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ORIGINAL ARTICLE

**Mikiko Shinozaki · Eisuke Inoue · Ayako Nakajima
Masako Hara · Taisuke Tomatsu · Naoyuki Kamatani
Hisashi Yamanaka**

Elevation of serum matrix metalloproteinase-3 as a predictive marker for the long-term disability of rheumatoid arthritis patients in a prospective observational cohort IORRA

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Abstract Matrix metalloproteinases (MMPs) are the proteases responsible for the destruction of cartilage in rheumatoid arthritis (RA) patients; especially the role of MMP-3 in RA has been highlighted from both pathophysiological studies and clinical studies. However, the role of serum MMP-3 in a large observational cohort of RA patients has not been well demonstrated. In a large observational cohort of RA patients in our Institute (IORRA, October 2000–October 2005, n = 3834–5049/phase), disease activity and functional status were routinely assessed biannually. In October 2001, serum MMP-3 was measured in 1265 patients in this cohort, and the data of these patients in the subsequent 4 years were analyzed. The functional status of disability was assessed by JHAQ, the verified Japanese version of HAQ. A cut-off point of 121.0 ng/ml (men) and 59.7 ng/ml (women) was used for MMP-3 positive/negative categorization. The baseline data of these 1265 patients include 81.5% women, mean age 57.9, mean duration 11.1 years, and 71.7% of patients were rheumatoid factor (RF)-positive. Serum MMP-3 levels at the baseline (195.1 + 227.9 ng/ml) were weakly correlated with C-reactive protein (CRP), but qualitative elevation of serum MMP-3 using cut-off points correlated significantly with corticosteroids use, DAS28, CRP, erythrocyte sedimentation rate, JHAQ, or other markers for the disease activity, but not with age or the disease duration. Thus, elevation of serum MMP-3 level represents the disease activity of RA patients regardless of age or the disease duration. In the longitudinal analysis, the slope of JHAQ progression in patients with MMP-3 positive and RF positive, MMP-3 positive and RF negative, MMP-3 negative and RF positive and MMP-3 negative and RF negative were 0.0179, 0.0162, 0.0156, and 0.0119, respectively, indicating that JHAQ increased most progressively in RA patients with MMP-3 positive and RF positive patients, although statistically apparent differences were not identified. In 502 female patients without talking corticosteroid, patients with MMP-3 positive and RF positive were statistically more progressive in the disability than patients with MMP-3 negative and RF negative. In conclusion, elevation of serum MMP-3 in RA patients is an indicator of inflammation, and together with RF, elevation of serum MMP-3 is a predictive marker for the progression in disability especially in female patients without corticosteroid.

Key words Cohort study · HAQ (J-HAQ) · MMP-3 · Rheumatoid arthritis

M. Shinozaki (✉) · E. Inoue · A. Nakajima · M. Hara · T. Tomatsu · N. Kamatani · H. Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1711; Fax +81-3-5269-1726
e-mail: mshinozaki@ior.twmu.ac.jp

Introduction

Rheumatoid arthritis (RA) is a systemic disorder characterized by chronic proliferative synovitis followed by marked destruction of joints that leads patients into severe disability. Considering the burden of the disease to the patients and the large number of patients in all ethnic population (0.5%–1.0%), RA is a disease that requires the strategic approach for the better management in the long-term illness. Recently, introduction of the potent anti-rheumatic drugs including biologic agents has dramatically improved the outcome of patients,[1,2] and together with this, progress in the therapeutic strategy has been achieved by the extensive research into the clinical course of RA, and this also clearly contributed to the better outcome of patients. Early introduction of anti-rheumatic drugs and strict control of the disease activity are the two major well-recognized therapeutic strategies in the management of RA. One of the major issues in the management of RA is the clinical assessment of the disease activity. The number of swollen joints or tender joints, duration of morning stiffness, patients or physicians assessment by visual analog scale (VAS) are frequently used in the daily practice of rheumatology, and the composite scores such as DAS,[3] DAS28,[4] SDAI,[5] or CDAI[6] have been used for the clinical measures in the clinical trials. However, most of these measures are the subjective

approach to the disease activity, and the variation by the observer (rheumatologist) is not neglected, and standardization of these measures is not easy to perform.

