# Serum and synovial matrix metalloproteinases 1 and 3 in patients with early rheumatoid arthritis: potentially prospective biomarkers of ultrasonographic joint damage and disease activity

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**Background**
Matrix metalloproteinase-1 (MMP-1) and MMP-3 play important roles in the pathogenesis of rheumatoid arthritis (RA) and have been suggested as markers of disease activity and joint damage.
Objective The aim was to analyze the clinical significance of MMP-1 and MMP-3 in relation to markers of disease activity and degree of joint destruction in patients with early RA at presentation and after 6 months.
**Patients and methods**
Baseline levels of serum MMP-1 and MMP-3 were assessed in 50 patients with early RA (symptoms <1 year), 20 patients with osteoarthritis (OA), and 20 age-matched and sex-matched healthy controls. Serum MPP-1 and MPP-3 were correlated with disease activity markers [erythrocyte sedimentation rate (ESR), C-reactive protein, disease activity score 28–ESR] and radiographic joint damage using simple erosion narrowing score and musculoskeletal ultrasound of wrist and hand joints. Baseline synovial fluid MMP-1 and MMP-3 levels were evaluated for 20 patients indicated for arthrocentesis.
**Results**
Baseline serum MMP-1 and MMP-3 were significantly higher in RA group versus OA group and healthy controls ($P<0.001$). Synovial MMP-1 and MMP-3 levels were significantly higher in RA versus OA group. Serum MMP-1 and MMP-3 levels significantly correlated with rheumatoid factor titers, anticyclic citrullinated peptide, disease activity score 28-ESR score, joint erosions, and Outcome Measures in Rheumatology score of synovitis and Doppler signals. Serum MMP-1 did not correlate with C-reactive protein, but significantly correlated with the number of erosions at presentation and on follow-up. The number of patients with erosions and the number of erosions per patient increased after 6 months and correlated with serum MMP-1 and MMP-3. The best cutoff values of serum MMP-1 and MMP-3 to discriminate between RA and healthy controls were greater than 20 and greater than 50 ng/ml, respectively.
**Conclusion**
Elevated serum levels of MMP-1 and MMP-3 can be used as an indicator of disease activity in patients with early RA and can reflect the degree of joint damage and correlate with the number of new joint erosions.

**Keywords:**
matrix metalloproteinase-1, matrix metalloproteinase-3, Outcome Measures in Rheumatology score, rheumatoid arthritis

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## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovitis and progressive joint destruction leading to deterioration in functional capacity, work disability, and reduced quality of life [1]. The progress of joint erosions is unpredictable and may continue despite active suppression of inflammation [2]. However, RA is considered a potentially curable disease especially during its early stages if it is appropriately treated [3].

Common disease activity indicators are nonspecific for arthritis. Novel biomarkers have been developed for predicting structural destruction and progression in RA [4]. It has been proposed that the pathophysiologic mechanisms of synovial inflammation and articular erosion may be somewhat different [5].

Matrix metalloproteinases (MMPs) are a group of extracellular enzymes. In normal homeostasis, they have a key role in tissue remodelling, but in disease states, they cause tissue destruction [6]. Both MMP-1 andMMP-3 play important roles in the destruction and degradation of bone and cartilage [7]. They are locally produced by synovial fibroblasts and chondrocytes in the inflamed joint, activated as a result of cytokine-mediated stimulation, and released into the blood stream; that is why they could represent a direct reflection of joint inflammation and destruction in rheumatic diseases especially RA [8]. In a previous study on Egyptian patients with systemic lupus erythematosus, serum MMP-3 was found to be high and associated with arthritis, nephritis, disease activity, and damage [9]. Cartilage oligomeric matrix protein, a substrate for MMPs [10], was elevated in the serum and synovial fluid (SF) of Egyptian patients with RA [11] and also pointed to subclinical RA in patients with systemic sclerosis [12].

Serum and SF MMP-3 levels are usually higher than MMP-1. In addition, MMP-3 is more widely distributed in the synovial membrane than MMP-1. These differences propose different pathophysiologic actions for each of them [13].

The need for easy tools that help early prediction of RA course is a must, because joint erosions may continue despite effective suppression of synovitis [2]. From this point of view, we aimed to evaluate serum and SF levels of MMP-1 and MMP-3 in patients with early RA, and to study their relation to disease activity and degree of ultrasonographic joint destruction during a 6-month period.

