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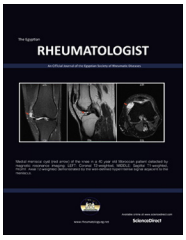

ORIGINAL ARTICLE

Serum matrix metalloproteinase-3 in rheumatoid arthritis patients: Correlation with disease activity and joint destruction

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KEYWORDS

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Abstract *Aim of the work:* This study was designed to measure the serum level of matrix metalloproteinase-3 (MMP-3) in rheumatoid arthritis (RA) patients and its correlation with functional status, disease activity and joint damage.

Patients and methods: The study included 50 RA patients satisfying 2010 ACR/EULAR classification criteria recruited from Bani-Suef University Hospital and 20 controls. Functional disability was assessed according to Modified Health Assessment Questionnaire (MHAQ). Disease activity score in 28-joints (DAS28) and visual analogue scale (VAS) of pain were evaluated. Radiological joint damage was assessed by Van der Heijde-modified Sharp Score (vdHSS). Serum levels of MMP-3 were measured for all subjects.

Results: RA patients (44 females and 6 males) had a mean age of 46.36 ± 13.63 years and disease duration of 5.6 ± 4.75 years. Serum MMP-3 levels were higher in patients than in controls (46.78 ± 46.99 versus 1.98 ± 1.71 ng/ml respectively, $p = 0.0001$) and significantly correlated with erythrocyte sedimentation rate ($p = 0.001$) and were significantly higher in patients with positive C-reactive protein, rheumatoid factor and anti-cyclic citrullinated peptide ($p = 0.0001$, $p = 0.009$, $p = 0.042$, respectively). MMP-3 significantly correlated with DAS28 ($p = 0.0001$) and vdHSS ($r = 0.78$, $p = 0.0001$) and a significant difference was shown in those with erosions compared to those without ($p = 0.001$). Serum MMP-3 levels significantly correlated negatively with cumulative steroid dose ($r = -0.2$, $p = 0.03$) and were significantly higher in patients who never received disease-modifying antirheumatic drugs ($p = 0.001$). There were no significant relations of MMP-3 with age, MHAQ, VAS for pain.

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Conclusion: These results indicate that serum MMP-3 is a measurable, useful specific marker of disease activity and joint damage in RA patients.

1. Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease of unknown etiology characterized by destructive joint disease, impaired function, progressive disability and increased mortality [1]. Synovial inflammation underlies the cardinal manifestations of this disease, which include pain, swelling, and tenderness followed by cartilage destruction, bone erosion, and subsequent joint deformities [2]. In RA, joint involvement is typically symmetric, a character usually not found in other forms of arthritis [3]. In Egyptian RA patients cytokines [4], oxidative stress [5,6] and biomarkers of apoptosis [7] were found to play a key role in the pathogenesis of RA with a prominent relation to disease activity. In another study, synovitis and tenosynovitis detected by ultrasound in Egyptian RA patients showed a significant relation with the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, disease activity and functional impairment [8]. Indeed, the rate of cartilage and joint damage is correlated with plasma elevations in inflammatory acute phase reactants, such as CRP and ESR, rheumatoid factor positivity, and the synovial concentrations of matrix metalloproteinase (MMP), a matrix digesting enzymes directly responsible for joint destruction [9].

The MMPs are thought to play a critical role in the degradation of many components of the extracellular matrix in the synovial joint [10]. Matrix metalloproteinase-3 (stromelysin-1) is a proteolytic enzyme which is thought to play a pivotal role in joint destruction in RA through breaking down various extracellular components, including collagens (types III, IV, V, IX, and XI), matrix proteins and proteoglycans and activating other pro-MMPs such as pro-MMP-7, pro-MMP-8 and pro-MMP-9 [11]. The serum level of MMP-3 was increased in Egyptian patients with other rheumatic as it was associated with arthritis in systemic lupus erythematosus patients and considered a potential biomarker of disease activity and damage [12], related to disease activity in ankylosing spondylitis [13] and was significantly higher in polyarticular juvenile idiopathic arthritis [14].

In RA, MMP-3 is locally produced in the inflamed joint, and released into the blood stream [15]. It has been suggested that serum MMP-3 levels correlate with levels produced by the synovium, and thus reflect the level of activity of rheumatoid synovitis [11,16]. MMP-3 plays a pivotal role in the destruction of bone and degradation of cartilage components in RA and the baseline levels were significantly higher in those with high-progression making it a strong prognostic marker of disease activity and an early predictor of progressive joint damage in recent-onset Egyptian RA patients [17]. Another study displayed a significantly elevated MMP-3 level in the serum and synovial fluid of RA patients compared to patients with osteoarthritis [18].

