated as the sum of the PPD of BOP-positive sites in the total dentition, can be calculated from the periodontal chart. This method quantifies the surface area ( $\text{mm}^2$ ) of inflamed periodontal tissue as an indicator of the inflammatory and infectious burden of periodontitis. Also, it can be used to distinguish subjects with actively inflamed from those with noninflamed or healthy periodontal tissues. The PISA score was calculated after the PPD data and the incidence of BOP were entered into the PISA spreadsheet, which is publicly available at [www.parsprototo.info](http://www.parsprototo.info).<sup>12</sup>

## Questionnaires

Height, body weight, and lifestyle factors were evaluated using a self-administered questionnaire. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Smoking status was classified as never, former, or current smoker. A former smoker was defined as a patient who had smoked before but who did not smoke at the time of the investigation.

## Statistical analyses

Each of the 2 RA evaluation indices was divided into 3 subcategories: class (I, II, and III-IV) and stage (I, II, and III-IV). RA drug type was classified into 2 categories: bDMARDs and other. The PISA score was divided at the 20th percentile ( $\leq 550$  and  $> 550$  mm<sup>2</sup>), where this cutoff value has been used in a previous study.<sup>19</sup> The Mann–Whitney *U*-test and  $\chi^2$  test were used to analyse the relationships between PISA score and other variables. The Kruskal–Wallis and  $\chi^2$  tests were used to analyse the relationships between RA severity and other variables. Multinomial logistic regression analyses were performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the effects of PISA score and other variables on RA severity (class or stage). Age, sex, BMI, smoking status, number of teeth, PISA score, duration of RA treatments, duration of current RA drug use, and type of RA drug were included as independent variables in univariate and multivariate multinomial logistic regression analyses. In the multivariate analyses, we used 2 models. Model 1 included all independent variables of interest except duration of current RA drug use and type of RA drug, and model 2 included variables about RA drugs as independent variables. In all analyses,  $P < .05$  was taken to indicate statistical significance. The statistical analyses were performed using SPSS version 23.0 software (IBM).

## Results

Table 1 shows the characteristics of the RA patients and the relationships between the PISA score and other variables. Patients with PISA score  $> 550$  mm<sup>2</sup> had significantly higher PPD and BOP values than those with PISA score  $\leq 550$  mm<sup>2</sup>. No significant relationships between PISA score and other variables in RA patients were observed.

Table 2 shows the relationships between RA severity (class, stage) and other variables in patients with RA. The patients in a higher class were significantly older, had fewer teeth, higher BOP value, longer duration of RA treatment, and higher rates of bDMARD use. The patients in a higher stage had a longer duration of RA treatment, longer duration of current RA drug use, higher rates of bDMARD use, and longer duration of DMARDs, corticosteroids, NSAIDs, and MTX use.

Table 3 shows the results of univariate and multivariate multinomial logistic regression analyses of the effects of PISA score and other variables on RA severity (class). Older patients had significantly higher ORs for class II and class III-IV in multivariate analyses. Compared to the patients with PISA  $\leq 550$  mm<sup>2</sup>, those with PISA score  $> 550$  mm<sup>2</sup> had

significantly higher ORs for class III-IV in model 2 (OR, 20.24; 95% CI, 1.78–229.85).

Table 4 shows the results of univariate and multivariate multinomial logistic regression analyses of the effect of PISA score and other variables on RA severity (stage). In model 1, patients with a longer duration of RA treatment had significantly higher ORs for stage III-IV. In model 2, patients with PISA score  $> 550$  mm<sup>2</sup> had a significantly higher OR (12.42; 95% CI, 1.79–86.49) for stage III-IV compared to patients with PISA score  $\leq 550$  mm<sup>2</sup>. Patients taking bDMARDs had a significantly higher OR for stage III-IV in model 2.

## Discussion

The RA patients who had severe periodontal tissue inflammation, as evaluated by the PISA score, had more severe RA, suggesting that periodontal tissue inflammation is linked to RA severity.

A previous study indicated that the prevalence of RA was higher in patients with periodontitis compared to those without periodontitis.<sup>20</sup> A study following patients with arthralgia but not RA for 2 years indicated that those with periodontal pockets  $\geq 4$  mm had a significantly higher risk of developing RA.<sup>9</sup> Patients with RA and periodontitis had greater RA disease activity than those without periodontitis.<sup>8</sup> In this study, patients with RA and severe periodontal inflammation had more severe RA. Because periodontal tissue inflammation may affect RA severity by causing citrullination,<sup>21,22</sup> it might be important for patients with RA to visit a dental clinic and receive appropriate periodontal treatment to reduce periodontal inflammation to prevent worsening of RA.

