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Functional Impairment and Periodontitis in Rheumatoid Arthritis

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ABSTRACT

Background: This study explored the association of functional impairment due to rheumatoid arthritis (RA) and RA disease activity with periodontal disease in patients with RA.

Methods: Ninety-three patients with RA were included. Their RA functional status was assessed using the Steinbrocker classification. The serum level of matrix metalloproteinase-3 (MMP-3) was used as an indicator of RA disease activity. Probing depth (PD) and clinical attachment level (CAL) were used as indicators of periodontal status. We examined the association of RA severity and MMP-3 levels with periodontal status using a generalised linear model (GLM).

Results: In a multivariate GLM, the coefficient for the mean PD was significantly positive in those with RA severity classes III or IV (reference: class I; \( b = 0.14; 95\% \) confidence interval [CI], 0.03–0.25; \( P = .02 \)) independent of other confounding variables. In multivariate GLM using the mean CAL as the dependent variable, the coefficient was significant in patients with high MMP-3 levels (10 ng/mL; \( b = 0.005; 95\% \) CI, 0.001–0.008; \( P = .02 \)).

Conclusions: Functional impairment due to RA may affect PD, and high serum levels of MMP-3 may affect CAL.

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Introduction

Periodontitis is a chronic inflammatory disease prevalent amongst adults. It is caused by periodontal bacterial infection that triggers inflammation and, ultimately, the destruction of periodontal tissues. In addition to the pathogenicity of periodontal bacteria, continuous, excessive host biological reactions due to the hyperproduction of inflammatory cytokines in the inflamed tissues cause periodontal tissue destruction. 1 Rheumatoid arthritis (RA) is an autoimmune disorder that results in swollen and painful joints. It is characterised by chronic synovitis, synovial cell proliferation in joints, and production of cytokines and proteolytic enzymes in the synovium and cartilage, which eventually leads to bone destruction. 2

The relationship between periodontitis and RA has been reported frequently. Patients with RA have a higher prevalence of periodontitis and loss of clinical attachment level (CAL) than those in healthy individuals. 3,4 Amongst patients with RA, those with severe periodontitis have a higher disease activity score (DAS) than those with mild to moderate periodontitis. 5 Inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-\( \alpha \)) are common in the aetiologies of RA and periodontitis, 6 being involved in the onset of periodontitis and pathogenesis of RA. 7,8 In addition, IL-6 and TNF-\( \alpha \) levels are significantly higher in patients with RA having greater disease activity and are positively correlated with DAS. 9 Moreover, there is a positive correlation between TNF-\( \alpha \) and bleeding on probing, which indicates gingival inflammation, in RA. 9

Matrix metalloproteinase-3 (MMP-3) is a proteolytic enzyme induced by inflammatory cytokines and is used as a serum indicator of RA activity; it plays a central role in progressive joint destruction in RA and thus is attracting attention as a marker for predicting joint destruction. 10,11 Tuncer et al 12 reported significantly higher MMP-3 levels in patients with RA with high DASs. Furthermore, MMP-3 levels increase
with Steinbrocker stage and class, indicating RA severity. Therefore, higher MMP-3 levels in RA may negatively influence periodontal status; however, information is scarce on the effects of MMP-3 levels on the periodontal status in patients with RA. There is also limited information on the impact of RA-induced functional impairment on periodontal health.

This study aimed to clarify the association of the functional impairment due to RA and RA disease activity suggested by MMP-3 level with periodontal disease.

Methods

Study population

We recruited 93 patients with RA (mean age, 63.5 ± 14.3 years), who satisfied the American College of Rheumatology 1987 revised criteria for RA, from an orthopaedic clinic in Aichi Prefecture, Japan, from April 2015 to March 2016. Individuals with RA aged older than 18 years who provided informed consent were included. Pregnant and edentulous patients were excluded. The study was approved by the Ethics Committee of Aichi Gakuin University, School of Dentistry (approval number: 405) and was conducted in full accordance with the version 2008 of the Declaration of Helsinki.

