Levels of Serum Matrix Metalloproteinase-3 Correlate with Disease Activity in the Enthesitis-related Arthritis Category of Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** Serum matrix metalloproteinase-3 (MMP-3) has been shown to reflect disease activity in ankylosing spondylitis (AS) and rheumatoid arthritis. Elevated levels have been found in juvenile idiopathic arthritis (JIA). In the enthesitis-related arthritis category of JIA (JIA-ERA), we studied whether serum MMP-3 levels and ratios of MMP-3/tissue inhibitor of metalloproteinase (TIMP-1) are correlated with disease activity and whether they are sensitive to change in disease activity.

Methods. A total of 54 patients with JIA-ERA (International League of Associations for Rheumatology criteria) were enrolled for study. Baseline disease activity measures included tender and swollen joint counts, Maastricht AS Enthesitis Score, Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), patient assessment of pain and global disease activity, physician assessment of global disease activity, and erythrocyte sedimentation rate (ESR). Serum MMP-3 and TIMP-1 levels were measured using ELISA. A group of 24 patients were followed up for longitudinal study.

Results. The mean age of 54 patients (48 males) at disease onset was 11.8 ± 4.19 years and duration of disease was 5.2 ± 4.3 years. Median ESR was 65 mm/h (range 46.5–97) and median BASDAI was 3.4 (range 2.5–4.7). Median MMP-3, TIMP-1, and MMP-3/TIMP-1 ratio were 50.4 ng/ml (IQR 13.0–193.8), 228.9 ng/ml (IQR 108.2–290.4), and 0.3 (IQR 0.07–1.13), respectively. At inclusion MMP-3 levels correlated directly with various disease activity measures: tender joint count (TJC; r = 0.60), swollen joint count (SJC; r = 0.45), BASFI (r = 0.29), BASDAI (r = 0.32), ESR (r = 0.49), physician global assessment (r = 0.40), patient visual analog scale for pain (r = 0.28), and patient global assessment (r = 0.38; all $p < 0.05$). MMP-3/TIMP-1 ratio correlated only with TJC (r = 0.51), SJC (r = 0.39), and ESR (r = 0.34; $p < 0.05$). At followup, change in MMP-3 correlated with changes in TJC (r = 0.42) and SJC (r = 0.44; $p < 0.05$), while change in ESR did not correlate with change in any disease activity measure.

Conclusion. MMP-3 levels are a good marker for disease activity in JIA-ERA. (First Release Sept 1 2011; J Rheumatol 2011;38:2482–7; doi:10.3899/jrheum.110352)

Key Indexing Terms:
JUVENILE ARTHRITIS
DISEASE ACTIVITY
INFLAMMATION
MATRIX METALLOPROTEINASE-3

Enthesitis-related arthritis (ERA) is recognized as a distinct category of juvenile idiopathic arthritis (JIA). Presence of enthesitis, male bias, occurrence beyond the age of 6 years, association with HLA-B27, and positive family history clearly distinguish it from the other JIA categories[1]. Worldwide, the reported prevalence of ERA among patients with JIA is 8%–14%, but studies from India have shown it to be the most prevalent category of JIA[2,3,4,5]. Even a multicultural cohort from Canada showed ERA to be more prevalent in an Asian community[6]. In a case-control study of longterm outcome in ERA, Flato, *et al* had shown that at a median duration of 15.3 years (range 11.7–21.9 yrs), 35% of the patients developed radiological sacroilitis[7]. Outcome studies in JIA have shown that among its categories patients with ERA have high morbidity, with pain, disability, and poor quality of life[7]. At the same time, measurement of disease activity in these patients is far from perfect, with sparse data on the utility of biomarkers or composite indices for disease activity assessment.