From this notion, serum markers are one of the objective approaches to estimate the disease activity of each patient if the usefulness and the limitation of the measurement in diary clinical setting are well documented. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most frequently used markers for the assessment of disease activity of RA patients, and indeed, are used as a component of DAS or DAS28. CRP and ESR are the established markers for the disease activity in RA; however, those are the essentially markers for the non-specific inflammation but not for the specific inflammation in rheumatoid synovium.

Matrix metalloproteinases are the enzymes responsible for the degradation of the collagen fibrils, thus, have significant roles in the irreversible destruction of cartilage in RA. Among MMPs, MMP-3 is highly expressed in the synovial lining cells of RA patients, and augmentation of MMP-3 in synovial fluid is associated with the rapid destruction of cartilage in RA patients.[7] The serum level of MMP-3 has been well studied to have correlation with disease activity or inflammatory parameters.[8] However, the clinical significance of serum MMP-3 in the long-term outcome of RA patients has not been fully understood.

The main purpose of this study is to clarify the predictive value of serum MMP-3 for the disability of RA patients using the database from a large observational cohort.

Patients and methods

We have established a large observational cohort of RA patients in our Institute (IORRA, October 2000–October 2005, n = 3834–5049/phase), where the disease activity and functional status were routinely assessed biannually. All the RA patients who had visited our clinic were asked to answer questionnaires every 6 months assessing variables such as disability level, assessment of pain, global assessment of disease activity, use of medication, adverse events, health care utilization, and satisfaction with care.

A combined database was prepared including patient-reported data, physician's assessment, and laboratory data. From April 2000 to October 2005, 3834–5049 patients with RA participated in this cohort study. Those patients with missing data in patient or physician's assessments, and those whose diagnosis of RA was eventually changed were excluded.

The serum level of MMP-3 at October 2001 was determined by enzyme-linked immunosorbent assay method (Panaclear MMP-3, Daiichi Fine Chemicals, Takaoka, Japan) in randomly selected 1265 patients who completed all biannual surveys from the phase 3 (October 2001) to phase 7 (October 2003) and all the necessary data for the analysis are available.

Table 1 shows the baseline characteristics of patients in this study. We evaluated such variables as age, sex, concomitant drugs and so on, and summarized using mean,

Table 1. Baseline characteristics of 1265 patients as of October 10, 2001

	Mean or frequency	SD	Median	IQR
MMP-3 (ng/ml)	195.2	228.0	119	66.06–221
Women (%)	81.50	–	–	–
DMARD (%)	86.88	–	–	–
MTX (%)	42.85	–	–	–
Steroid (%)	50.43	–	–	–
Age (years)	57.92	12.26	59	51–67
Duration (years)	11.19	8.568	10	4–16
Height (cm)	156.6	7.142	156	152–161
Weight (kg)	52.39	8.785	52	46–58
BMI (kg/m^2)	21.33	2.879	21.17	19.31–23.07
HAQ	0.7603	0.7198	0.625	0.125–1.25
JHAQ	0.8055	0.7493	0.625	0.125–1.25
TJC (max:45)	3.135	4.763	1	0–4
SJC (max:45)	2.713	3.491	2	0–4
General VAS (cm)	34.47	24.82	30	13–52
Pain VAS (cm)	33.22	26.22	27	10–53
Doctor VAS (cm)	20.84	17.74	16	7–31
DAS28	3.741	1.234	3.718	2.873–4.547
DAS28-CRP	3.138	1.144	3.049	2.268–3.916
CRP (mg/dl)	1.339	1.789	0.7	0.2–1.6
ESR (mm/1h)	35.11	23.84	29.2	16.4–50.3
RF (IU/ml)	122.2	205.6	52	15–125
MTX dosage (mg/week)	5.999	2.519	6	4–7.5
PSL dosage (mg/day)	4.554	2.454	4.375	3–5.5