Assessment of clinical rheumatological parameters

Assessments of RA parameters were performed based on our previous studies. The severity of RA was identified according to the Steinbrocker functional classification: class I, patients performing all usual activities without limitation; class II, adequate performance of normal activities despite discomfort or limited motion in one joint; class III, limited performance with little or none of the usual activities or self-care; class IV, incapacitated, largely or wholly bedridden, or confined to a wheelchair with little or no self-care. The measurements of MMP-3, IL-6, and TNF-α levels were outsourced to a pathological laboratory. We obtained data on the RA drugs being taken by the patients from their medical records and classified the drugs accordingly into nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatoid drugs (DMARDs), methotrexate (MTX), and biological DMARDs (bDMARDs). Additionally, information regarding the duration of RA treatment was obtained from the medical records of the patients.

Oral examination

Oral health evaluation was conducted based on our previous study. A single dentist examined the oral health status of all the patients at the orthopaedic clinic using a portable chair under adequate artificial light; the dentist was blinded to the patients’ health data including those concerning RA. The total number of teeth, excluding third molars, was noted. The parameters of periodontal health, probing depth (PD), and CAL were assessed at 6 points (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, and distolingual) around all teeth using a periodontal probe (PCPUNC15, Hu-Friedy, Chicago, IL, USA). The PD and CAL were recorded to the nearest millimetre; as an example, 1.4 would be rounded to 1 and 1.6 would be rounded to 2. Reliability of periodontal examination was verified by intra-examiner calibration of 4 volunteers; the percentage of agreement (within ± 1 mm) ranged from 81.0% to 98.8% for PD and 97.0% to 98.2% for CAL. The kappa value ranged from 0.69 to 0.98 for PD and 0.95 to 0.97 for CAL.

Questionnaire assessment

Lifestyle factors, history of present illness, and oral hygiene habits were assessed using a self-administered questionnaire, as in our previous study. Patients were classified regarding their smoking status as never smoker, former smoker, or current smoker. A former smoker was defined as a patient who used to smoke but was not a smoker at the time of the investigation. We recorded the frequency of periodic dental check-up as once a month, every 2–3 months, every 6 months, once a year, every few years, or never. The frequency of tooth brushing (times/day) was recorded as a measure of oral hygiene habits.

Statistical analyses

The RA evaluation indices were subdivided into classes I, II, and III–IV. The RA drugs taken by patients were classified into 3 categories: bDMARDs, MTX, and other. Number of teeth was divided into 2 categories: ≥20 and <19 teeth. We used the mean values of all PD and CAL measurements in the analysis. The frequency of tooth brushing (times/day) was divided into 2 categories: ≥2 or ≤1. The data on periodic dental check-up were divided into 2 categories: no, more than 1 year since check-up and yes, within the last year. The Spearman rank correlation coefficient, Mann–Whitney U test, or Kruskal–Wallis test were used to analyse the associations between PD and CAL and other variables. The distributions of the mean PD and mean CAL were continuous but not normal. Therefore, a generalised linear model (GLM) with the gamma distribution and log link was used to analyse the relationships of RA status and other variables with periodontal status. The crude effects of each independent variable (age; duration of RA treatment; MMP-3, IL-6, and TNF-α levels; sex; smoking status; diabetes status; frequency of tooth brushing; periodic dental check-up; number of teeth; RA severity [class]; and RA drugs) were analysed using the GLM. Multivariate analyses included variables with a P value <.2 in univariate analyses. All statistical analyses were performed using SPSS ver. 26.0 (IBM Japan, Tokyo, Japan). A P value <.05 was considered statistically significant.