The patients with RA and periodontitis had more severe joint destruction, as determined by radiography, and a higher disease activity score (based on the level of C-reactive protein [DAS 28-CRP]) than do patients with RA without periodontitis.<sup>8</sup> However, other studies have found no significant association between periodontal status and RA severity.<sup>23–25</sup> Most of those studies did not consider the effects of RA drugs on the association between periodontitis and the severity of RA. In this study, there was no significant association between periodontal inflammation and RA severity in the crude analysis, but their association was enhanced after adjustment for confounders. Furthermore, in multivariate analyses including variables pertaining to RA drugs, the strongest association was found between the PISA score and RA severity. RA medications may play an important role in the relationship between periodontal tissue inflammation and the severity of RA.

In a study of the associations among periodontal status, RA severity, and RA medication, patients with RA taking an interleukin-6 (IL-6) inhibitor showed decreased matrix metalloproteinase-3 (MMP-3; a serum marker of joint destruction), gingivitis index, BOP, and PPD compared to those not taking the drug.<sup>14</sup> Also, in a study in which patients with RA were given tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors, the DAS 28-CRP level, gingival index, BOP, and PPD decreased.<sup>15</sup> IL-6 and TNF- $\alpha$  are important inflammatory cytokines related to both RA and periodontitis,<sup>26</sup> and their inhibition by bDMARDs would ameliorate both RA and periodontitis.<sup>14,15,26</sup>

**Table 1 – Relationships between the PISA score and other variables in patients with RA.**

	Total RA patients (N = 98)	PISA score (mm <sup>2</sup> )		P value*
		≤550 (n = 78)	> 550 (n = 20)	
Age	62.5 (54.0, 74.0)	62.0 (51.8, 75.0)	65.5 (57.0, 71.0)	.55
Sex				
Male	29 (29.6)	22 (28.2)	7 (35.0)	.55
Female	69 (70.4)	56 (71.8)	13 (65.0)	
BMI (kg/m <sup>2</sup> )	21.3 (19.3, 23.5)	21.6 (19.6, 23.5)	19.3 (18.4, 23.0)	.06
Smoking status				
Never smoker	54 (55.1)	45 (57.7)	9 (45.0)	.38
Former smoker	21 (21.4)	17 (21.8)	4 (20.0)	
Current smoker	23 (23.4)	16 (20.5)	7 (35.0)	
Number of teeth	24.0 (16.8, 27.3)	24.0 (15.3, 28.0)	24.0 (19.0, 26.8)	.81
Mean PPD (mm)	2.85 (2.53, 3.30)	2.69 (2.50, 3.01)	3.38 (3.01, 3.86)	<.001
Mean BOP (%)	20.3 (9.97, 41.7)	16.1 (7.79, 27.1)	43.4 (35.9, 69.8)	<.001
PPD (mm)				
≤3	3 (3.1)	3 (3.8)	0 (0.0)	<.001
4-5	52 (53.1)	47 (60.3)	5 (25.0)	
≥6	43 (43.9)	28 (35.9)	15 (75.0)	
BOP (%)				
<10	24 (24.5)	24 (30.8)	0 (0.0)	<.001
10-29.9	38 (38.8)	37 (47.4)	1 (5.0)	
≥30	36 (36.7)	17 (21.8)	19 (95.0)	
RA severity (Class)				
I	68 (69.4)	57 (73.1)	11 (55.0)	.29
II	17 (17.3)	12 (15.4)	5 (25.0)	
III-IV	13 (13.3)	9 (11.5)	4 (20.0)	
RA severity (Stage)				
I	60 (61.2)	49 (62.8)	11 (55.0)	.39
II	19 (19.4)	16 (20.5)	3 (15.0)	
III-IV	19 (19.4)	13 (16.7)	6 (30.0)	
Duration of RA treatment (month)	25.5 (4.0, 74.5)	27.5 (3.75, 76.0)	21.5 (9.0, 62.2)	.49
Duration of current RA drug use (month)	12.0 (2.0, 34.8)	13.0 (2.0, 37.5)	10.0 (2.0, 17.0)	.13
Type of RA drug				
DMARDs/Corticosteroids/NSAIDs/MTX	74 (75.5)	57 (73.1)	17 (85.0)	.21
bDMARDs	24 (24.5)	21 (26.9)	3 (15.0)	
Duration of DMARDs/Corticosteroids/ NSAIDs/MTX use (month) (n = 74)	6.5 (2.0, 18.8)	6.5 (2.0, 25.5)	6.5 (1.3, 15.8)	.40
Duration of bDMARDs use (month) (n = 24)	36.0 (12.0, 66.0)	36.0 (15.0, 66.6)	21.0 (2.0, 36.0)	.26

bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; BOP, bleeding on probing; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PISA, periodontal inflamed surface area; PPD, probing pocket depth; RA, rheumatoid arthritis.

Data are presented as median (25 percentile, 75 percentile) or number with percentages given in parentheses.

\* Differences among groups, analysed using Mann-Whitney U test or  $\chi^2$  test.

In this study, the type of RA drug was significantly associated with the severity of RA, and patients with severe RA had a higher rate of taking bDMARDs. Our results were expected because the subjects in this study had taken RA drugs, and patients with severe RA were more frequently bDMARD users. By contrast, bDMARDs were reported to improve not only the symptoms of RA but also inflammation of periodontal tissue.<sup>14,15</sup> In this study, although there was no significant relationship between PISA score and the duration of bDMARD use, patients with lower PISA score had been taking bDMARDs for longer. Therefore, it is possible that bDMARDs ameliorated periodontal tissue inflammation in the patients with RA, and the real impact of periodontal inflammation on the severity of RA may have been underestimated in this study. In fact, in a multivariate analysis, the strength of the association between the PISA score and the severity of RA increased after adjustment for RA medications, suggesting

that severe inflammation of periodontal tissue may increase the severity of RA in patients not taking bDMARDs. Therefore, the influence of periodontal tissue inflammation on the severity of RA was demonstrated by adjusting for the influence of RA drugs in the multivariate analysis. In future studies, RA drugs should be included in evaluations of the effects of periodontal disease on RA severity.

Although bDMARDs have been reported to improve not only the symptoms of RA but also inflammation of periodontal tissue and periodontal pockets,<sup>14</sup> in a cross-sectional study, there were no significant differences in the PPD or CAL between bDMARD users and antirheumatic drugs users.<sup>27</sup> However bDMARD users had higher levels of gum inflammation as assessed by BOP and the papilla bleeding index.<sup>27</sup> In addition, another study showed that attachment loss decreased after patients took bDMARDs, but the gingivitis index increased.<sup>28</sup> Because bDMARDs suppress bone