The aim of the present study is to assess the serum level of MMP-3 in rheumatoid arthritis patients, and to evaluate its significance as a marker of functional disability, disease activity and joint destruction.

2. Patients and methods

Fifty adult RA patients (44 females and 6 males) as defined by the 2010 ACR/EULAR classification criteria [19] formed the basis of this study and were collected from the outpatient clinic of the Rheumatology and Rehabilitation department, Bani-Suef University Hospital. Twenty healthy adults (12 females and 8 males) served as a control group. The study was approved by the local ethical committee in accordance with the declaration of Helsinki ethical standards. Informed consent was obtained from all patients and controls for inclusion in the study.

2.1. Clinical assessment

Demographic data and disease history taking regarding onset, duration, course, progression and associated diseases were obtained from all patients. Number of painful and swollen joints (28 joints) and visual analogue scale (VAS) of pain (ranged from 0-10; 0 means there is no pain, 10 means that it is the worst possible pain patient had felt) were evaluated and disability was assessed according to the Modified Health Assessment Questionnaire (MHAQ) [20]. Disease activity was assessed with disease activity score in 28 joints (DAS28) [21].

2.2. Laboratory assessment

The following was done for all patients and controls: Complete blood count (CBC), ESR by Westergren method, CRP, urine analysis, full blood chemistry, including renal and liver function tests. Rheumatoid factor (RF IgM, U/L) was measured for all patients by agglutination slide for qualitative determination and serum anti-cyclic citrullinated peptide (anti-CCP) antibodies were measured. Test for Matrix Metalloproteinase-3 (MMP-3) using ELISA technique (R&D Systems, Catalog #DMP 300) was done for all patients and control.

2.3. Preparation of samples

Five ml of blood were withdrawn from each patient and the serum was separated by centrifugation; then sera were labeled and stored at −20 °C until used.

2.4. MMP-3 assay procedure

Add 100 μL standard or sample was added to each well and incubated 2 hours at 37 °C. 100 μL Detection Reagent A was aspirated, added and incubated 1 hour at 37 °C then washed 3 times. 100 μL Detection Reagent B was added and incubated

30 minutes at 37 °C then washed 5 times. 200 μL Substrate Solution was added and incubated 30 minutes at 37 °C. 50 μL Stop Solution was added and immediately read at 450 nm. A standard curve was created by blotting absorbance of each standard concentration against MMP-3 concentration. For each sample concentration was obtained from standard curve, then multiplied by 10 (dilution factor).

2.5. Radiological assessment

In all patients, plain radiographs of both hands and feet in the postro-anterior projections were obtained. Van der Heijde-modified Sharp Score (vdHSS) was used to assess radiological changes [22].

2.6. Statistical methods

Statistical package for social science (SPSS) software version 17 was used. Descriptive analysis of the results in the form of percentage distribution for qualitative data and minimum, maximum, mean and standard deviation calculation for quantitative data was done. Cross tabulation test was performed for comparison between percentage values, Student t-test for comparison between means of two groups and *F*-Test (One way ANOVA) for comparison between means of three groups. Pearson's correlation was done to describe the relationship between two variables. In all tests: $p < 0.05$ was significant.

3. Results

The study included 50 adult RA patients (6 males and 44 females); their age ranged from 20 to 70 years with a mean of 46.36 ± 13.63 years and their disease duration ranged from 1 to 15 years with a mean of 5.6 ± 4.75 years. The patients were classified into three groups according to the disease duration. The demographic and clinical characteristics as well as the DAS28, MHAQ, VAS for pain, ESR and CRP of the patients are shown in Table 1. 20 healthy controls included 8 males (40%) and 12 females (60%) with a mean age of 50.5 ± 9.6 years. The controls were age ($p = 0.17$) and sex ($p = 0.55$) matched with the patients.

Rheumatoid factor was positive in 38 patients (76%) and negative in 12 patients (24%); while Anti-CCP was positive in 42 patients (84%), and negative in 8 patients (16%). Radiological score (vdHSS) ranged between 3 and 420 with a mean of 95.36 ± 111.41.

