International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2014

ORIGINAL ARTICLE

Baseline serum level of matrix metalloproteinase-3 as a biomarker of progressive joint damage in rheumatoid arthritis patients

Sahar Mahfouz Abdel GALIL,[1,4] Abeer Mohamed EL-SHAFEY,[1] Hoda A. HAGRASS,[2] Faten FAWZY[3] and Ahmed El SAMMAK[3]

[1]*Departments of Rheumatology & Rehabilitation,* [2]*Clinical Pathology,* [3]*Radiology, Faculty of Medicine, Zagazig University, Zagazig, Egypt, and* [4]*Medicine Department, Faculty of Medicine, Umm Al-Qura University, Holly Markkah, Saudi Arabia*

Abstract

Aim: Matrix metalloproteinase-3 (MMP-3) plays a pivotal role in the destruction of bone and degradation of cartilage components in rheumatoid arthritis (RA). We aimed in this study to analyze the relation between baseline levels of MMP-3 and the progression of joint damage in RA.

Methods: Eighty-one untreated RA patients with joint symptoms for <1 year were evaluated at baseline and after 12 months as regards erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and plain X-ray of both hands and wrists. Baseline levels of MMP-3 were measured by enzyme-linked immunosorbent assay and magnetic resonance imaging (MRI) of hands/wrists was performed. Disease Activity Score (DAS28) and Health Assessment Questionnaire (HAQ) were performed at baseline evaluation and after 12 months.

Results: The baseline MMP-3 levels were significantly higher in the high-progression group compared with the low-progression one (95.75 ± 42.84 *vs.* 50.45 ± 12.83, $P < 0.001$). There was a positive correlation between baseline levels of MMP-3 and MRI erosion score and other baseline clinical parameters, except for HAQ and the van der Heijde modification of the Sharp scoring system (SvdH) scores, while after 12 months, there were high positive correlations between MMP-3 and SvdH score, as well as all parameters except for ESR.

Conclusion: Serum baseline levels of MMP-3 are strong prognostic markers of disease activity, and act well as an early predictor of progressive joint damage in recent-onset RA disease.

Key words: matrix metalloproteinase-3, prognostic marker, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology, characterized by chronic synovitis, tissue degradation and joint deformation.[1]

Correspondence: Sahar Mahfouz Abdel Galil, Department of Rheumatology & Rehabilitation, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
Email: dr_saharmahfouz@yahoo.com

The disease may progress in spite of decreased inflammatory activity and erosions may develop in patients without clinical signs of significant inflammation.[1,2]

It is important to identify patients with progressive, destructive disease from those with milder forms of the disease, for whom aggressive therapy may be less appropriate.[3] Sometimes traditional markers of outcome are unhelpful in patients who do not have traditional bad prognostic features (female sex, older age, rheumatoid factor [RF], anticyclic citrullinated peptide antibody

[anti-CCP] seropositivity, raised C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) and still have progressive, damaging arthritis.[4]

Matrix metalloproteinases (MMPs) are a group of extracellular enzymes playing a key role in normal and pathological tissue remodeling and have the ability to degrade all components of the extracellular matrix.[5]

MMP-3 plays a pivotal role in the destruction of bone and degradation of various components of cartilage, such as proteoglycans, gelatins, laminin, fibronectin and collagen types III, IV, IX and X, in RA.[2] Also, it activates pro-MMPs 1, 7, 8, 9 and 13,[6] which are capable of degrading intact collagen type II, into characteristic J and L fragments.[5]

Methods of objectively assessing, quantifying, and predicting joint damage in RA remain inadequate. Imaging provides a largely historical view of joint damage that has already occurred. Genetic and antibody markers are not dynamic, and serologic measures such as ESR or CRP are not specific to joint disease.[3]

Magnetic resonance imaging (MRI) extends visualization of disease effects beyond cortical bone to include processes in synovium, peri-articular soft tissues and the marrow space.[7] MRI is more sensitive in detecting erosive changes in RA earlier than conventional radiography,[8] making it a standard reference for early detection of minute erosions in RA.[9]

Depending on the fact that joint damage judged on conventional radiography occurs within the first 2 years of RA and early detection of erosions is closely related to poor outcome,[10] then the need for easy tools for early prediction of disease course is a must. From this point of view, we aimed in our study to investigate the usefulness of the serum concentration of MMP-3, not only as an indicator of disease activity,[2,11] but also as an early predictor of joint destruction in cases with recent-onset RA, confirming this role by correlating its baseline level with MRI findings.