Results

Table 1 summarises the characteristics of the patients. The median age, mean PD, mean CAL, and MMP-3 level were 64.0 years, 2.84 mm, 2.96 mm, and 63.9 ng/mL, respectively.
**Table 1 – Characteristics of patients with RA.**

| Characteristic                  | Median (25th percentile, 75th percentile) or n (%) |
|--------------------------------|---------------------------------------------------|
| Age (years old)                | 64.0 (54.5, 74.5)                                 |
| Duration of RA treatment (month)| 30 (5, 77)                                        |
| Mean PD (mm)                   | 2.84 (2.52, 3.34)                                 |
| Mean CAL (mm)                  | 2.96 (2.59, 3.60)                                 |
| MMP-3 (ng/mL)                  | 63.9 (42.1, 101.5)                                |
| IL-6 (pg/mL)                   | 2.0 (1.0, 4.6)                                    |
| TNF-α (pg/mL)                  | 1.7 (1.1, 2.9)                                    |
| Sex                            |                                                   |
| Male                           | 26 (28.0)                                         |
| Female                         | 67 (72.0)                                         |
| Smoking status                 |                                                   |
| Never smoker                   | 53 (57.0)                                         |
| Former smoker                  | 20 (21.5)                                         |
| Current smoker                 | 20 (21.5)                                         |
| Diabetes                       |                                                   |
| No                             | 83 (89.2)                                         |
| Yes                            | 10 (10.8)                                         |
| Frequency of tooth brushing (times/day) |                                         |
| ≥2                             | 71 (76.3)                                         |
| ≤1                             | 22 (23.7)                                         |
| Periodic dental checkup        |                                                   |
| Yes                            | 44 (47.3)                                         |
| No                             | 49 (52.7)                                         |
| Number of teeth                |                                                   |
| ≥20                            | 62 (66.7)                                         |
| ≤19                            | 31 (33.3)                                         |
| RA severity (class)            |                                                   |
| I                              | 62 (66.7)                                         |
| II                             | 17 (18.3)                                         |
| III, IV                        | 14 (15.1)                                         |
| RA drugs                       |                                                   |
| NSAIDs/DMARDs                  | 30 (32.3)                                         |
| MTX                            | 38 (40.9)                                         |
| bDMARDs                        | 25 (26.9)                                         |

RA, rheumatoid arthritis; PD, probing depth; CAL, clinical attachment level; MMP, matrix metalloproteinase; IL, interleukin; TNF, tumor necrosis factor; NSAID, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; bDMARDs, biologic disease-modifying antirheumatic drugs.

Of the patients, 66.7% had class I RA severity and 26.9% were taking bDMARDs.

Table 2 shows the associations of mean PD and mean CAL with other variables. Age and IL-6 level were significantly positively correlated with mean PD. Age and MMP-3 and IL-6 levels were significantly positively correlated with mean CAL. Patients who brushed their teeth ≤1 time/day had a significantly higher mean PD and mean CAL than those who brushed their teeth ≥2 times/day. Patients with ≤19 teeth had significantly poorer periodontal status than those with ≥20 teeth. The mean PD and mean CAL were higher in those with RA severity classes III or IV than in those with class I or II.

Table 3 shows the results of the GLM using gamma distribution and log link for the mean PD. In multivariate analyses, the coefficient for the mean PD had a significant positive value for those who brushed their teeth ≤1 time/day (reference: ≥2 per day; β = 0.11; 95% confidence interval [CI], 0.03–0.19; P = .01), had ≤19 teeth (reference: ≥20; β = 0.23; 95% CI, 0.15–0.31; P < .001), and had an RA severity of class III or IV (reference: class I; β = 0.14; 95% CI, 0.03–0.25; P = .02).

The results of the GLM using the gamma distribution and log link for the mean CAL are shown in Table 4. In multivariate analyses, the coefficients for the mean CAL had a significant positive value for those who had a higher MMP-3 level (10 ng/mL; β = 0.005; 95% CI, 0.001–0.008; P = .02), were current smokers (reference: never smoker; β = 0.13; 95% CI, 0.03–0.22; P = .01), and had ≤19 teeth (reference: ≥20; β = 0.30; 95% CI, 0.21–0.38; P < .001).

**Discussion**

Patients with increased RA severity had significantly higher PD than those with less severe disease, and those with high MMP-3 levels had significantly higher CAL than those with lower MMP-3 levels. This suggests that the severity of RA and the joint destruction activity of patients with RA affect their periodontal status.