There were 30 RA patients using methotrexate (60%) with a dose ranging from 12.5-25 mg/week with a mean of 17.5 + 3.25 mg/week, 15 patients were using leflunomide (30%), 22 patients were using antimalarial (38%), and 36 patients were using steroids (72%) with a dose ranging from 2.5 to 15 mg/day with a mean of 8.63 + 2.35 mg/day with total cumulative dose (20.65 ± 10.97 g). Some patients were under more than one line of treatment at the same time.

Testing the level of serum MMP-3 in RA patients, it ranged from 5.3 to 162.8 ng/ml with a mean of 46.78 ± 46.99 ng/ml. On the other hand, the levels of MMP-3 in the sera of normal controls ranged from 0.16 to 6.88 ng/ml with a mean of 1.98 ± 1.71 ng/ml. The mean serum level of MMP-3 in RA patients was significantly higher than those in healthy controls ($p = 0.0001$) (Fig. 1).

Table 1 Demographic, clinical and laboratory characteristics of RA patients.

Characteristic mean ± SD (range) or *n* (%)	RA patients ($n = 50$)
Age (years)	46.4 ± 13.6 (20–70)
Age of onset (years)	40.9 ± 12.6 (19–64)
Disease duration (years)	5.6 ± 4.8 (1–15)
Sex	
Female	44 (88)
Male	6 (12)
Disease duration groups	
Group 1 (1–5 years)	27 (54)
Group 2 (5–10 years)	12 (24)
Group 3 (> 10 years)	11 (22)
DAS28	5.2 ± 2 (2.6–8.6)
MHAQ	1.5 ± 0.6 (0.5–2.8)
VAS	53.3 ± 22.96 (20–95)
ESR (mm/1st hr)	56.04 ± 29.8 (15–120)
CRP (mg/L)	25.5 ± 28.1 (3–96)
TLC (cells/mm^3)	7.2 ± 2.9 (3.9–13.6)
Hb (gm/dl)	11.6 ± 1.7 (7.8–15)
Pl ($\times 10^3$/mm^3)	350 ± 96 (190–447)
AST (mg/dl)	24.1 ± 9.5 (12–50)
ALT (mg/dl)	24.3 ± 19.1 (7–55)
Serum creatinine (mg/dl)	0.53 ± 0.11 (0.4–0.8)

DAS28: 28 joint disease activity score, MHAQ: modified health assessment questionnaire, VAS: visual analogue scale of pain, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TLC: total leukocytic count; Hb: hemoglobin, Pl: platelets.

There was an insignificant correlation between serum MMP-3 levels and the age of the patients ($r = 0.22$, $p = 0.12$). There was no significant difference between mean MMP-3 levels in male patients compared to females ($p = 0.24$). On comparing the serum levels of MMP-3 among different disease duration groups of RA patient; it was statistically significant ($r = 0.32$, $p = 0.03$); with the highest mean levels found in patients with disease duration > 10 years (Group 3).

Serum MMP-3 levels significantly correlated with DAS28 score ($r = 0.57$, $p = 0.0001$). The mean values of MMP-3 were higher in patients with highly active disease than those with moderate or low disease activity score (Fig. 2). MMP-3 insignificantly correlated with the VAS for pain ($r = 0.15$) and MHAQ ($r = 0.24$).

Comparison of MMP-3 serum levels between CRP, RF and anti-CCP positive and negative groups showed a significant difference ($p = 0.0001$; $p = 0.009$ and $p = 0.042$ respectively) (Table 2). The serum level of MMP-3 showed a significant correlation with the ESR ($r = 0.62$, $p = 0.001$) (Fig. 3a).

Serum MMP-3 significantly correlated with the vdHSS, ($r = 0.78$, $p < 0.0001$) in RA patients (Fig. 3b); the difference was significant in those with erosions compared to those without ($p = 0.001$) (Fig. 4).

Serum MMP-3 levels significantly negatively correlated with total cumulative steroid dose in the RA patients ($r = -0.2$, $p = 0.03$) and when compared between patients receiving and those who never received steroids, there was a highly significant difference ($p = 0.004$). There was a highly significant difference between MMP-3 serum levels in RA