Matrix metalloproteinases (MMP) are zinc-related endopeptidases that directly damage cartilage and synovium. They are secreted in a pro-form and are activated by catalytic cleavage by other MMP[8]. MMP-3 is an important enzyme in this process. Tissue inhibitors of metalloproteinases (TIMP) are the natural inhibitors of MMP, in a 1:1 stoichometry, TIMP-1 being the natural inhibitor of MMP-3. MMP levels are elevated in serum and synovial fluid of patients with various forms of inflammatory arthritis[9,10,11,12,13,14]. In patients with ankylosing spondylitis (AS), serum levels of MMP-3 and MMP-3/TIMP-1 ratios correlate with disease activity meas-

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Submitted for publication June 29, 2011.

ures, and their levels diminish after treatment with tumor necrosis factor (TNF) antagonist coinciding with clinical remission[13]. Two studies in JIA have also shown increased levels of serum MMP-3 compared to controls, and MMP levels correlated with various disease activity indices[15,16]. However, none of these studies did a subgroup analysis for patients with ERA. Previous studies from our group had shown that the MMP-3 levels and MMP-3/TIMP-1 ratios were elevated in serum and synovial fluid of patients with JIA including ERA[17,18]. In contrast to systemic-onset and polyarticular JIA, where there are good laboratory markers for assessment of disease activity, there are currently no validated disease activity measures for ERA.

We investigated the relationship between levels of MMP-3 and MMP-3/TIMP-1 ratios and disease activity in ERA and also whether these are sensitive to change in disease activity.

MATERIALS AND METHODS

A total of 54 patients with JIA-ERA satisfying International League of Associations for Rheumatology criteria[1] and attending the outpatient clinic of the Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, were enrolled in the study. Twenty-four patients were followed up at a second visit. Patients received treatment according to the treating physician's assessment. The study was approved by the institutional ethics committee and written informed consent was obtained from all patients/parents.

Disease activity was measured by using swollen (SJC) and tender joint counts (TJC), Maastricht AS Entheses Score (MASES), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and Bath AS Metrology Index (BASMI)[19]. MASES is a measure of enthesitis based on assessment of 13 entheseal sites. These include the first and seventh costochondral junction, anterior and posterior superior iliac spine, iliac crest, Achilles tendon on either side, and fifth lumbar spine. One point is given for positive tenderness in each of these areas, while absence of tenderness is scored zero. BASDAI and BASFI are questionnaire composite indices for disease activity and functional disability, respectively, used in patients with AS. BASDAI assesses the disease activity based on fatigue, axial, entheseal and peripheral joint pain, and early morning stiffness, while BASFI assesses the disability in certain predefined activities of daily living. BASMI measures cervical rotation, tragus to wall distance, lateral and forward lumbar flexion, and intermalleolar distance on an 11-point scale. MASES, BASDAI, BASFI, and BASMI are validated measures of disease activity in adult spondyloarthropathy, although they have not yet been validated in patients with JIA-ERA. A 10-cm visual analog scale (VAS; 0–100) was used to assess physician and patient global disease activity assessments (PhyVAS G and PatVAS G). PhyVAS G was based on overall assessment of symptoms including pain in spine and peripheral joints and entheseal involvement, early morning stiffness, and examination findings related to them. PatVAS G was the response to the question, "If your disease can be measured in a scale of 0–100, 0 being the best possible state and 100 being the worse possible state, how active was your disease in the last 1 week?". Patient pain (PatVAS P) was also measured on 0–100 scale (0 = no activity and 100 = maximum activity). Inactive disease was defined as absence of active arthritis or enthesitis.

Patients' blood was drawn (6-ml sample) and serum was separated by centrifuge at 1000 g for 10 min. Serum was stored in aliquots at –40°C. Erythrocyte sedimentation rate (ESR) was determined by Westergren technique. MMP-3 and TIMP-1 were estimated by ELISA using a commercial kit (R&D Systems, Minneapolis, MN, USA). The assay measured pro-MMP-3, active MMP-3, and MMP-3 bound to TIMP-1. The procedure recommended by the manufacturer was followed. Both assays were done in 1:200 dilution and had the lowest detection limit of 6.25 ng/ml. Samples with values less than the detectable limit were assigned a value of 0.

Statistical analysis. All statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Rainbow Technologies, Somers, NY, USA). Spearman's rank correlation coefficient was used to ascertain the relation between the concentration of MMP-3 and MMP-3/TIMP-1 ratio and various disease activity measures. Change in MMP-3 levels between 2 timepoints (ΔMMP-3) was correlated with change in disease activity measures over the same period.