METHODS

Subjects

In this prospective study, 81 Egyptian non-smoker RA female patients were enrolled between May 2010 and November 2011, from the out-patient clinics of Rheumatology and Rehabilitation Departments, Zagazig University Hospitals, Egypt. They were diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA.[12]

The research protocol was approved by the Zagazig University ethics committee. All study participants provided written informed signed consent.

Patients were complaining from arthritis for a few months (<12 months) before being enrolled in our study. They did not receive any specific treatments for RA previously, and they were disease-modifying antrheumatic drug (DMARD)-naïve at study entry. They started a combination therapy of leflunomide, hydroxychloroquine and a full dose of any non-steroidal anti-inflammatory drugs after entry in the study. They did not receive methotrexate or biological DMARDs during the period of follow-up, as these drugs may affect the serum level of MMP-3.[2,13]

Clinical and laboratory evaluation

All participants were subjected to thorough clinical evaluation by history taking and physical examination, with particular focus on the joints involved. Routine biochemical blood analysis for ESR, CRP, RF titers (Integra; Roche Diagnostics GmbH, Mannheim, Germany) and anti-CCP antibody titers (Cobas, Roche Diagnostics GmbH) were measured at the start of the study and after 12 months of follow-up. Serum baseline (at the beginning of the study) levels of MMP-3 were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) (Ray Biotech, Norcross, GA, USA). This assay detects both pro- and active enzyme levels.

Disease activity was determined by using the 28-joint Disease Activity Score (DAS-28) and categorized as low (<3.2), moderate (between 3.2 and 5.1), or high activity (>5.1).[14] Functional disabilities of all patients were determined by using the Health Assessment Questionnaire (HAQ).[15] Both were done at baseline and after 12 months.

Radiological evaluation

Postero-anterior plain radiographs of the hands/wrists were obtained at baseline and after 12 months of follow-up then scored for the presence of and change in erosions by using the van der Heijde modification of the Sharp scoring system (SvdH).[16] The maximal possible score is 160 for imaged joints of both hands (80 for each hand).

The baseline SvdH was subtracted from that after 12 months for each patient and a value representing radiographic progression was obtained, and named as delta SvdH. Patients were classified into low- and high-progression groups based on the median of change in SvdH score (median of delta SvdH). The median of

delta SvdH = 5 and accordingly, patients whose delta SvdH <5 were allocated as the low-progression group while the high-progression group were those with delta SvdH ≥5.

Baseline MRI films for both hands/wrists of all patients were performed. They were performed on a 1.5-T scanner (Achieva; Philips, UK/Ireland.) using a receiver coil designed for the hand. The imaging field of view was 10 cm. T1-weighted spin-echo imaging was performed in the axial and coronal planes without fat saturation, before and after administration of gadopentetatedimeglumine at a dose of 0.1 mmol/kg. Images were acquired at a 1-mm slice thickness in an interleaved, contiguous (no gap) fashion (time to repeat [TR] range/echo time [TE], 600–650/11; matrix = 256 × 256; average = 1). Fast spin-echo T2-weighted imaging was performed in axial and coronal planes using frequency-selective pre-saturation to suppress signal from fat (TR range/TEeff, 2500–2800/68; echo train length, 4; matrix, 256 × 256; average, 2). Images were acquired with a 3-mm slice thickness and a 1-mm interslice gap.

Bones of all hand joints were assessed separately for erosions on MRI according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI scoring system.[17] By this method, erosions are scored on a scale from 0 to 10 based on the proportion of eroded bone compared to the 'assessed bone volume' judged on all available images: grade 0 = no erosion; 1 = 1–10% of the bone eroded; 2 = 11–20% of the bone eroded; 3 = 21–30% of the bone eroded, and so on.