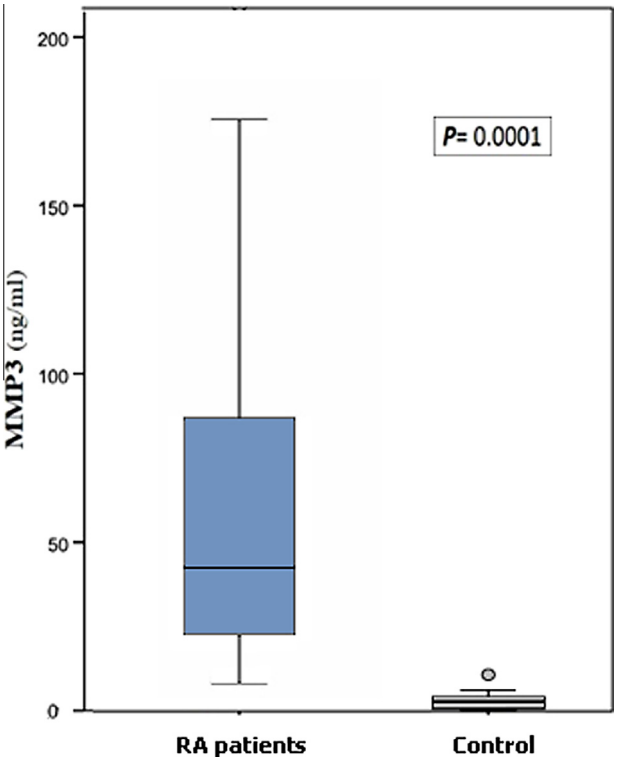

Figure 1 Serum MMP-3 level in rheumatoid arthritis patients and controls.

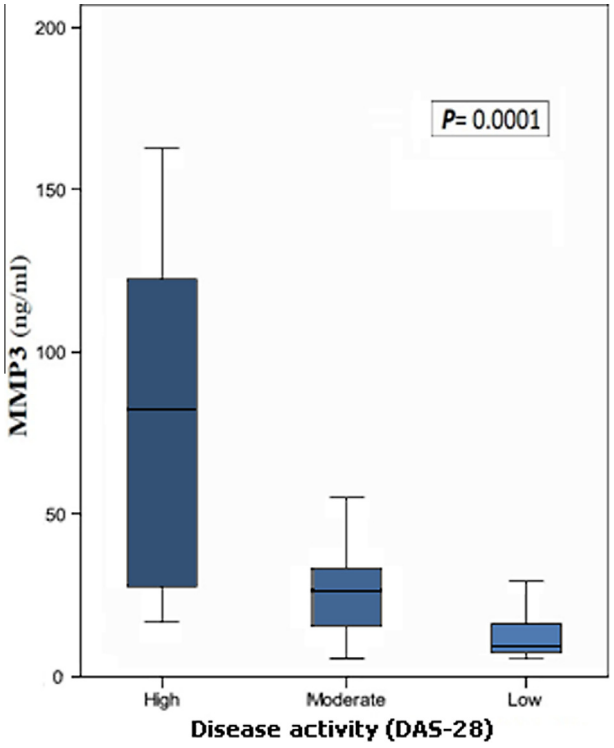

Figure 2 Serum MMP-3 levels in relation to DAS 28 score in rheumatoid arthritis patients.

patients who never received DMARDs (63.71 ± 49 ng/ml) and those receiving (11.183 ± 5.66 ng/ml) ($p = 0.001$).

4. Discussion

Some baseline demographic and laboratory markers in RA (e.g. female sex, older age, RF, anti-CCP seropositivity, raised CRP or ESR) have been associated with a poor prognosis. Surprisingly, none of these markers specifically reflect ongoing destructive processes within bone and synovium [23]. The increased MMP-3 serum level is associated with the presence of synovitis, reflecting the inflammatory reaction occurring in the joints, whether acute or chronic, of erosive potential or not and positively correlated with the number of joints affected [24].

In the present study, serum MMP-3 levels were significantly higher in the RA patients than in controls ($p = 0.0001$). This nearly coincides with the results of Ally et al. [1] and Tchetverikov et al. [25]. There was no significant difference in the level between male and female patients ($p = 0.24$). In agreement was the study of Sun et al. [26] that reported no sex differences in MMP-3 levels in their RA patients. In contrast to our results, Ribbens et al. [24] reported that serum levels of MMP-3 were significantly higher in men than in women ($p < 0.0001$).

On correlating serum MMP-3 levels with the age of our patients we had found no significant correlation ($p = 0.12$) and this agrees with the results of Keyszer et al. [27], since the influence of inflammatory processes on MMP-3 levels, probably outweighs the effect of age. There was a significant correlation between serum MMP-3 levels and disease duration with the highest levels in patients with disease duration >10 years. This may be due to the destructive progression which is thought to be mediated by potent enzymes which breakdown the tissues of the joint. The MMP family is heavily implicated in these processes, as collectively they are able to degrade most components of cartilage [28].