The relationship between periodontal status and RA has been reported often, and previous studies have shown more severe periodontitis in patients with RA than in healthy individuals. A DAS 28-joint count calculated using C-reactive protein, which reflects RA activity, indicated that patients with high RA activity had worse periodontal status than those in remission. Our finding that patients with severe RA had severe periodontal disease concurs with these results. Rheumatologists should encourage patients with severe RA, especially those not receiving periodontal treatment or scheduling regular dental checkups, to visit a dental clinic and receive oral hygiene guidance and periodontal treatment to keep periodontal disease in check.

Healthy individuals with high MMP-3 levels in the gingival crevicular fluid are at an increased risk for periodontitis. Patients with chronic or aggressive periodontitis have higher MMP-3 levels than healthy individuals. Yamanaka et al showed that patients with RA have higher MMP-3 levels than healthy individuals. These findings suggest that there is some association between high MMP-3 levels and periodontal tissue destruction, but better evidence is needed to clarify the mutual causal relationship.

In this study, a significant relationship between functional class and PD was observed. Patients with RA having functional impairment may have difficulty maintaining oral hygiene and may be at a high risk for periodontal inflammation. Progressive inflammation of the periodontium leads to alveolar bone resorption. We observed a significant relationship between CAL and MMP-3 level, which indicates joint destruction. MMP-3 level is additionally associated with the Larsen score, which also reflects joint destruction. Furthermore, MMP-3 level was found to be associated with CAL, independent of the functional class. The mechanism by which PD and CAL worsen in patients with RA remains unclear; the mechanism of bone destruction in joints in RA may also affect alveolar bone destruction.
All our study patients were taking medications for RA at the beginning of the study. Kobayashi et al. reported that RA drugs suppress gingival swelling and redness but not alveolar bone resorption.\textsuperscript{24} Therefore, whilst RA drugs suppress systemic bone destruction, the suppression of alveolar bone destruction may be insignificant. However, RA treatments decrease MMP-3 levels and RA severity.\textsuperscript{25,26} In our study, patients with RA having high MMP-3 levels had a high CAL despite RA treatment; therefore, systemic bone destruction due to severe RA may influence alveolar bone destruction. Furthermore, Uemura et al. found that patients with RA having high MMP-3 levels had severe functional impairment,\textsuperscript{13} whilst we found no significant association between the functional class and CAL, although functional class seemed associated with PD. It is thought that dysfunction due to RA causes inability to maintain oral hygiene, leading to gingival inflammation. However, as this study was cross-sectional, it was impossible to identify a causal relationship.

The results of this study represent an intriguing divergence in findings related to PD and CAL in patients with RA. Although PD and CAL are inherently mutually correlated indices, they do not always correspond in clinical response and interpretation.\textsuperscript{27} The results of multivariate analysis in this study suggest that PD and loss of CAL have different mechanisms of progression. Smoking is an important risk factor for periodontitis because it leads to loss of CAL through alveolar bone loss.\textsuperscript{28,29} Multivariate analysis in the present study showed that active smoking was significantly associated with CAL, whilst it was not significantly associated with PD, suggesting that different biological processes are involved in the progression of PD and CAL. Greater alveolar bone loss in the smokers included this study may be caused by smoking itself and not due to RA. Further, the results of the present study showed that higher MMP-3 levels were significantly associated with CAL, but not with PD. It has been reported that high MMP-3 levels in gingival crevicular fluid were significantly associated with worsening of both PD and CAL.\textsuperscript{21} The MMP-3 levels in this study were obtained from serum, and high MMP-3 levels in the systemic bloodstream may have an effect on alveolar bone resorption in addition to the local effects of smoking.