All radiographs (X-ray and MRI films) were evaluated randomly by two experienced musculoskeletal radiologists who were blinded to all patient clinical data and to the chronological order of radiographs being evaluated.

Statistical analysis

Data of this study were presented by the mean value, range and standard deviation for all parameters, except the percentages of changes of clinical and laboratory parameters were presented by the median and range. Student's *t*-test was used for parametric variables, while Mann–Whitney *U*-test was used for non-parametric variables. We assessed the correlation between MMP3 biomarkers and other diagnostic parameters (CRP, ESR, RF, anti-CCP, DAS, HAQ, X-ray and MRI) at baseline and after 12 months follow-up by using Spearman's rank correlation. The median percentage of changes in clinical and laboratory data in the studied groups of patients after 12 months was analyzed by using the Mann–Whitney *U*-test. The predictive accuracy of MMP-3 association with severity of RA was estimated by the receiver operating characteristic (ROC) curve analysis, area under curve (AUC) with 95% confidence intervals (CIs). We set the cutoff value for MMP-3 level as a biomarker of progressive joint destruction. Linear regression analysis was used to identify the prediction model of joint damage. All variables were entered in this model. All statistical analyses were performed by SPSS version 18 (SPSS Inc., Chicago, IL, USA), and statistical significance was defined as $P < 0.05$.[18]

RESULTS

The baseline demographic, clinical and radiological characteristics of all patients enrolled in our study are shown in (Table 1). They were all female patients with mean age of 35.17 ± 5.88 years and disease duration of 6.82 ± 3.15 months. All patients were RF and anti-CCP positive. There were 14/81 patients free from erosion by X-ray, while five of these 14 patients showed erosions by MRI.

Grouping of patients included in the study

After 12 months of follow-up, the 81 RA patients were divided into two subgroups, according to the median of delta SvdH score; the high-progression group (n = 59, delta SvdH ≥ 5) and low-progression group (n = 22, delta SvdH <5).

Table 1 Baseline demographic and clinical characteristics of all rheumatoid arthritis (RA) patients

	RA patients (n = 81)		
	Mean	SD	Range
Age (years)	35.17	5.88	23–45
Disease duration (months)	6.82	3.15	3–12
ESR mm/1st h	42.95	13.73	19–85
CRP mg/dL	31.9	16.1	12–81
RF titer IU/mL	54.22	21.22	21–141
Anti-CCP titer U/mL	43.53	12.73	29–79
MMP-3 level ng/mL	83.44	43.02	41–175
SvdH score	9.51	4.28	0–27
OMERACT erosion score	11.57	7.06	0–30
DAS-28 score	4.37	0.72	2.8–6.7
HAQ score	1.47	0.46	0.8–2.8

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MMP-3, matrix metalloproteinase-3; OMERACT, Outcome Measures in Rheumatology Clinical Trials erosion score; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system.

Comparison of the clinical and laboratory variables between the two groups of patients

The baseline differences between the two subgroups of patients are shown in Table 2, where there can be seen significant increased levels of CRP and MMP-3 as well as OMERACT erosion scores in the high-progression than in the low-progression group of patients.

The differences between both groups of patients after 12 months follow-up are given in Table 3. There are significantly higher levels in all parameters, except for ESR, in the high-progression as compared with the low-progression group.

Table 4 demonstrates comparison between the two studied groups of patients as regards the percentage of change occurring in the clinical and laboratory data of each group. There was significantly higher percentage of changes in RF, anti-CCP, DAS-28 and HAQ scores in the high- as compared to the low-progression group.