**Table 2 – Relationships between the severity of RA (class, stage) and other variables in patients with RA.**

	RA severity (Class)			P value*	RA severity (Stage)			P value*
	I (n = 68)	II (n = 17)	III-IV (n = 13)		I (n = 70)	II (n = 19)	III-IV (n = 19)	
Age	59.5 (50.0, 66.8)	68.0 (58.0, 78.0)	79.0 (72.0, 85.5)	<.001	62.0 (54.0, 71.8)	65.0 (55.0, 81.0)	65.0 (50.0, 79.0)	.58
Sex								
Male	23 (33.8)	5 (29.4)	1 (7.6)	.17	21 (35.0)	5 (26.3)	3 (15.8)	.26
Female	45 (66.2)	12 (70.5)	12 (92.3)		39 (65.0)	14 (73.7)	16 (84.2)	
BMI (kg/m <sup>2</sup> )	21.7 (19.2, 23.5)	20.5 (19.6, 22.8)	19.9 (17.8, 22.8)	.50	21.3 (19.2, 23.5)	21.4 (19.5, 27.3)	20.0 (19.1, 23.1)	.63
Smoking status								
Never smoker	31 (45.6)	13 (76.5)	10 (76.9)	.05	29 (48.3)	10 (52.6)	15 (78.9)	.23
Former smoker	16 (23.5)	3 (17.6)	2 (15.4)		15 (25.0)	4 (21.1)	2 (10.5)	
Current smoker	21 (30.9)	1 (5.9)	1 (7.7)		16 (36.7)	5 (26.3)	2 (10.5)	
Number of teeth	25.5 (20.0, 28.0)	23.0 (18.0, 26.0)	12.0 (7.5, 25.0)	.01	24.5 (18.0, 27.0)	23.0 (16.0, 28.0)	24.0 (11.0, 27.0)	.93
Mean PPD (mm)	2.75 (2.52, 3.19)	2.84 (2.45, 3.17)	3.07 (2.83, 4.4)	.06	2.79 (2.54, 3.32)	2.88 (2.52, 3.02)	2.90 (2.52, 3.78)	.63
Mean BOP (%)	18.1 (8.90, 36.0)	14.8 (10.6, 33.3)	44.9 (18.6, 69.0)	.03	20.4 (8.90, 41.3)	18.3 (12.7, 40.7)	21.7 (14.8, 61.1)	.62
PISA score (mm <sup>2</sup> )								
≤550	57 (83.8)	12 (70.6)	9 (69.2)	.29	49 (81.7)	16 (74.2)	13 (68.4)	.39
>550	11 (16.2)	5 (29.4)	4 (30.8)		11 (18.3)	3 (15.8)	6 (31.6)	
Duration of RA treatment (month)	18.0 (3.0, 62.3)	53.0 (15.0, 82.5)	49.0 (24.5, 88.0)	.03	15.5 (2.0, 45.3)	66.0 (4.0, 81.0)	86.0 (26.0, 96.0)	<.001
Duration of current RA drug use (month)	8 (2.0, 27.0)	17.0 (2.25, 48.0)	24.0 (7.0, 62.0)	.15	6.0 (2.0, 19.0)	24.0 (4.0, 66.0)	23.5 (9.75, 66.2)	<.001
Type of RA drug								
DMARDs/Corticosteroids/NSAIDs/MTX	60 (88.2)	10 (58.8)	4 (30.8)	<.001	54 (90.0)	13 (68.4)	7 (36.8)	<.001
bDMARDs	8 (11.8)	7 (41.2)	9 (69.2)		6 (10.0)	6 (31.6)	12 (63.2)	
Duration of DMARDs/Corticosteroids/ NSAIDs/MTX use (month) (n = 74)	6.0 (2.0, 18.0)	4.0 (1.5, 20.5)	21.0 (13.0, 51.5)	.19	4.0 (2.0, 16.5)	14.0 (4.0, 69.0)	16.5 (9.75, 34.5)	.02
Duration of bDMARDs use (month) (n = 24)	33.5 (15.0, 66.0)	49.0 (17.0, 68.0)	24.0 (2.0, 73.0)	.78	26.0 (12.7, 36.0)	58.0 (18.3, 66.5)	42.5 (5.7, 70.7)	.46

bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; BOP, bleeding on probing; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PISA, periodontal inflamed surface area; PPD, probing pocket depth; RA, rheumatoid arthritis.

Data are presented as median (25 percentile, 75 percentile) or number with percentages giving in parentheses.

\* Differences among groups, analysed using Kruskal-Wallis test or  $\chi^2$  test.

**Table 3 – Associations of periodontal status and other variables with the severity of RA (class) by univariate and multivariate multinomial logistic regression analyses.**

Independent variable	Dependent variable: Class		Model 1		Model 2	
	II vs I	III-IV vs I	II vs I	III-IV vs I	II vs I	III-IV vs I
	Crude OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.07 (1.02, 1.12)*	1.17 (1.08, 1.26)†	1.08 (1.01, 1.15)*	1.18 (1.06, 1.32)†	1.10 (1.02, 1.18)*	1.19 (1.05, 1.34)†
Sex						
Male	1	1	1	1	1	1
Female	1.23 (0.39, 3.91)	6.13 (0.75, 50.13)	0.57 (0.11, 2.91)	5.30 (0.34, 81.67)	0.51 (0.09, 2.88)	4.51 (0.20, 100.72)
BMI (kg/m <sup>2</sup> )	0.95 (0.82, 1.11)	0.90 (0.75, 1.08)	0.93 (0.76, 1.15)	0.93 (0.72, 1.20)	0.92 (0.73, 1.17)	0.92 (0.69, 1.22)
Smoking status						
Never smoker	1	1	1	1	1	1
Former smoker	0.45 (0.11, 1.80)	0.39 (0.08, 1.99)	0.38 (0.07, 2.05)	0.62 (0.07, 5.50)	0.39 (0.07, 2.21)	0.60 (0.05, 6.98)
Current smoker	0.11 (0.01, 0.94)*	0.15 (0.01, 1.24)	0.09 (0.01, 1.18)	0.57 (0.02, 14.78)	0.13 (0.01, 1.87)	0.72 (0.02, 30.13)
Number of teeth	0.99 (0.92, 1.06)	0.89 (0.83, 0.96)†	1.02 (0.93, 1.12)	0.93 (0.83, 1.04)	1.03 (0.93, 1.14)	0.94 (0.82, 1.06)
PISA score (mm <sup>2</sup> )						
≤550	1	1	1	1	1	1
>550	2.16 (0.63, 7.36)	2.30 (0.60, 8.82)	2.11 (0.46, 9.61)	7.94 (0.98, 64.66)	4.07 (0.76, 21.63)	20.24 (1.78, 229.85)*
Duration of RA treatment (month)	1.01 (1.00, 1.02)*	1.01 (1.00, 1.01)	1.01 (1.00, 1.02)*	1.01 (1.00, 1.02)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Duration of current RA drug use (month)	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)			1.02 (0.98, 1.05)	1.02 (0.98, 1.07)
Type of RA drug						
DMARDs/Corticosteroids/NSAIDs/MTX	1	1			1	1
bDMARDs	5.25 (1.56, 17.70)†	16.88 (4.20, 67.73)†			4.31 (0.74, 25.14)	7.35 (0.81, 66.64)

bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; CI, confidence interval; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PISA, periodontal inflamed surface area; RA, rheumatoid arthritis.

Model 1 used age, sex, BMI, smoking status, number of teeth, PISA score, and duration of RA treatment as independent variables. Model 2 used age, sex, BMI, smoking status, number of teeth, PISA score, duration of RA treatment, duration of current RA drug use, and type of RA drug as independent variables.

\* P < .05.

† P < .01.



**Table 4 – Associations of periodontal status and other variables with the severity of RA (stage) by univariate and multivariate multinomial logistic regression analyses.**

Independent variable	Dependent variable: Stage		Model 1		Model 2	
	II vs I	III-IV vs I	II vs I	III-IV vs I	II vs I	III-IV vs I
	Crude OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)	1.02 (0.98, 1.07)	0.99 (0.94, 1.05)	1.02 (0.97, 1.08)	0.98 (0.92, 1.05)
Sex						
Male	1	1	1	1	1	1
Female	1.51 (0.48, 4.77)	2.87 (0.75, 10.99)	1.84 (0.45, 7.43)	1.35 (0.25, 7.24)	1.69 (0.36, 7.92)	0.96 (0.13, 6.95)
BMI (kg/m <sup>2</sup> )	1.10 (0.97, 1.26)	1.01 (0.88, 1.18)	1.11 (0.95, 1.29)	1.07 (0.90, 1.28)	1.12 (0.94, 1.34)	1.08 (0.88, 1.32)
Smoking status						
Never smoker	1	1	1	1	1	1
Former smoker	0.77 (0.21, 2.89)	0.26 (0.05, 1.28)	0.83 (0.18, 3.71)	0.25 (0.04, 1.52)	0.74 (0.15, 3.68)	0.21 (0.03, 1.66)
Current smoker	0.91 (0.26, 3.12)	0.24 (0.05, 1.19)	1.12 (0.25, 5.10)	0.12 (0.01, 1.09)	1.05 (0.20, 5.53)	0.16 (0.01, 1.98)
Number of teeth	0.99 (0.93, 1.06)	0.98 (0.92, 1.05)	1.02 (0.94, 1.12)	0.96 (0.87, 1.06)	1.03 (0.93, 1.13)	0.97 (0.86, 1.09)
PISA score (mm <sup>2</sup> )						
≤550	1	1	1	1	1	1
>550	0.84 (0.21, 3.37)	2.06 (0.64, 6.61)	1.02 (0.22, 4.66)	3.43 (0.77, 15.3)	1.84 (0.35, 9.62)	12.42 (1.79, 86.49)*
Duration of RA treatment (month)	1.01 (1.00, 1.03)*	1.02 (1.01, 1.04)†	1.01 (1.00, 1.03)	1.02 (1.01, 1.04)†	1.01 (0.98, 1.04)	1.03 (1.00, 1.06)
Duration of current RA drug use (month)	1.04 (1.02, 1.07)†	1.04 (1.02, 1.07)†			1.03 (1.00, 1.07)	1.02 (0.98, 1.06)
Type of RA drug						
DMARDs/Corticosteroids/NSAIDs/MTX	1	1			1	1
bDMARDs	4.15 (1.15, 14.99)*	15.43 (4.39, 54.23)†			2.08 (0.39, 11.14)	9.10 (1.48, 55.82)*

bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; CI, confidence interval; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PISA, periodontal inflamed surface area; RA, rheumatoid arthritis.