## Patients and methods

This case–control observational prospective study included 50 patients with RA with early disease onset (<1 year duration), fulfilling the 2010 ACR/EULAR classification criteria [14]. The control groups included 20 patients with knee osteoarthritis diagnosed according to the corresponding ACR classification criteria [15] and 20 age-matched and sex-matched healthy volunteers. All patients were recruited from Rheumatology Outpatient Clinic and inpatients admitted to Internal Medicine Department, Rheumatology unit at Ain Shams University Hospitals. Patients with malignancy, connective tissue diseases, and autoimmune diseases causing inflammatory arthritis other than RA were excluded. Informed consents were obtained from all patients and controls for inclusion in the study. The study was approved by Ain Shams Medical Ethical Committee.

All patients with RA were subjected to full clinical assessment, including complete history taking, disease duration, tender and/or swollen joint counts, and assessment of disease activity using the disease activity score in 28 joints (DAS28) [16]. Remission was considered with a DAS28 (≤2.6, low activity was considered at a DAS28 between >2.6 and ≤3.2; moderate between >3.2 and ≤5.1, and high activity >5.1). Five milliliter of blood was withdrawn at baseline. The erythrocyte sedimentation rate (ESR/h) was assessed by Westergren method, and C-reactive protein (CRP) and rheumatoid factor (RF) titers were measured by rapid latex agglutination tests (AVITEX CRP/RF kits: Omega Diagnostics Ltd. Omega House, Scotland, UK), with a detection limit for CRP=6 mg/l and for RF=8 IU/ml. Anticyclic citrullinated peptide (anti-CCP) antibodies titer was also assessed by enzyme-linked immunosorbent assay (ELISA) (CCP3 IgG kit; Inova Diagnostics, San Diego, California, USA). Serum and SF samples were stored in aliquots at −70°C till assay. ESR and CRP were re-assessed after 6 months.

SF was aspirated from participants eligible for knee arthrocentesis (16 RA and four OA patients) using the same method.

Serum and synovial MMP-1 and MMP-3 were assessed using double-antibody sandwich ELISA technique (Origene System, Beijing, China) at baseline, and the serum level was reassessed only for patients with RA after 6 months. Samples or standards containing MMP-1/MMP-3 were captured between two antibodies: the first was fixed to the inner wall of ELISA plate wells and the second was labeled with biotin to which horse radish peroxidase was combined forming immune complex. Addition of the 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate solution initiates a kinetic reaction which leads to color development that can be measured spectrophotometrically at a wavelength of 450 nm.

Radiological assessment was done at baseline and after 6 months by one observer who was blind to patients' clinical details. Radiological joint damage was assessed in RA by plain radiography (posteroanterior view) of both hands and feet in the posteroanterior view using simple erosion narrowing score (SENS) [17] and of knee joints in OA with severity assessed by the Kellgren and Lawrence system (K/l) [18]. Logiq P7 ultrasound device (GE, Yorba Linda, California, USA) was used for musculoskeletal ultrasound of metacarpophalangeal

(MCP), proximal interphalangeal, and wrist joints, with assessment of synovitis in B Mode (gray-scale) and Color Doppler Flow using Outcome Measures in Rheumatology (OMERACT) semiquantitative scale to assess effusion, synovial hypertrophy, Doppler flow, and erosions [19]. The probe was linear and high resolution (7.5–12 MHz).

### Statistical analysis

Data were analyzed using Statistical Program for Social Sciences (SPSS, IBM, Armonk, New York,United States) version 20.0. The quantitative data were expressed as mean, SD, and range, whereas qualitative data were expressed as frequency and percentages. $\chi^2$-Test was used to compare qualitative variables. Differences between the two groups were assessed via *t*-test or Mann–Whitney *U*-test, as appropriate. Analysis of variance test was used when comparing between more than two means in quantitative data. Correlations among variables were assessed using Spearman's correlation co-efficient rank. Receiver operator characteristic curve analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity. The confidence interval was set to 95%, and the *P* value less than 0.05 was considered significant.

## Results

The patients with RA comprised 45 (90%) females and five (10%) males, with a mean age of 34.5±5.8 years (20–45 years), and disease duration was 7.3±3.38 months (2–11 months). The OA control patients comprised 17 (85%) females and three (15%) males, with a mean age of 38.5±4.31 years (27–48 years). The healthy controls comprised 16 (80%) females and four (20%) males, with a mean age of 33.0±5.5 years (25–42 years). Demographic, clinical, and serological characteristics of patients with early RA are listed in Table 1. Ultrasound assessment of wrists, MCP, and proximal interphalangeal joints in patients with RA according to the OMERACT score and erosions is presented in Table 2.