| Table 2 – Association of mean PD and mean CAL with other variables in patients with RA. |
|---------------------------------|---------------------------------|
|                                 | Mean PPD (mm) | P value | Mean CAL (mm) | P value |
| **Age (years old)**            | \(\rho = 0.25\) | .02     | \(\rho = 0.29\) | .01     |
| **Duration of RA treatment (month)** | \(\rho = 0.15\) | .14     | \(\rho = 0.54\) | .07     |
| **MMP-3 (ng/mL)**              | \(\rho = 0.17\) | .10     | \(\rho = 0.21\) | .05     |
| **IL-6 (pg/mL)**               | \(\rho = 0.28\) | .01     | \(\rho = 0.34\) | .001    |
| **TNF-\(\alpha\) (pg/mL)**    | \(\rho = 0.14\) | .17     | \(\rho = 0.16\) | .12     |
| **Sex**                        |                  |         |               |         |
| Male                           | 3.01 (2.60, 3.65) | .16     | 3.12 (2.60, 3.75) | .45     |
| Female                         | 2.75 (2.51, 3.20) |         | 2.88 (2.57, 3.50) |         |
| **Smoking status**             |                  |         |               |         |
| Never smoker                   | 2.75 (2.51, 3.07) | .27     | 2.88 (2.57, 3.36) | .29     |
| Former smoker                  | 2.94 (2.54, 3.60) |         | 3.04 (2.64, 4.02) |         |
| Current smoker                 | 3.16 (2.47, 3.83) |         | 3.23 (2.51, 3.89) |         |
| **Diabetes**                   |                  |         |               |         |
| No                             | 2.83 (2.52, 3.37) | .80     | 2.93 (2.57, 3.64) | .80     |
| Yes                            | 2.89 (2.46, 3.19) |         | 2.97 (2.65, 3.22) |         |
| **Frequency of tooth brushing (times/day)** |                  |         |               |         |
| \(\geq 2\)                     | 2.69 (2.49, 3.08) | .001    | 2.88 (2.54, 3.40) | .01     |
| \(\leq 1\)                     | 3.29 (2.80, 3.98) |         | 3.33 (2.83, 4.03) |         |
| **Periodic dental checkup**    |                  |         |               |         |
| Yes                            | 2.79 (2.50, 3.06) | .15     | 2.87 (2.56, 3.40) | .12     |
| No                             | 2.94 (2.53, 3.66) |         | 3.15 (2.63, 3.91) |         |
| **Number of teeth**            |                  |         |               |         |
| \(\geq 20\)                    | 2.63 (2.48, 2.99) | .001    | 2.70 (2.51, 3.06) | .001    |
| \(\leq 19\)                    | 3.44 (2.91, 4.28) |         | 3.89 (3.18, 4.33) |         |
| **RA severity (class)**        |                  |         |               |         |
| I                              | 2.74 (2.52, 3.19) | .01     | 2.86 (2.55, 3.40) | .04     |
| II                             | 2.69 (2.37, 3.17) |         | 2.99 (2.63, 3.64) |         |
| III, IV                        | 3.40 (2.83, 4.36) |         | 3.41 (2.93, 4.37) |         |
| **RA drugs**                   |                  |         |               |         |
| NSAIDs/DMARDs                  | 2.65 (2.46, 3.23) | .18     | 2.72 (2.47, 3.26) | .07     |
| MTX                            | 2.96 (2.62, 3.65) |         | 3.07 (2.70, 3.67) |         |
| bDMARDs                        | 2.86 (2.51, 3.41) |         | 2.97 (2.63, 3.84) |         |

PD, probing depth; CAL, clinical attachment level; RA, rheumatoid arthritis; MMP, matrix metalloproteinase; IL, interleukin; TNF, tumor necrosis factor; NSAID, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; bDMARDs, biologic disease-modifying antirheumatic drugs.
Table 3 – Univariate and multivariate generalised linear models for mean PD in patients with RA.