Table 2 Comparison of baseline demographic characteristics, clinical and biomarker measures (mean ± SD) between the two groups of rheumatoid arthritis (RA) patients

	RA patients (n = 81)		P-value
	High-progression group (n = 59)	Low-progression group (n = 22)	
Age (years)	35.29 ± 6.16	34.86 ± 4.70	0.771
Disease duration (months)	6.83 ± 3.17	6.59 ± 2.82	0.756
ESR mm/1st h	43.56 ± 15.17	40.59 ± 9.39	0.394
CRP mg/dL	35.29 ± 17.62	24.27 ± 5.79	0.005*
RF titer IU/mL	56.41 ± 23.13	49.95 ± 16.47	0.235
Anti-CCP titer U/mL	45.32 ± 15.57	39 ± 4.69	0.066
MMP-3 level ng/mL	95.75 ± 42.84	50.45 ± 12.83	<0.001**
SvdH score	10.29 ± 4.43	7.46 ± 3.13	0.007
OMERACT erosion score	13.66 ± 6.6	6.36 ± 4.99	<0.001**
DAS-28 score	4.29 ± 0.74	4.48 ± 0.63	0.299
HAQ score	1.51 ± 0.49	1.43 ± 0.19	0.452

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MMP-3, matrix metalloproteinase-3; OMERACT, Outcome Measures in Rheumatology Clinical Trials erosion score; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system. *Significant at $P < 0.05$; **Highly significant at $P < 0.001$.

Table 3 Comparative analysis between the two groups of rheumatoid arthritis (RA) patients after 12 months follow-up

	RA patients (n = 81)		P-value
	High-progression group (n = 59)	Low-progression group (n = 22)	
ESR mm/1st h	48.51 ± 11.42	46.68 ± 12.20	0.614
CRP mg/dL	41.53 ± 15.69	31 ± 14.09	0.007**
RF titer IU/mL	86.61 ± 45.82	46.64 ± 16.25	<0.001**
Anti-CCP titer U/mL	46.86 ± 17.01	33.5 ± 7.82	0.001*
SvdH score	16.03 ± 4.78	11.23 ± 3.09	<0.001**
DAS-28 score	6.04 ± 1.62	4.33 ± 0.51	<0.001**
HAQ score	2.30 ± 0.97	1.78 ± 0.65	0.023*

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system. *Significant at $P < 0.05$; **Highly significant at $P < 0.001$.

Table 4 Comparative analysis of the percentage of changes in clinical and laboratory data in the two studied groups of rheumatoid arthritis (RA) patients after 12 months

	RA patients (n = 81)		P-value
	High-progression group (n = 59)	Low-progression group (n = 22)	
ESR %			
Median	12.50	4.42	0.987
Range	−56.92 to 176.19	−40.82 to 124.14	
CRP %			
Median	20.69	13.14	0.844
Range	−67.65 to 315.79	−33.33 to 166.67	
RF %			
Median	46.67	0.00	0.001*
Range	−46.15 to 309.52	−67.09 to 73.58	
Anti-CCP %			
Median	0.00	−13.85	0.050*
Range	−48.78 to 180.95	−52.50 to 62.50	
DAS-28 %			
Median	42.86	0.00	0.000**
Range	−37.78 to 182.76	−38.24 to 6.32	
HAQ %			
Median	50	15	0.039*
Range	−5.38 to 90	−6.67 to 110	

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system. *Significant at $P < 0.05$; **Highly significant at $P < 0.001$.

Correlation between serum MMP-3 and other clinical and inflammatory markers in the high-progression group

At baseline evaluation, there was a highly significant positive correlation between MMP-3 levels and ESR, CRP, RF and anti-CCP titers. Also, there was a significant positive correlation between MMP-3 levels and DAS-28 score (Table 5). There was no significant correlation with HAQ scores.

After 12 months follow-up, baseline MMP-3 is still highly positively correlated with RF and anti-CCP titers, in addition to a highly significant positive correlation with DAS-28. Also, baseline MPP-3 showed significant positive correlation with CRP levels and HAQ scores, while there was not any significant correlation with ESR (Table 5).

Table 5 Correlation between serum baseline levels of MMP-3 and other parameters in the high-progression group of rheumatoid arthritis patients at baseline and after 12 months

	MMP-3 baseline level (ng/mL) *r*	*P*-value
ESR mm/1st h		
At baseline	0.372**	0.004
After 12 months	0.125	0.346
CRP mg/dL		
At baseline	0.757**	<0.001
After 12 months	0.283*	0.030
RF titer IU/mL		
At baseline	0.556**	<0.001
After 12 months	0.691**	<0.001
Anti-CCP titer U/mL		
At baseline	0.605**	<0.001
After 12 months	0.871**	<0.001
SvdH score		
At baseline	0.179	0.276
After 12 months	0.588**	<0.001
OMERACT erosion score		
At baseline	0.697**	<0.001
After 12 months	–	–
DAS-28 score		
At baseline	0.306*	0.019
After 12 months	0.881**	<0.001
HAQ score		
At baseline	0.245	0.061
After 12 months	0.390*	0.002

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; OMERACT, Outcome Measures in Rheumatology Clinical Trials erosion score; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system. *Significant at $P < 0.05$; **Highly significant at $P < 0.001$.