**Table 1 Demographic, clinical, and serological characteristics of patients with early rheumatoid arthritis at baseline**

| Parameters | Patients with early RA (*n*=50) [mean±SD (range)] or [*n* (%)] |
|---|---|
| Sex: female : male | 45/5 |
| Age (years) | 34.5±5.8 (20–45) |
| Disease duration (months) | 7.3±3.38 (2–11) |
| ESR (mm/h) | 44.2±23.5 (12–100) |
| CRP (mg/l) | 41.15±24.68 (10–96) |
| RF (IU/ml) | 55.05±70.26 (11–280) |
| Anti-CCP (IU/ml) | 116.25±115.3 (14–412) |
| DAS28 | 4.85±1.57 (2.38–7.8) |
| Remission | 4 (8) |
| Low activity | 6 (12) |
| Moderate activity | 17 (34) |
| High activity | 23 (46) |
| SENS score | 15.63±7.16 (4–34) |
| Drug therapy | |
| Steroids | 35 (70) |
| Methotrexate | 35 (70) |
| Azathioprine | 2 (4) |
| Leflunomide | 7 (14) |
| Hydroxychloroquine | 38 (76) |
| Sulfasalazine | 3 (6) |
| Biological therapy | 0 (0) |

Anti CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SENS, simple erosion narrowing score.

**Table 2 Ultrasound assessment of wrists, metacarpophalangeal, and proximal interphalangeal joints in patients with early rheumatoid arthritis by Outcome Measures in Rheumatology score and erosions**

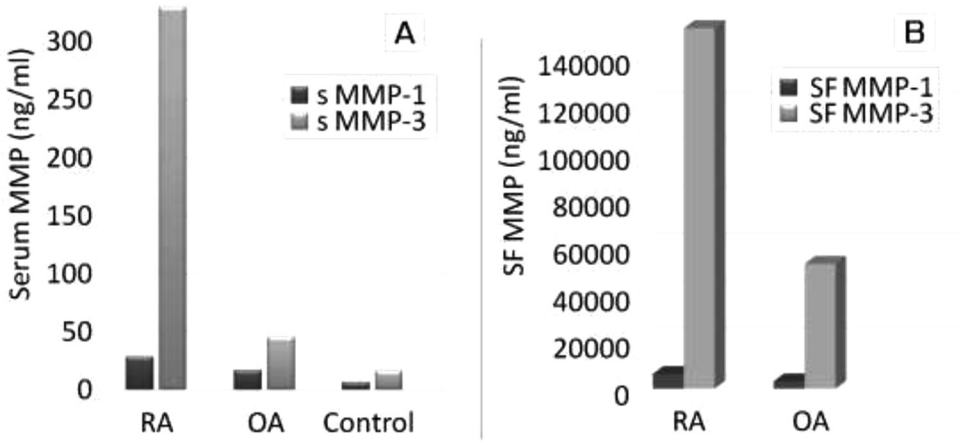
| Ultrasound variables OMERACT score | Patients with early RA (*n*=50) |
|---|---|
| B Mode (synovitis and effusion) | |
| Grade 1 | 27 (54) |
| Grade 2 | 23 (46) |
| Grade 3 | 0 (0) |
| Power Doppler signals | 24 (48) |
| Grade 1 | 6 (12) |
| Grade 2 | 18 (36) |
| Grade 3 | 0 (0) |
| Erosions | 8 (16) |

OMERACT, Outcome Measures in Rheumatology; RA, rheumatoid arthritis.

At presentation, mean serum levels of both MMPs were significantly higher in patients with RA than in patients with OA and healthy controls. Mean serum levels of MMP-3 were consistently higher than those of MMP-1 in all patients. The MMP-1 level of RA was 28.2±8.1 ng/ml (4.4–45.7 ng/ml) vs 16.6±3.93 ng/ml (1.0–24.61 ng/ml) for OA and 6.2 ±0.34 ng/ml (0.50–9.35 ng/ml) for the healthy controls ($P<0.001$). Serum MMP-3 level in patients with RA was 329.63±182.15 ng/ml (47.14–520.60 ng/ml) vs 45.15±34.44 ng/ml (6.50–65.45 ng/ml) for OA and 15.85±11.14 ng/ml (2.53–28.0 ng/ml) for control ($P<0.001$). There were significant differences between serum levels of both MMP-1 and MMP-3, being higher for OA group versus healthy controls ($P=0.01$) (Fig. 1).