Disease-modifying anti-rheumatic drugs (DMARDs) include methotrexate (n = 542), bucillamine (n = 331), sulfasalazine (n = 254), D-penicillamine (n = 123), gold thiomalate (n = 94), auranofin (n = 40), and others (n = 94). Because methotrexate is a standard drug for the current therapy of rheumatoid arthritis (RA), the number of patients with methotrexate is shown separately as well

SD, standard deviation; IQR, interquartile range

Table 2. Comparison of clinical variables between MMP-3 positive and negative patients with RA in the cross-sectional analysis

	Correlation	Quantitative analysis		Qualitative analysis		*P*
		MMP-3 negative (n = 361)		MMP-3 positive (n = 904)		
		Mean or %	Median (IQR)	Mean or %	Median (IQR)	
Women (%)	–0.05734	68.42	–	86.73	–	3.769×10^{-13}
DMARD (%)	–0.007264	87.26	–	86.73	–	0.8539
MTX (%)	0.1092	35.18	–	45.91	–	5.333×10^{-4}
Steroid (%)	0.2181	29.36	–	58.85	–	1.199×10^{-21}
Age (years)	0.004640	57.89	59 (52–66)	57.93	59 (51–67)	0.9994
Duration (years)	0.04001	11.21	10 (4–16)	11.19	10 (4–15)	0.7302
Height (cm)	–0.02698	158.6	158 (153–163)	155.8	156 (151–160)	1.157×10^{-8}
Weight (kg)	–0.01014	54.23	54 (48–60)	51.64	51 (46–57)	1.218×10^{-5}
BMI (kg/m^2)	0.008185	21.48	21.36 (19.45–23.24)	21.27	21.08 (19.27–23.05)	0.1608
HAQ	0.24347	0.5017	0.25 (0–0.75)	0.8631	0.75 (0.250–1.375)	7.757×10^{-21}
JHAQ	0.2441	0.5306	0.25 (0–0.875)	0.9150	0.75 (0.25–1.50)	2.425×10^{-21}
TJC (max: 45)	0.1256	2.120	1 (0–3)	3.545	2 (0–4)	1.808×10^{-6}
SJC (max: 45)	0.2505	1.737	1 (0–2)	3.106	2 (1–4)	3.021×10^{-14}
General VAS (cm)	0.2832	24.58	18 (6–41)	38.40	38 (18–55)	8.247×10^{-21}
Pain VAS (cm)	0.2849	23.19	15 (5–33)	37.22	33 (14–58)	1.046×10^{-19}
Doctor VAS (cm)	0.2870	14.93	10 (4–20)	23.22	19 (9–34)	1.124×10^{-17}
DAS28	0.3552	3.124	3.104 (2.310–3.802)	3.986	3.995 (3.141–4.785)	1.05×10^{-28}
DAS28-CRP	0.3736	2.587	2.490 (1.776–3.162)	3.360	3.304 (2.520–4.149)	6.515×10^{-28}
CRP (mg/dl)	0.4215	0.6900	0.3 (0.1–0.8)	1.598	0.9 (0.3–2.1)	2.91×10^{-27}
ESR (mm/1h)	0.3241	25.55	20.05 (10.98–35.67)	38.89	34.30 (19.50–54.50)	1.566×10^{-21}
RF (IU/ml)	0.1229	114.1	48.00 (11.00–109.5)	125.4	53.00 (17.00–130.0)	0.01754
MTX dosage (mg/week)	0.02168	6.097	6 (4–8)	5.969	6 (4–7.5)	0.7720
PSL dosage (mg/day)	0.1590	3.844	3.792 (2–5)	4.698	4.833 (3–6)	1.836×10^{-4}