Model 1 used age, sex, BMI, smoking status, number of teeth, PISA score, and duration of RA treatment as independent variables. Model 2 used age, sex, BMI, smoking status, number of teeth, PISA score, duration of RA treatment, duration of current RA drug use, and type of RA drug as independent variables.

\* P < .05.

† P < .01.

destruction systemically, they may exert a beneficial effect on periodontitis by suppressing the destruction of alveolar bone but may promote local inflammation in gum tissue. The plaque index did not improve after taking a bDMARDs,<sup>15,28</sup> and it is difficult to improve periodontal tissue inflammation with medication alone in patients with poor oral hygiene; in such cases, attempts to improve oral health are needed. Patients' oral health status, RA severity, and medication status appeared to be different between previous studies,<sup>14,15,28</sup> and research on the effects of RA drugs, including bDMARDs, on periodontal tissue is limited. Therefore, further studies are needed to determine the impact of RA treatments on the association of periodontitis with the severity of RA.

In this study, we used class classification of functional disability and stage classification of joint destruction based on X-ray findings to categorise RA severity, and the PISA score was more strongly associated with the class classification. This suggests that periodontal tissue inflammation is more strongly associated with dysfunction than the morphological findings in patients with RA. Because bDMARDs suppress bone destruction, they are used for many patients with a high stage classification, and the type of RA medication may affect the association between periodontal tissue inflammation and RA severity. The RA medication is selected based on disease severity and activity.<sup>29</sup> In this study, when the use of MTX did not improve severe RA, physicians often used a bDMARD to avoid a decline in activities of daily living and progression of disease. In fact, many of the patients taking bDMARDs had severe RA. We considered the duration of RA treatment and current RA drug use. However, we were not able to examine the changes of RA medications or combination drug treatments. Further studies should obtain more information to better understand the impact of RA drugs on the association between periodontitis and RA severity.

In this study, we examined the effect of periodontal tissue inflammation on RA severity. Many studies have shown that RA severity is associated with periodontitis,<sup>30-32</sup> patients with RA had more severe gingival inflammation and chronic periodontal destruction compared to controls matched for age, sex, smoking status, and oral hygiene status.<sup>30</sup> Therefore, a reciprocal relationship may exist between these 2 variables. Although cross-sectional studies cannot indicate the direction of an association, it is important to note the 2-way relationship between these 2 variables.

Smoking is a risk factor for RA, and the incidence of RA has been reported to be higher in smokers than in nonsmokers.<sup>33</sup> However, in this study, the percentage of smokers was higher among patients with lower RA severity. All participants in this study were patients with RA; we did not perform comparisons between non-RA and RA subjects. Therefore, it is possible that there is no statistically significant relationship between RA severity and smoking status.

This study had several limitations. Because this was a cross-sectional study, it was impossible to infer causality regarding the association between periodontitis and RA severity. As this study involved a small group of patients who visited a particular orthopaedic clinic, the distribution of RA severity may differ from that in the general population. Because the number of participants in this study was small, the changes in OR in each analysis were large, and the CIs

were relatively wide. To obtain more reliable results, more patients should be analysed. In addition, this study enrolled patients who could attend a clinic, and it did not include those with severe RA who required hospitalisation. To clarify the association between RA and periodontal disease, a large-scale study of patients with RA of varying severity and using various medications is needed. We did not consider the dose of medication, the use of multiple medications in each patient, or changes in medication during the course of treatment. In addition, the effects of environmental factors related to RA, such as viral infection, diet, and hormones, were not considered. Future studies should consider other environmental factors that aggravate RA.

## Conclusion

Patients with RA who had a high PISA score (indicating inflammation of periodontal tissue) were more likely to have severe RA; thus, inflammation of periodontal tissue in patients with RA may affect RA symptoms. Also, the relationship increased when RA drug type and duration of current RA drug use was considered, suggesting that RA drugs should be included in analyses of the relationship between periodontal tissue inflammation and the severity of RA. It is important to reduce inflammation of periodontal tissue in patients with RA by improving their oral hygiene and providing appropriate periodontal treatment. Further prospective studies are needed to understand how periodontal inflammation affects the severity of RA.

## Conflict of interest

None disclosed.

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The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: <http://www.textcheck.com/certificate/FqvP3r>

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