SF MMP-1 and MMP-3 levels were measured only for 20 patients (16 RA and four OA patients). Levels of MMP-1 and MMP-3 were significantly higher in SF

**Figure 1**




Serum (A) and synovial fluid (B) MMP-1 and MMP3 levels (ng/ml) in RA, OA and healthy control groups.

than in serum ($P$=0.0001 for RA and OA patients). MMP-3 showed significantly higher SF levels than MMP-1. Both were significantly higher in patients with RA (MMP-1=6200±1200 ng/ml and MMP-3=153 000±8600.14 ng/ml) than in OA (MMP-1=3100±350.15 ng/ml, and MMP-3=53 000 ±3900.78 ng/ml) ($P$=0.035) (Fig. 1).

The serum MMP-1 significantly correlated with SF levels of MMP-1 ($r$=0.799, $P$=0.026), and serum MMP-3 correlated with SF MMP-3 levels ($r$=0.89, $P$=0.043). No significant correlation was found between SF levels of MMP-1 and MMP-3. Serum MMP-1 and MMP-3 significantly correlated with the DAS28 ($P$<0.05 and <0.001, respectively). Serum MMP-1 was significantly higher in patients with RA with US-detected erosions compared with nonerosive ($P$<0.001) (Table 3). The CRP significantly correlated with serum MMP-3 but not with MMP-1 ($P$<0.001 and 0.32, respectively). US B-mode (assessing synovitis and effusion) and OMERACT score showed similar correlations. A significant correlation was established between the number of US joint erosions at presentation and serum levels of MMP-1 ($P$<0.001) (Table 4). Baseline serum levels of MMP-1 and MMP-3 in RA significantly correlated with RF titers, anti-CCP titers, and DAS28 (Table 4).

After 6 months, only patients with RA were re-evaluated. All continued treatment with disease-modifying antirheumatic drugs, with occasional steroid dose (7.5–20 mg/day). Six (12%) patients achieved remission at follow-up. RA activity was low in 18% (nine patients), moderate in 50% (25 patients), and 10 (20%) patients continued to have severe activity. Serum MMP-1 and MMP-3 values tended to be lower than the baseline levels (16.9±7.6 and 189.40±62.1 ng/ml, respectively) and showed no significant differences in correlations with clinical parameters (Table 4). Sustained elevations of serum MMP-3 levels correlated with CRP levels ($r$=0.799, $P$<0.0001) and with the number of new US bony erosions ($r$=0.421, $P$=0.03). Serum MMP-1 significantly correlated with the number of new joint erosions ($r$=0.226, $P$=0.04 for SENS score and $r$=0.497, $P$<0.001 for US erosions) (Table 4).

Receiver operator characteristics curve showed the best cutoff value of serum MMP-1 to differentiate RA from healthy individuals was greater than 20 ng/ml (sensitivity 95%, specificity 100%), and from OA was greater than 45 ng/ml (90% sensitivity and 89% specificity). For serum MMP3, the best cutoff value to differentiate between RA and healthy controls was greater than 50 ng/ml (sensitivity of 95%, specificity 100%) and between RA and OA was greater than 120 ng/ml (sensitivity 90% and specificity 100%) (Table 5).

## Discussion

RA is an inflammatory polyarthritis that can lead to joint destruction through erosions of cartilage and bone. The pathogenesis of RA is complex, involving multiple genetic, environmental, and immunologic factors leading to disease expression [20]. MMPs are a group of proteolytic enzymes playing an essential role in destruction of all the extracellular matrix components. MMP-1 and MMP-3 are thought to have a special role in joint ruin in RA. It has been suggested that their serum levels correlate with levels produced by the synovium, and thus reflect the level of inflammation and activity of rheumatoid synovitis