MMP-3 significantly correlated with disease activity as measured by DAS28, being higher in the patients with high disease activity than those with moderate or low disease activity. However, no significant correlation was found between MMP-3 and VAS for pain or MHAQ. On the contrary, it has been postulated that an over-expression of MMP-3 in synovial fluid, rheumatoid synovium and cartilage as well as an increased level of MMP-3 in the serum obtained from RA patients clearly reflects its contribution in chronic inflammation and joint destruction [29]. This comes in agreement with

Table 2 Comparison of serum MMP-3 between CRP, RF and Anti-CCP positive and negative groups.

	MMP-3 (ng/ml) in RA patients		
		Mean ± SD	*p*
CRP	Negative	12.19 ± 5.67	**0.0001**
	Positive	64.6 ± 49	
RF	Negative	27.72 ± 41.8	**0.009**
	Positive	52.8 ± 47.42	
Anti-CCP	Negative	16.01 ± 9.15	**0.042**
	Positive	52.64 ± 49.03	

CRP, C-reactive protein; RF, Rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide. Bold values are significant at $p < 0.05$.

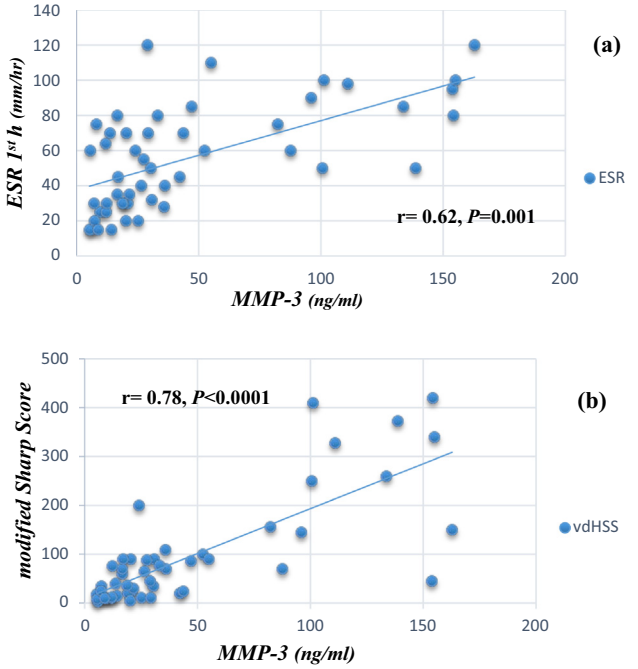

Figure 3 Correlation between serum levels of MMP-3 and (a) ESR (b) modified Sharp Score in RA patients.

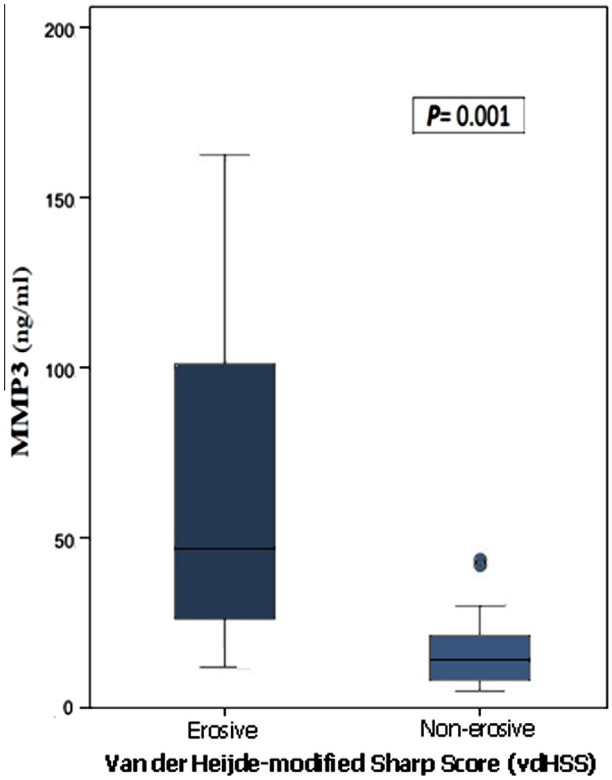

Figure 4 Serum MMP-3 levels in rheumatoid arthritis patients with and without erosions according to the Van der Heijde-modified Sharp Score (vdHSS).