Correlation between serum MMP-3 and radiological findings

At baseline evaluation, there was a highly significant positive correlation between baseline MMP-3 levels and OMERACT erosion score, while no correlation was found with SvdH erosion score that showed its highly significant positive correlation with base line MMP-3 after 12 months (Table 5).

Linear regression analysis of all factors involved in RA progression identified both baseline anti-CCP and serum MMP-3 as predictors of joint damage after 1 year of follow-up ($P = 0.002$ and 0.000, respectively) as displayed in Table 6, where elevated baseline serum MMP-3 is shown to be the strongest independent predictor of radiographic progression after 1 year.

The predictive accuracy of MMP-3 as a marker of progressive joint destruction as assessed by ROC analysis revealed an AUC of 0.831 (0.74–0.91), with sensitivity of 81.4%, specificity of 63.6%, at a cutoff value of 45 ng/mL at 95% CI. The positive and negative predictive values were 85.7% and 56%, respectively; kappa measure of agreement was 0.431 ($P = 0.000$) (Fig. 1).

DISCUSSION

Radiographic erosions and/or periarticular osteopenia monitored by conventional radiography are one of the ACR 1987 revised criteria for the classification of RA.[19,20] However, it has been reported that minor ero-

Table 6 Linear regression analysis of baseline data of all rheumatoid arthritis patients for prediction of joint damage

	Beta coefficient	SE	*t*	*P*-value
Age	0.01661	0.018	−0.917	0.363
Disease duration	0.01301	0.030	−0.433	0.667
ESR	0.01390	0.008	−0.178	0.859
CRP	0.01686	0.011	−0.153	0.879
RF	0.06789	0.005	−1.285	0.203
Anti-CCP	0.03562	0.011	−3.207	0.002*
DAS	0.03035	0.133	−0.229	0.820
SvdH score	0.03399	0.031	0.109	0.914
OMERACT score	0.02320	0.022	1.070	0.288
HAQ score	0.07116	0.211	0.338	0.737
Baseline MMP-3	0.02473	0.005	4.791	0.000**

anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS-28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MMP-3, matrix metalloproteinase 3; OMERACT, Outcome Measures in Rheumatology Clinical Trials erosion score; RF, rheumatoid factor; SvdH score, van der Heijde modification of the Sharp scoring system. *Significant at $P < 0.05$; **Highly significant at $P < 0.001$.

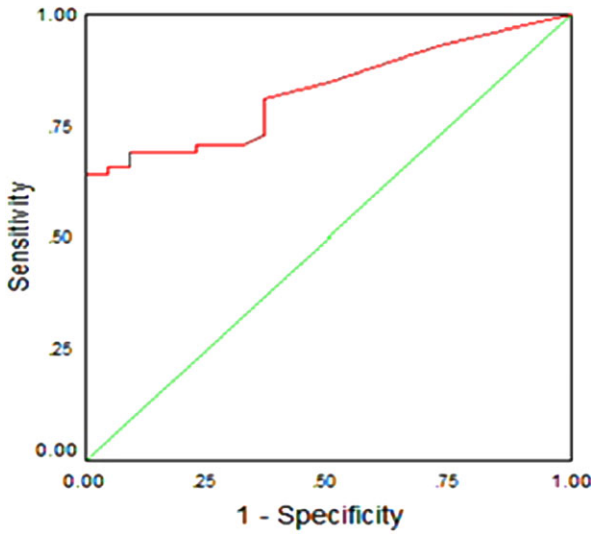

Figure 1 Receiver operating characteristic (ROC) curve, of a stepwise logistic regression analysis of matrix metalloproteinase 3 (MMP-3) (sensitivity is 81.4%, specificity is 63.6%, at a cutoff value of 45 ng/mL with a confidence interval of 95%).