P values were calculated using Fisher's exact test or Mann–Whitney's *U* test as appropriate
IQR, interquartile range

standard deviation (SD), median, and inter-quartile range (IQR). Methotrexate is a DMARD; however, methotrexate is the most commonly prescribed drug to patients with RA, thus, we analyzed the dosage of methotrexate also separately in Tables 1 and 2. As a cut-off point of serum MMP-3, we used 121.0 ng/ml (men) and 59.7 ng/ml (women), and the patients who had a MMP-3 value above this cut-off point were categorized as positive, and else otherwise as negative. Similarly, we categorized the patients as RF positive and RF negative by using the cut-off point of 15 (IU/ml).

In the cross-sectional analysis, we conducted quantitative and qualitative analyses. In the quantitative analysis, we calculated Spearman's correlation between serum MMP-3 and baseline variables. In the qualitative analysis, the differences between MMP-3 positive and negative were evaluated by Fisher's exact test and Mann–Whitney's *U* test as appropriate. In the longitudinal analysis, we evaluated the slope of linear regression and its 95% confidence limits for each group such as the combination of categories of RF and MMP-3 in 1255 patients, because 10 cases were excluded as the RF values were missing. As a sub-group analysis, we conducted the same analysis in female patients who had not taken taking corticosteroids. The functional status of disability was assessed by JHAQ, culturally modified and scientifically verified by the Japanese version of original HAQ.[9] The calculation of DAS28 was based on the original formula in the DAS28 website (http://www.das-score.nl).

We set the significance level as 0.05, and we indicated the two-tailed *P* values. Statistical analyses were conducted using R (version 2.4.1).

Results

Cross-sectional analysis

The baseline data of these 1265 patients include 81.5% women, mean age 57.9, mean duration 11.1 years, and 71.7% of patients were rheumatoid factor (RF) positive (Table 1). The percentage of patients who were taking DMARDs (including methotrexate) and corticosteroids at the baseline were 86.8%, and 50.4%, respectively. Percentages of patients taking DMARDs were as follows: methotrexate 48.9%, bucillamine 26.2%, sulfasalazine 20.1%, D-penicillamine 9.7%, gold thiomalate 7.4%, auranofin 3.3%, actarit 4.3%, and mizoribine 3.1%.

When the correlation between quantitative measures of serum MMP-3 and baseline variables was analyzed, only CRP had a relatively high correlation (R = 0.4215, Table 2). Thus, correlations between elevation of serum MMP-3 and baseline variables were also analyzed qualitatively by using the cut-off point of MMP-3 as written in "Patients and Methods" section. As shown in Table 2, more patients with elevated serum MMP-3 levels (MMP-3 positive) had taken corticosteroids in comparison to those with normal MMP-3 levels (MMP-3 positive). Also, patients with an elevated serum MMP-3 level had significantly higher DAS28, CRP, ESR, JHAQ, global assessment of patients/physicians, pain scale, dosage of corticosteroid and titer of RF than those with normal serum MMP-3 levels, however, age or the disease duration was not significantly different between

these two groups (Table 2). Thus, the elevation of serum MMP-3 level represents the disease activity of RA patients regardless of age or the duration of the disease.

Longitudinal analysis

In the longitudinal analysis, the association of serum MMP-3 with the subsequent progression of disability in RA patients was examined using JHAQ as the outcome measure.

At first, simple correlations between the quantitative value of serum MMP-3, CRP, ESR, or RF and yearly progression of JHAQ were evaluated; however, no significant correlations were identified between these laboratory markers including RF and the progression of disability (Table 3).