the findings of Ateş et al. [30]; Serum pro-MMP-3 levels were found to be significantly higher their patients having high (54.6 ng/ml) or moderate disease activity (46.2 ng/ml) than those with low disease activity (27.3 ng/ml) ($p < 0.01$); while there were no significant differences of the VAS ($r = 0.13$, $p > 0.05$). In contrast, the correlation of MMP-3 with the health assessment questionnaire (HAQ) investigated by Green et al. [31], found a significant correlation ($r = 0.23$, $p < 0.01$) in early untreated RA patients and concluded that baseline serum MMP-3 levels predict functional outcome.

In our work, on correlating MMP-3 serum levels, with some established laboratory markers of RA as ESR, CRP, RF and anti-CCP we found that, serum MMP-3 levels significantly correlated with ESR ($p = 0.001$), with significant differences between positive and negative CRP, RF and Anti-CCP patients ($p = 0.0001$, $p = 0.009$, $p = 0.042$, respectively). In support to our results Ally et al. [1]; found that MMP-3 correlated significantly with laboratory measures, specifically ESR, CRP, and RF but there was no significant association of MMP-3 with anti-CCP. Another study [26] also found that MMP-3 levels correlated with markers of inflammation (ESR and CRP) and Visvanathan et al. [32] showed significant correlations with CRP ($r = 0.6$, $p < 0.001$). Confirming our results, the study of Peake et al. [33] found that MMP-3 levels correlated significantly with ESR ($r = 0.41$, $p = 0.01$). In a study on Egyptian RA patients, MMP-3 strongly correlated with the CRP [18].

In our study, according to the Van der Heijde-modified Sharp Score (vdHSS), serum MMP-3 levels were significantly higher in erosive RA patients than non-erosive ($p = 0.001$). Our results agreed with Tchetverikov et al. [34], who had examined 109 patients with RA of recent onset, and had followed the patients for 2 years. They had found that MMP-3 levels were significantly higher in the group of severe joint damage progression compared with mild disease at all times, at baseline, at 1 and 2 years ($p = 0.02$, $p = 0.001$ and $p = 0.004$ respectively). Houseman et al. [23] demonstrated that the measurement of serum MMP-3 levels at baseline adds to the predictive value of anti-CCP in determining the long-term radiographic outcome in patients with RA. Young-Min et al. [35] had stated that serum levels of MMP-3 predicted and correlated with radiographic progression and joint destruction. These results supported the notion that MMP-3 has a significant role in the pathogenesis of RA. The relationship between MMP-3 serum levels and the progression of joint damage in early RA, was also studied by Cunnane et al. [36] who had noted that serum MMP-3 were higher in RA versus non-RA patients (seronegative spondylarthropathy, undifferentiated arthritis, and self-limiting arthritis) and that the number of joint erosions at presentation significantly correlated with baseline MMP-3 ($p = 0.003$). Moreover, in a 1-year follow up study on Egyptian RA patients there was a significant correlation between baseline levels of MMP-3 and MRI erosion score while after 1-year there was a significant correlation with the van der Heijde modification of the Sharp scoring system score [17].

The serum MMP-3 levels were significantly higher in patients receiving and those who never received steroids ($p = 0.004$); Serum MMP-3 levels negatively correlated with cumulative steroid therapy in our RA patients ($r = -0.2$, $p = 0.03$) and this is matched with results of Ribbens et al. [24] and Green et al. [31]. There was a highly significant difference between MMP-3 serum levels in RA patients who never received and those receiving different conventional DMARDs ($p = 0.001$). In agreement to our findings; serum MMP-3

levels in patients treated with MTX are consistent with Catrina et al. [37] that have shown a decrease in circulating MMP-3 levels with conventional and biological DMARDs therapy. Supporting evidence for the prognostic significance of MMP-3 in RA, however, includes its expression in RA synovial tissue and the decreasing serum MMP-3 levels following DMARD treatment [38].

In conclusion, elevated MMP-3 serum levels reflect disease activity in RA patients and can be used as a specific marker for joint damage but the cross sectional design of this study did not allow us to produce conclusions with respect to disease course and prognosis. Thus we recommend further studies on large numbers of patients and serial measurements of MMP-3 to determine the rate of disease progression or erosion development and we recommend using MMP-3 level as a useful marker for disease activity.

Conflicts of interest

The authors declare no conflicts of interest.

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