| Independent variable                              | Univariate Coefficient (95% CI) | P value | Multivariate Coefficient (95% CI) | P value |
|---------------------------------------------------|---------------------------------|---------|-----------------------------------|---------|
| Age (10 years old)                                | 0.04 (0.01 to 0.07)             | .01     | -0.01 (-0.04 to 0.02)             | .58     |
| Duration of RA treatment (month)                  | 0.000 (-0.001 to 0.001)         | .67     | 0.000 (-0.004 to 0.004)           | .90     |
| MMP-3 (10 ng/mL)                                  | 0.004 (0.03 to 0.06)            | .09     | 0.000 (-0.004 to 0.004)           | .90     |
| IL-6 (pg/mL)                                      | 0.001 (-0.002 to 0.003)         | .64     | 0.001 (-0.004 to 0.004)           | .90     |
| TNF-α (pg/mL)                                     | 9.19e-6 (0.00 to 0.00)          | .96     |                                   |         |
| Sex (ref: male)                                   |                                 |         |                                   |         |
| Female                                            | -0.08 (-0.18 to 0.02)           | .10     | -0.05 (-0.14 to 0.03)             | .21     |
| Smoking status (ref: never smoker)                |                                 |         |                                   |         |
| Former smoker                                     | 0.08 (-0.03 to 0.19)            | .14     | 0.05 (-0.04 to 0.14)              | .24     |
| Current smoker                                    | 0.10 (-0.01 to 0.20)            | .09     | 0.07 (-0.02 to 0.16)              | .12     |
| Diabetes (ref: no)                                |                                 |         |                                   |         |
| Yes                                               | -0.05 (-0.19 to 0.10)           | .53     |                                   |         |
| Frequency of tooth brushing (times/day) (ref: ≥2) | 0.17 (0.07 to 0.27)             | .001    | 0.11 (0.03 to 0.19)               | .01     |
| ≤1                                                |                                 |         |                                   |         |
| Periodic dental checkup (ref: yes)                | 0.09 (0.005 to 0.18)            | .04     | 0.02 (-0.05 to 0.09)              | .53     |
| ≤19                                               | 0.27 (0.19 to 0.35)             | .001    | 0.23 (0.15 to 0.31)               | <.001   |
| RA severity (class) (ref: I)                      |                                 |         |                                   |         |
| II                                                | -0.02 (-0.13 to 0.09)           | .77     | -0.03 (-0.12 to 0.06)             | .54     |
| III, IV                                           | 0.21 (0.09 to 0.32)             | .001    | 0.14 (0.03 to 0.25)               | .02     |
| RA drugs (ref: NSAIDs/DMARDs)                     |                                 |         |                                   |         |
| MTX                                               | 0.08 (-0.02 to 0.18)            | .12     | 0.05 (-0.03 to 0.13)              | .20     |
| bDMARDs                                           | 0.05 (-0.06 to 0.16)            | .39     | -0.02 (-0.10 to 0.08)             | .74     |

CAL, clinical attachment level; RA, rheumatoid arthritis; CI, confidence interval; MMP, matrix metalloproteinase; IL, interleukin; TNF, tumor necrosis factor; ref, reference; NSAID, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; bDMARDs, biologic disease-modifying antirheumatic drugs.

Table 4 – Univariate and multivariate generalised linear models for mean CAL in patients with RA.