**Table 3 Relation of serum matrix metalloproteinase (MMP-1 and MMP-3) levels in patients with rheumatoid arthritis to disease activity and erosive-rheumatoid arthritis disease**

| Parameters | Serum MMP (ng/ml) in patients with RA (*n*=50) [mean±SD (range)] | |
|---|---|---|
| | MMP-1 | MMP-3 |
| Disease activity | | |
| Remission (*n*=4) | 9.1±4.7 (10–15) | 88.8±55.1 (40–170) |
| Low (*n*=6) | 10.5±5.3 (11–17) | 120±62.2 (30–170) |
| Moderate (*n*=17) | 19.9±8.1 (15–36) | 276.7±108.4 (130–450) |
| High (*n*=23) | 34.3±10.1 (26–63) | 451.5±146.1 (250–750) |
| *P* value | <**0.05** | <**0.001** |
| Erosions on US | | |
| Erosive-RA (*n*=8) | 41.32±4.4 (7.42–45.71) | 433±122.1 (186.97–520.60) |
| Nonerosive (*n*=42) | 18.36±4.71 (4.40–26.52) | 273.6±130.4 (47.1–340.61) |
| *P* value | <**0.001** | <**0.05** |

MMP, matrix metalloproteinase; RA, rheumatoid arthritis; US, ultrasound. Bold values are significant at $P<0.05$.

**Table 4 Correlations between serum matrix metalloproteinase (MMP-1 and MMP-3) levels with different disease parameters in patients with rheumatoid arthritis at presentation and after 6 months**

| Parameters (p) | Serum MMP (ng/ml) in patients with RA (*n*=50) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | | | | After 6 months | | | |
| | MMP1 | | MMP3 | | MMP1 | | MMP3 | |
| Disease duration | –0.02 | (0.76) | –0.004 | (0.98) | – | – | – | – |
| Rheumatoid factor | 0.45 | (0.02) | 0.39 | (**0.01**) | – | – | – | – |
| Anti-CCP | 0.5 | (<**0.001**) | 0.54 | (<**0.001**) | – | – | – | – |
| ESR | –0.2 | (0.32) | –0.19 | (**0.02**) | –0.12 | (0.42) | 0.48 | (**0.001**) |
| C-reactive protein | –0.26 | (0. 21) | 0.77 | (<**0.001**) | 0.21 | (0. 33) | 0.8 | (<**0.001**) |
| DAS-28 | 0.79 | (<**0.001**) | 0.81 | (<**0.001**) | 0.67 | (<**0.001**) | 0.92 | (<**0.001**) |
| SENS score | 0.28 | (0.06) | 0.28 | (0.07) | 0.23 | (**0.04**) | 0.22 | (<0.07) |
| US (synovitis/effusion) | 0.31 | (0.06) | 0.57 | (<**0.001**) | 0.32 | (0.07) | 0.62 | (<**0.001**) |
| Doppler signals | 0.33 | (0.09) | 0.63 | (<**0.0001**) | 0.42 | (0.08) | 0.57 | (<**0.001**) |
| Number of US erosions | 0.54 | (<**0.001**) | 0.22 | (0.1) | 0.5 | (<**0.001**) | 0.42 | (**0.03**) |
| Synovial MMP1 (*n*=20) | 0.8 | (**0.03**) | 0.32 | (0.21) | – | – | – | – |
| Synovial MMP3 (*n*=20) | 0.3 | (0.13) | 0.89 | (**0.04**) | | | | |

anti-CCP, Anti-cyclic citrullinated peptide; ESR, Erythrocyte sedimentation rate; MMP, matrix metalloproteinase; RA, Rheumatoid arthritis; SENS, simple erosion narrowing score. Bold values are significant at $P<0.05$.

[3,13]. The pathophysiologic mechanisms of joint inflammation and bony erosion may be partially independent; each might be determined by a principal cytokine or protease in different disease conditions [5].

This study was designed to investigate the relations of serum levels of MMP-1 and MMP-3 to disease activity and the degree of joint damage in patients with early RA. Serum MMP-1 and MMP-3 were significantly higher in patients with early RA compared with OA and healthy controls. Significantly higher serum levels of these metalloproteinases were also reported in RA compared with OA [6,13,21–24]. This could be explained by abundant expression of MMP-1 and MMP-3 by articular synovial cells, fibroblasts, and chondrocytes in inflamed rheumatoid synovium, and then they are released into the blood stream. Therefore, their serum concentrations may be considered as alternative noninvasive biomarkers of RA activity in clinical practice [13,25,26].

**Table 5 Cutoff values of matrix metalloproteinase (MMP-1 and MMP-3) to discriminate rheumatoid arthritis from osteoarthritis and healthy controls**

| Items | Cutoff values of matrix metalloproteinase to discriminate RA from OA and control (*n*=50) | | | |
|---|---|---|---|---|
| | MMP-1 | | MMP-3 | |
| | OA | Control | OA | Control |
| Cut-off (ng/ml) | >45 | >20 | >120 | >50 |
| Sensitivity (%) | 90 | 95 | 90 | 95 |
| Specificity (%) | 89 | 100 | 100 | 100 |

MMP, matrix metalloproteinase; OA, osteoarthritis; RA, rheumatoid arthritis.