Table 3. Correlations between baseline JHAQ or ΔJHAQ at 1, 2, and 3 year and clinical laboratory values

	Baseline JHAQ	ΔJHAQ at		
		1 year	2 year	3 year
MMP-3	0.1442	–0.03972	–0.04367	–0.03130
CRP	0.2774	–0.06745	–0.07283	–0.09358
ESR	0.3343	–0.07613	–0.06852	–0.08493
RF	0.1713	–0.02715	–0.04901	–0.02836

All values indicate correlation coefficient (r)

Thus, we tried to compare the predictive value of serum MMP-3 and RF using qualitative method as MMP-3 positive/negative and RF positive/negative. And patients were categorized by the combination of serum MMP-3 positive or negative and serum RF positive or negative into four categories.

Next, the transition of JHAQ in these four groups was demonstrated (Fig. 1). In all groups of RA patients, JHAQ increased gradually over the four years after the baseline, however, JHAQ of RA patients with MMP-3 positive and RF positive was the highest at baseline and increased constantly (Fig. 1A).

Thus, we tried to compare the slopes of regression lines for each group of patients based on the mean value of JHAQ at each time point (Table 4). The slopes for patients with MMP-3 positive and RF positive (n = 569), MMP-3 positive and RF negative (n = 330), MMP-3 negative and RF positive (n = 204) and MMP-3 negative and RF negative (n = 152) were 0.0179, 0.0162, 0.0156 and 0.0119, respectively, indicating that JHAQ increased most progressively in RA patients with MMP-3 positive and RF positive patients, although statistically apparent differences were not demonstrated between these patient groups.

Because serum MMP-3 is influenced by sex and concomitant use of corticosteroid as shown in Table 2, the same analysis was conducted in 502 female patients who had not taken corticosteroids (Fig. 1B, Table 4). Similarly, the slopes