sive changes (≤30% of the assessed bone volume; OMERACT grades 1–3) as judged on MRI in rheumatoid metacarpophalangeal joints (MCP) joints were most often not detected on conventional radiography.[8] None of the traditional baseline clinical and demographic prognostic markers specifically reflect ongoing destructive processes within bone and synovium.[21,22]

In this study, baseline evaluation demonstrated statistically significant higher serum MMP-3 levels in the high-progression group than in the low-progression one. In earlier studies by Green *et al.*,[4] Mamehara *et al.*,[2] and Houseman *et al.*,[23] it was found that serum MMP-3 levels were higher in the RA patients with higher radiographic progression over a period of 1 year, 18 months and 8 years, respectively. Also, Tchetverikov *et al.*,[11] reported higher pro-MMP-3 levels in RA patients with severe progressive disease in comparison with the mild form of the disease. Yamanaka *et al.*,[24] partially agreed with our results in that baseline MMP-3 levels correlated with radiologic disease progression in the subsequent several months. This difference may be as a result of using a different diagnostic tool for erosions as they assessed joint destruction by the Larsen method, while in our study joint erosions were assessed by MRI at baseline and by SvdH score on plain X-ray after 12 months. On the other hand, Cunnane *et al.*[25] documented that the development of new joint erosions and radiographic progression in RA were correlated with MMP-1 rather than with MMP-3, but this may be due to measuring pro-MMP-3 only while we measured the pro- and the active forms of MMP-3. They concluded that MMP-3 plays a pivotal role in the initiation of joint damage, possibly through the activation of MMP-1 as well as MMP-3-induced aggrecan disruption which is a necessary first step in allowing MMP-1 access to collagen fibrils.[25]

In this study, there were highly statistically significant positive correlations between MMP-3 level, RF and anti-CCP titers. This result is in accordance with the fact that seropositivity and higher levels of RF and anti-CCP are associated with more liability to the development of severe and erosive RA disease.[26,27] Thus MMP-3 can act as a marker of an erosive course in RA. At the same time, the highly significant positive correlation with inflammatory markers (ESR and CRP) also confirms its role as an inflammatory marker in early RA. Ribbens *et al.*[6] and Green *et al.*[4] also found that baseline serum levels of MMP-3 correlated significantly with baseline CRP. Furthermore, Cunnane *et al.*[25] added that there is positive correlation between MMP-3 levels and CRP in patients with RA, concluding that MMP-3 is a marker of joint inflammation.

After 12 months, baseline serum MMP-3 levels showed a highly statistically significant positive correlation with RF, anti-CCP, SvdH and DAS-28, as well as HAQ scores. In line with this, Green *et al.*[4] and Mamehara *et al.*[2] also stated that MMP-3 was directly linked to disease activity and is a marker of inflamed synovium. The absence and decrease of positive correlation between MMP-3 and ESR and CRP after 12 months, respectively, in our study may be due to their turnover period, or due to an effect of the current treatment on these acute phase reactants that does not affect MMP-3 levels. In addition, CRP is a non-specific inflammatory marker, produced in the liver away from the site of inflammation and is affected by many cytokines, making its predictive ability less accurate, and some patients may have normal CRP measures but continue to erode.[4] These results and ours confirm the fact that serum MMP-3 is a synovial-derived marker of inflammation, specific for chronic joint inflammation[6] and should be targeted by another line of RA treatment.