SF levels of MMP-1 and MMP-3 reflect local joint involvement and both pass through the blood-synovial barrier [13,25,26]. In this study, few SF samples were assessed for MMP-1 and MMP-3 levels (16 RA and

four OA patients). SF MMP-1 and MMP-3 levels significantly correlated with their corresponding serum levels, and each was higher in RA versus OA. Limited studies [13,27] assessed SF metalloproteinases and agreed with these findings.

In agreement with previous literatures [8,24,27–30], serum MMP-3 significantly correlated with RA disease activity. Reports from different ethnic populations showed the same correlations in patients with RA: in Chinese [31], Japanese [32], and Egyptians patients with RA [30]. All clearly state that MMP-3 is a consistent synovial-derived inflammatory marker and can serve as a potential biomarker of RA synovitis in early RA disease activity. Serum MMP-1 showed similar but less significant correlation, in agreement with one study [13].

A striking observation in this study is that serum levels of MMP-1 correlated strongly with US-detected joint erosions (a parameter of joint damage) but not with CRP, whereas serum MMP-3 correlated strongly with CRP. The same correlations continued after 6 months of follow-up. In addition, serum MMP-3 showed new significant correlation with the newly developed US bone erosions on follow-up. Overall, 50% of patients with RA continued moderate activity and 20% had severe activity on follow-up. Ma *et al.* [33] proved that MMP-3 predicts 1-year radiographic progression in patients with RA. This proposes the possibility of a separation of the mechanisms causing inflammation and joint damage in RA. Additionally, MMP-3-induced aggrecan disruption may be an important introductory step to permit MMP-1 to access collagen fibrils [9]. Both metalloproteinases may act differently but have synergistic effects on bony and cartilaginous ruin.

No significant correlations were reported between serum MMP-1 or MMP-3 and total SENS score at baseline. This is likely owing to the higher sensitivity of US to detect bony erosions than conventional radiography, especially in early patients with RA [13,34]. Few prior studies reported similar correlations of MMP-1 and/or MMP-3 with US erosion scores in patients with RA [13,21,34]. Furthermore, serum MMP-1 and MMP-3 levels significantly correlated with anti-CCP and RF, which indicated a more aggressive RA disease. Cunnane *et al.* and Galil *et al.* [13,35] reported similar observations. In contrast, Kobayashi *et al.* [26] reported no correlations with anti-CCP titers in patients with drug-naive early RA.

The best cutoff values of MMP-1 that discriminate between patients with RA and OA and healthy controls were greater than 20 and greater than 45 ng/ml, respectively, with 95% sensitivity and 100% specificity for controls and 90% sensitivity and 89% specificity patients with for OA. However, the best cutoff values of MMP-3 that discriminate between patients with RA and OA and healthy controls were 50 and greater than 120 ng/ml, respectively (95% sensitivity and 100% specificity for controls and 90% sensitivity and100% specificity for OA). Shinozaki *et al.* [36] reported that serum MMP-3 can differentiate patients with RA from other patients with arthritis at a cutoff value of 59.7 ng/ml. In contrast, Ali *et al.* [25] defined the best cutoff point at 4.1 ng/ml with 90% sensitivity and 90% specificity. Galil *et al* [35] confirmed that elevated serum MMP-3 with a cutoff value of 155 ng/ml is an applicable predictor for 1-year radiographic progression in RA. These differences may be owing to the use of different ELISA kits with different detection limits, different sample size, and differences in ethnicity of patients with RA. To the best of our knowledge, no prior reports mentioned a cutoff value for MMP-1 for RA.

The main limitations of this study were the small sample size (especially SF samples) and being a single-center study.

## Conclusion

In conclusion, serum and SF levels of MMP-1 and MMP-3 are elevated in patients with early RA. Serum MMP-3 levels are mainly related to joint inflammation and activity, whereas serum levels of MMP-1 are more related to the formation of joint erosions. On follow-up of patients with RA, MMP-3 correlates with new formation of US bone erosions. Further studies with longer follow-up are recommend, and future treatments that suppress the activity of MMP-1 and MMP-3 may limit the development of new joint erosions and improve the long-term functional outcome of patients with RA.

### Conflicts of interest

There are no conflicts of interest.

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