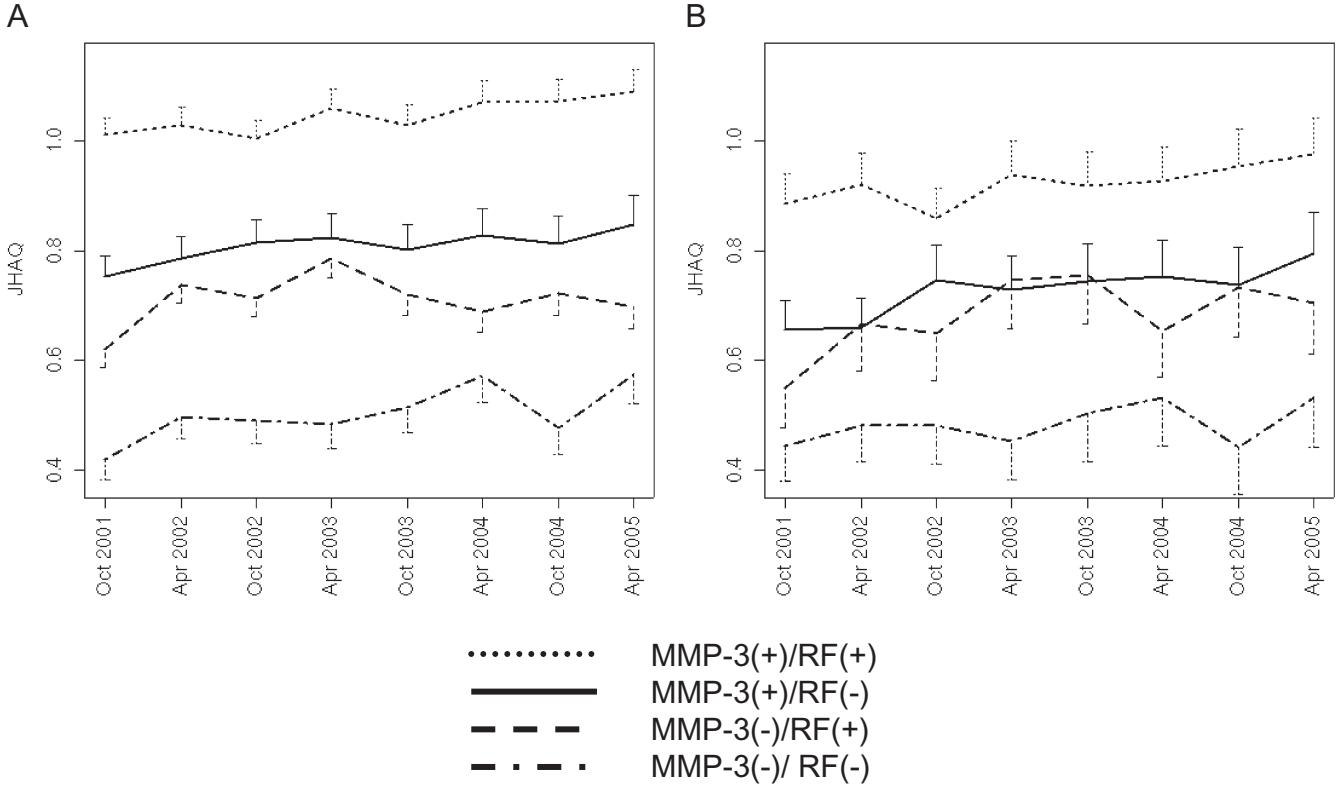

Fig. 1. Transition of JHAQ over 4 years after the measurement of serum matrix metalloproteinase (MMP)-3 in all cases (**A**) and in female cases without corticosteroid use (**B**). Transition of JHAQ over 4 years after the measurement of serum MMP-3 in the four categories of patients by the combination of serum MMP-3 positive or negative and serum RF positive or negative. Results were demonstrated in all cases (**A**) and in female cases without corticosteroid use (**B**). Note that rheumatoid arthritis (RA) patients with MMP-3 positive and rheumatoid factor positive was the highest at baseline and increased constantly in both analyses

Table 4. Linear regression analysis of JHAQ over 4 years after the measurement of serum MMP-3

MMP-3	RF	Total				Women without steroids			
		N	Slope	CL	CU	*N*	Slope	CL	CU
+	+	569	0.0179	0.0140	0.0217	195	0.0227	0.0127	0.0327
+	–	330	0.0162	0.0118	0.0206	134	0.0164	0.00720	0.0256
–	+	204	0.0156	–0.00152	0.0327	89	0.0229	0.00492	0.0408
–	–	152	0.0119	0.00427	0.0195	84	0.0047	–0.00242	0.0119

CL, 95% confidence lower limit; CU, 95% confidence upper limit

for patients with MMP-3 positive and RF positive ($n = 195$), MMP-3 positive and RF negative ($n = 134$), MMP-3 negative and RF positive ($n = 89$) and MMP-3 negative and RF negative ($n = 84$) were 0.0227, 0.0164, 0.0229 and 0.0047, respectively. Considering the confidence intervals of these slopes, patients who were MMP-3 positive and RF positive were statistically more progressive in the disability than the patients who were MMP-3 negative and RF negative in female patients without corticosteroids.

Discussion

The disease activity of RA patients is essentially evaluated from signs and symptoms of patients; in this regard, composite scores like DAS of DAS28 or disability index like HAQ or JHAQ have been developed. Thus, serum markers in RA are subsidiary instruments useful for the decision-making in the clinical situations, and we have to emphasize that no single serum marker can represent the disease activity of RA patients.

Our study on the serum level of MMP-3 in RA patients demonstrated that the qualitative elevation of serum MMP-3 in RA patients is an indicator of disease activity in our cross-sectional analysis, and that the progression in disability assessed by JHAQ was demonstrated in RA patients with elevated MMP-3 and RF positive at least in female patients without corticosteroids in our longitudinal analysis. Thus, together with RF, serum MMP-3 is considered to be a predictive marker for the progression in disability in RA patients at least in a selected patient population.