| Independent variable                              | Univariate Coefficient (95% CI) | P value | Multivariate Coefficient (95% CI) | P value |
|---------------------------------------------------|---------------------------------|---------|-----------------------------------|---------|
| Age (10 years old)                                | 0.06 (0.02 to 0.09)             | .001    | -0.002 (-0.03 to 0.03)            | .92     |
| Duration of RA treatment (month)                  | -9.15e-5 (0.001 to 0.001)       | .84     |                                   |         |
| MMP-3 (10 ng/mL)                                  | 0.008 (0.003 to 0.014)          | .001    | 0.005 (0.001 to 0.008)            | .02     |
| IL-6 (pg/mL)                                      | 0.000 (-0.002 to 0.003)         | .91     |                                   |         |
| TNF-α (pg/mL)                                     | -8.42e-5 (0.00 to 0.00)         | .62     |                                   |         |
| Sex (ref: male)                                   |                                 |         |                                   |         |
| Female                                            | -0.08 (-0.19 to 0.03)           | .16     | -0.02 (-0.11 to 0.07)             | .62     |
| Smoking status (ref: never smoker)                |                                 |         |                                   |         |
| Former smoker                                     | 0.07 (-0.05 to 0.19)            | .26     | 0.04 (-0.06 to 0.13)              | .44     |
| Current smoker                                    | 0.14 (0.02 to 0.26)             | .03     | 0.13 (0.03 to 0.22)               | .01     |
| Diabetes (ref: no)                                |                                 |         |                                   |         |
| Yes                                               | -0.07 (-0.23 to 0.09)           | .40     |                                   |         |
| Frequency of tooth brushing (times/day) (ref: ≥2) | 0.14 (0.03 to 0.25)             | .01     | 0.06 (-0.03 to 0.14)              | .18     |
| ≤1                                                |                                 |         |                                   |         |
| Periodic dental checkup (ref: yes)                | 0.09 (-0.003 to 0.19)           | .06     | 0.03 (-0.04 to 0.11)              | .35     |
| ≤19                                               | 0.34 (0.26 to 0.42)             | .001    | 0.30 (0.21 to 0.38)               | <.001   |
| RA severity (class) (ref: I)                      |                                 |         |                                   |         |
| II                                                | 0.06 (-0.06 to 0.19)            | .34     | 0.03 (-0.07 to 0.13)              | .52     |
| III, IV                                           | 0.18 (0.04 to 0.31)             | .01     | 0.05 (-0.07 to 0.17)              | .44     |
| RA drugs (ref: NSAIDs/DMARDs)                     |                                 |         |                                   |         |
| MTX                                               | 0.10 (-0.02 to 0.21)            | .10     | 0.03 (-0.06 to 0.11)              | .52     |
| bDMARDs                                           | 0.10 (-0.03 to 0.22)            | .13     | 0.00 (-0.10 to 0.10)              | .99     |

PD, probing depth; RA, rheumatoid arthritis; CI, confidence interval; MMP, matrix metalloproteinase; IL, interleukin; TNF, tumor necrosis factor; ref, reference; NSAID, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; bDMARDs, biologic disease-modifying antirheumatic drugs.
In this study, no significant relationship between IL-6 and TNF-α (serum markers of the onset and progression of periodontitis) levels and periodontal status (PD and CAL) was observed. Patients with RA taking a DMARD IL-6 inhibitor showed not only decreased RA disease activity but also improved periodontal status.30 Periodontal status and RA disease activity also decreased after treatment with a TNF-α inhibitor.24 It is thought that whilst IL-6 and TNF-α levels are known to be associated with periodontitis, the levels of inflammatory cytokines in our study patients might have decreased due to the RA treatment during our study period.

This study had several limitations. Due to a cross-sectional design, it was impossible to determine causal associations amongst the serum data, RA severity, and periodontitis. It may be possible that older patients with poorer functional status are unable to perform appropriate oral hygiene. As we targeted a limited number of patients with RA at a single clinic, the distribution of serum data and RA severity may have differed from that of the general population. Furthermore, we did not include patients with severe RA who required hospitalisation. Although MMP-3 level is an index used to evaluate RA disease activity, more indices should be used in future studies to evaluate the pathogenesis of RA in detail. We used the Steinbrocker index as a method to assess the severity of RA, but a more precise assessment index such as the Health Assessment Questionnaire-Disability Index could be used. It was impossible to consider the impact of RA medication on periodontitis and altered serum levels because the patients were already under treatment. Further longitudinal studies must be conducted to clarify the relationship between RA and periodontal status to identify the changes in RA severity and serum data due to RA treatment.

Functional impairment due to RA may affect PD, and high serum levels of MMP-3 may affect the CAL. Dental interventions to reduce periodontal tissue inflammation may be necessary in patients with RA having functional impairment. The inhibition of joint destruction in severe RA may reduce the destruction of periodontal tissue. Further investigations must be performed to clarify this relationship.

**Conflict of interest**

None disclosed.

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**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.identj.2022.01.002.

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