RESULTS

Of the 54 patients, 48 were male. The mean age at onset of disease was 11.8 years (SD 4.19) and duration of disease was 5.2 years (SD 4.3) at the time of inclusion into the study (Table 1). The mean age at inclusion was 16.8 years (SD 4.0). Forty-eight patients were receiving nonsteroidal antiinflammatory drugs (NSAID) and 23 disease-modifying antirheumatic drugs (DMARD; methotrexate, n = 19; sulfasalazine, n = 8; leflunomide, n = 1). Seven patients were also receiving low-dose corticosteroid. HLA-B27 was positive in 47/53 patients. HLA-B27 could not be assessed due to nonavailability of sample in 1 patient. Twenty-three (53%) of 43 patients had unilateral or bilateral sacroiliitis, grade ≥ 2.

At enrollment, out of 54 patients, 18 had arthritis with enthesitis, 11 arthritis only, 8 enthesitis only, and 17 had inactive disease (Table 2).

The median MMP-3 values at inclusion were 50.4 ng/ml (IQR 13.0–193.8). MMP-3 levels were undetectable in 10 of 54 patients. MMP-3 values at inclusion correlated significantly with various disease activity indicators (Figure 1, Figure 2). The correlations were strong with TJC ($r = 0.60$, 95% CI 0.42–0.76, $p < 0.01$), SJC ($r = 0.45$, 95% CI 0.21–0.64, $p < 0.01$), ESR ($r = 0.49$, 95% CI 0.26–0.67, $p < 0.01$), and PhyVAS ($r = 0.40$, 95% CI 0.15–0.60, $p < 0.01$; Figure 1). However, MMP3 levels did not show significant correlation with the MASES entheseal index or TIMP-1 values.

The median level of MMP-3 in patients with active disease (arthritis/enthesitis) was 110 (IQR 19.5–220.7) ng/ml in comparison to median levels of 29.7 (IQR 0–75.5) ng/ml in those with inactive disease. In a subgroup analysis, the median MMP-3 level in patients with arthritis with/without enthesitis was higher than in those with enthesitis alone, 164 (IQR 47.9–251.4) ng/ml vs 11.3 (IQR 0–18.6) ng/ml ($p < 0.01$).

Table 1. Clinical data of patients with ERA included in the study (n = 54).

Characteristic	Value
Males:females	49:5
Mean age at onset (SD), yrs	11.8 (4.19)
Mean duration of disease onset (SD), yrs	5.2 (4.3)
HLB-27-positive	47/53
Sacroiliitis (%)	23/43 (53)
Drugs, n	NSAID 48, DMARD 23
No. patients with arthritis only	11
No. patients with enthesitis only	8
No. patients with arthritis and enthesitis	18
No. patients without arthritis or enthesitis	17

NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug.

Table 2. Disease activity in patients at inclusion (n = 54).

Feature	Median (IQR)
Tender joint count	0 (0–2)
Swollen joint count	0 (0–2)
MASES	0 (0–1)
BASDAI	3.4 (2.5–4.7)
BASFI	2.1 (0.6–3.8)
Physician global assessment (0–100)	50 (37.5–61.3)
Patient global assessment (0–100)	50 (30–71.3)
Patient pain (0–100)	50 (30–72.3)
ESR, mm/h	65 (46.5–97)

MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

The median TIMP-1 level at inclusion was 228.9 (IQR 108.2–290.4) ng/ml. The median MMP-3/TIMP-1 ratio was 0.35 (IQR 0.07–1.13). The MMP-3/TIMP-1 ratio also showed significant correlations with TJC (r = 0.51, 95% CI 0.28–0.68), SJC (r = 0.39, 95% CI 0.14–0.59), and ESR (r = 0.34, 95% CI 0.08–0.56; all $p < 0.05$; Figure 3). However, the ratio did not correlate with any other measure of disease activity.

Followup results. Twenty-four patients were followed up at a second visit after a median followup period of 7 months (range 3–10 mo; Table 3). They were treated according to treating physician's assessment and were included again on followup. Most patients received NSAID, intraarticular steroids, or DMARD. No patient received anti-TNF agents.

The change in MMP-3 (ΔMMP-3) between first and followup visit was determined, and was found to correlate with changes in disease-related indicators. Significant correlations were seen between ΔMMP-3 and ΔTJC (r = 0.42, 95% CI 0.02–0.70, $p < 0.05$) and ΔSJC (r = 0.44, 95% CI 0.44–0.72, $p < 0.05$; Figure 4]. In contrast, change in ESR did not correlate with change in SJC or TJC (Figure 4).