A strong correlation between serum MMP-3 and radiological progression of joint damage has been shown from our group;[10] however, a large number of cases ($n = 1265$) in this study enabled us to read X-ray films of all patients. Thus, we used JHAQ as an established surrogate marker for the disability of RA patients for the longitudinal analysis in this study.

Serum concentration of MMP-3 is usually expressed as a quantitative measure, thus we tried to show the direct correlations between the concentration of serum MMP-3 and baseline variables; however, we failed to show the clear relationships in both the cross-sectional and longitudinal analyses. As shown in Table 3, quantitative value of laboratory markers had no significant correlations between the yearly progression of disability assessed by JHAQ. It is remarkable that even RF, an established marker for the progression of disability, we failed to show the clear relationship between the progression of disability.

It is likely that many factors of patients influenced the value of MMP-3 because the patients in this study are quite heterogeneous in age, disease duration and therapeutic regimen. Indeed, serum MMP-3 level is sensitively influenced by the treatment for RA such as corticosteroids, biologic agents or methotrexate; thus, the further analysis using the quantitative value of MMP-3 is thought to be quite complicated. Thus, we conducted the qualitative analysis of MMP-3 using a cut-off value in this study. Conversion of a numerical data to a categorized data is not uncommon to identify the significance of parameter such as RF or DAS28.

In longitudinal analysis, we tried to show the relationship between serum MMP-3 and subsequent increment of JHAQ over 4 years. The slope of JHAQ in MMP-3 positive and RF positive patients was the highest (0.0179) than other three groups of patients; however, statistically no clear difference was demonstrated. Thus, we conducted the same analysis in 502 female patients without corticosteroids, and we identified the statistically significant progression of JHAQ in MMP-3 positive and RF positive patients.

Usefulness of serum MMP-3 has been reported but not well documented in longitudinal analysis.[10–12] We have reported that early RA patients with high serum MMP-3 developed the joint destruction at 12 months after the measurements.[10] Similarly, Ribbens et al.[8] reported the usefulness of MMP-3 as a predictor of clinical response in 20 patients with RA in a clinical study for 12 months. Also, Green et al.[11] showed that baseline serum MMP-3 has correlation with CRP ($R = 0.42$) delta Larsen's score ($R = 0.23$) and delta HAQ ($R = 0.32$) at 12 months after the baseline in 98 patients with early RA. The correlation between serum MMP-3 and CRP was $R = 0.42$ in Green's report[11] and $R = 0.35$ in our present study. Compared with these reports, our present study has demonstrated the usefulness of elevated serum MMP-3 in a longer (4 years) follow-up period in a larger ($n = 1265$) and randomly selected population of RA patients.

There are many prognostic factors that predict the joint destruction of RA patients, and among those factors, RF is the most established one. The progression of joint damage assessed by the modified Sharp method in RF positive patients compared with RF negative patients was reported to be 2.5 times more rapid in 1 year,[13] or 3.3 times more

rapid in 12 years;[14] thus, RF is a well-established prognostic marker.

The advantage of serum MMP-3 over the rheumatoid factor is that RF is a genetically restricted factor and does not change over time;[14] on the other hand, serum MMP-3 may change according to the disease activity. However, a disadvantage of serum MMP-3 for the assessment of disease activity of RA is that the value is influenced by the use of corticosteroid or methotrexate as shown in our cross-sectional study, thus, rheumatologists should pay attention to this fact to understand the value of serum MMP-s in clinical situations. In our study, qualitative but not quantitative analysis of serum MMP-3 demonstrates the association to the long-term outcome in a selected patient group. We will plan to investigate the relationship between the fluctuation of serum MMP-3 levels and the long-term outcome of RA patients in the next step, and also, the relationship between other markers including anti-CCP antibodies should be examined.

In conclusion, elevation of serum MMP-3 in RA patients is an indicator of inflammation, and together with RF, elevation of serum MMP-3 is a predictive marker for the progression in disability, especially in female patients without corticosteroid.

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