Contradictory to our results are those of Yamanaka *et al.*,[24] who stated that baseline MMP-3 correlated strongly with ESR and CRP in early and late disease course, and that of Tchetverikov *et al.*,[11] who mentioned that MMPs correlated significantly with the CRP levels and DAS at baseline, 1 and 2 years of follow-up. There are also previous studies that suggest MMP-3 as a

marker of inflammation rather than marker of joint destruction.[25–27]

The highly significant positive correlation between baseline MMP-3 levels and baseline OMARACT erosion score, indicates that high MMP-3 level is associated with bone loss, even if this loss is not obvious by X-ray. Besides, the highly significant positive correlation between baseline MMP-3 levels and SvdH score after 1 year emphasizes that high baseline serum levels of MMP-3 are correlated with joint damage in the first year of RA disease. Moreover, the positive correlation with HAQ after 1 year shows that patients with high serum levels of MMP-3 at early stages of the disease are more prone to develop an early disability during the disease course. These findings outline the role of MMP-3 as a predictor of subsequent joint damage in the early phase of RA, that was confirmed also by the linear regression analysis in our model, in which MMP-3 was the strongest independent predictor of radiographic progression during the period of follow-up. Tchetverikov *et al.*[11] stated that pro-MMP-3 levels and joint damage progression (estimated by using the Sharp–van der Heijde joint damage score) was independent of other known predictive factors, such as shared epitope, RF and CRP, thereby suggesting that MMP-3 has a crucial role in joint destruction. In addition, earlier studies have stated that baseline serum MMP-3 was superior to both CRP and ESR in predicting changes in the Larsen score in the next 6 or 12 months.[24] Others concluded that baseline MMP-3 can predict radiographic progression in RA patients, as it was correlated with progression in Larsen score over a period of 1 year[4] and 2 years.[3] A recent study by Houseman *et al.*[23] identified elevated baseline MMP-3 as an independent predictor of radiographic outcome over a period of 8 years of follow-up, by stepwise logistic regression analysis. In contrast to our results, Hashimoto *et al.*[28] stated that baseline MMP-3 was not found to be predictive of radiographic progression in their patients who had longer disease duration (up to 5 years) and with active disease.

Morover, the predictive accuracy of MMP-3 as a predictor of progressive joint damage evaluated by AUC of ROC analysis, revealed an AUC comparable to that of Mamehara *et al.*[2] (0.83 *vs.* 0.87, respectively). Also, in our study, the cutoff value of serum MMP-3 was >45 ng/mL, while that of Mamehara *et al.*[2] was >62 ng/mL; this discrepancy could be attributed to the difference in the epidemiological characters of both patient groups.

In conclusion, MMP-3 is a reliable specific inflammatory marker of the synovium and its baseline serum level is a strong predictor of radiographic progression and development of disability in patients with early-stage RA, despite using various scores for radiographic assessment and various statistical methodologies. Patients with high baseline levels of MMP-3 are candidates for early aggressive therapy to prevent joint damage and subsequently, preventing disability. Suppression of MMP-3 production should be a therapeutic target in the near future.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1 Shovman O, Gilburd B, Zandman-Goddard G *et al.* (2005) The diagnostic utility of anti-cyclic citrullinated peptide antibodies, matrix metalloproteinase-3, rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein in patients with erosive and non-erosive rheumatoid arthritis. *Clin Dev Immunol* **12** (3), 197–202.

2 Mamehara A, Sugimoto T, Sugiyama D *et al.* (2010) Serum matrix metalloproteinase-3 as predictor of joint destruction in rheumatoid arthritis, treated with non-biological disease modifying anti-rheumatic drugs. *Kobe J Med Sci* **56**, E98–107.

3 Young-Min S, Cawston T, Marshall N *et al.* (2007) Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers. *Arthritis Rheum* **56** (10), 3234–47.

4 Green MJ, Gough AKS, Devlin J *et al.* (2003) Serum MMP-3 and MMP-1 and progression of joint damage in early rheumatoid arthritis. *Rheumatology* **42**, 83–8.

5 Tchetverikov I, Lohmander LS, Verzijl N *et al.* (2005) MMP protein and activity levels in synovial fluid from patients with joint injury, inflammatory arthritis, and osteoarthritis. *Ann Rheum Dis* **64**, 694–8.

6 Ribbens C, Martin y Porras M, Franchimont N *et al.* (2002) Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. *Ann Rheum Dis* **61**, 161–6.

7 Yao L, Magalnick M, Wilson M, Lipsky P, Goldbach-Mansky R (2006) Periarticular bone findings in rheumatoid arthritis: T2-weighted versus contrast-enhanced T1-weighted MRI. *AJR* **187** (2), 358–63.

8 Ejbjerg BJ, Vestergaard A, Jacobsen S, Thomsen H, Østergaard M (2006) Conventional radiography requires a MRI-estimated bone volume loss of 20% to 30% to allow certain detection of bone erosions in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* **8** (3), R59.

9 Freeston JE, Bird P, Conaghan PG (2009) The role of MRI in rheumatoid arthritis: research and clinical issues. *Curr Opin in Rheumatol* **21**, 95–101.

10 Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T (1989) Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* **16**, 585–91.
11 Tchetverikov I, Lard LR, DeGroot J *et al.* (2003) Matrix metalloproteinases-3, -8, -9 as markers of disease activity and joint damage progression in early rheumatoid arthritis. *Ann Rheum Dis* **62**, 1094–9.
12 Funovies J, Aletaha D, Bykerk V *et al.* (2010) The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis* **69**, 1589–95.
13 Yamanaka H (2002) Usefulness of serum matrix metalloproteinase-3 (MMP-3) levels in the diagnosis of rheumatoid arthritis. *Nihon Rinsho* **60** (12), 2325–30.
14 Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, Van de Putte LB, van Riel PL (1995) Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* **38**, 44–8.
15 Fries JF, Spitz PW, Kraines RG, Holman HR (1980) Measurement of patient outcome in arthritis. *Arthritis Rheum* **23**, 137–45.
16 Van der Heijde D (1999) How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* **26**, 743–5.
17 Østergaard M, Peterfy C, Conaghan P *et al.* (2003) OMERACT rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions and the OMERACT RA-MRI scoring system. *J Rheumatol* **30**, 1385–6.
18 SPSS (2010) *Statistical Package for Social Science, Computer Software, Ver.18, SPSS Company, London, UK.*
19 Arnett FC, Edworthy SM, Bloch DA et al. *(1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.* Arthritis Rheum **31**, 315–24.
20 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines (2002) Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* **46**, 328–46.
21 Emery P, McInnes B, van Vollenhoven R, Kraan MC (2008) Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis. *Rheumatology* **47**, 392–8.
22 Posthumus MD, Limburg PC, Westra J, Leeuwen MA, Ruswijk MH (2002) Serum matrix metalloproteinase 3 levels during treatment with sulfasalazine or combination of methotrexate and sulfasalazine in patients with early rheumatoid arthritis. *J Rheumatol* **29**, 883–9.
23 Houseman M, Potter C, Marshall N *et al.* (2012) Baseline serum MMP-3 levels in patients with Rheumatoid Arthritis are still independently predictive of radiographic progression in a longitudinal observational cohort at 8 years follow up. *Arthritis Res Ther* **14**, R30.
24 Yamanaka H, Matsuda Y, Tanaka M *et al.* (2000) Serum matrix metalloproteinase 3 as a predictor of the degree of joint destruction during the six months after measurement, in patients with early rheumatoid arthritis. *Arthritis Rheum* **43**, 852–8.
25 Cunnane G, FitzGerald O, Beeton C, Cawston TE, Bresnihan B (2001) Early joint erosions and serum levels of matrix metalloproteinase-1, matrix metalloproteinase -3, and tissue inhibitor of metalloproteinases-1 in rheumatoid arthritis. *Arthritis Rheum* **44**, 2263–74.
26 So A, Chamot AM, Peclat V, Gerster JC (1999) Serum MMP-3 in rheumatoid arthritis: correlation with systemic inflammation but not with erosive status. *Rheumatology (Oxford)* **38**, 407–10.
27 Keyszer G, Lambiri I, Nagel R *et al.* (1999) Circulating levels of matrix metalloproteinases MMP-3 and MMP-1, tissue inhibitor of metalloproteinases 1 (TIMP-1), and MMP-1/TIMP-1 complex in rheumatic disease: correlation with clinical activity of rheumatoid arthritis versus other surrogate markers. *J Rheumatol* **26**, 251–8.
28 Hashimoto J, Garnero P, van der Heijde D *et al.* (2009) A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. *Mod Rheumatol* **19**, 273–82.