DISCUSSION

Ours is the first study showing that MMP-3 is a good marker for disease assessment in the ERA category of JIA and that it is sensitive to change in disease activity. Further, the correlation of MMP-3 levels was consistent across multiple disease activity measures, both objective and subjective.

MMP-3 is produced in the joint by synovial fibroblasts and chondrocytes in an inactive proenzyme form and it is self-activated locally[8,20]. Since MMP-3 is produced locally at sites of joint inflammation and is a direct effector of cartilage and synovial damage, it is not surprising that we found the maximum association of MMP-3 levels with presence of peripheral

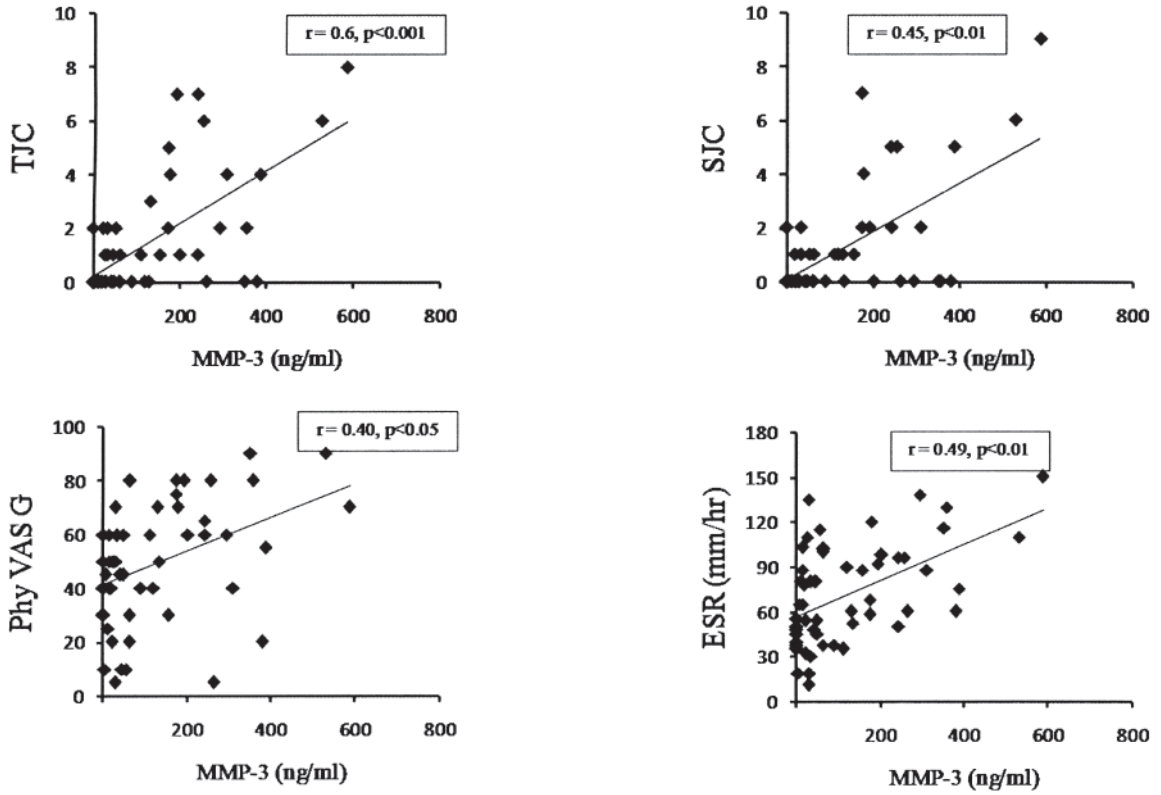

Figure 1. Scatterplot showing correlation of matrix metalloproteinase-3 (MMP-3; ng/ml) with disease activity measures: tender joint count (TJC), swollen joint count (SJC), physician VAS for global activity (PhyVAS G), and erythrocyte sedimentation rate (ESR). Correlation coefficient was calculated using Spearman's rank correlation and is shown as r. The 95% CI were 0.42–0.76 for TJC, 0.21–0.64 for SJC, 0.15–0.6 for PhyVAS G, and 0.26–0.67 for ESR.

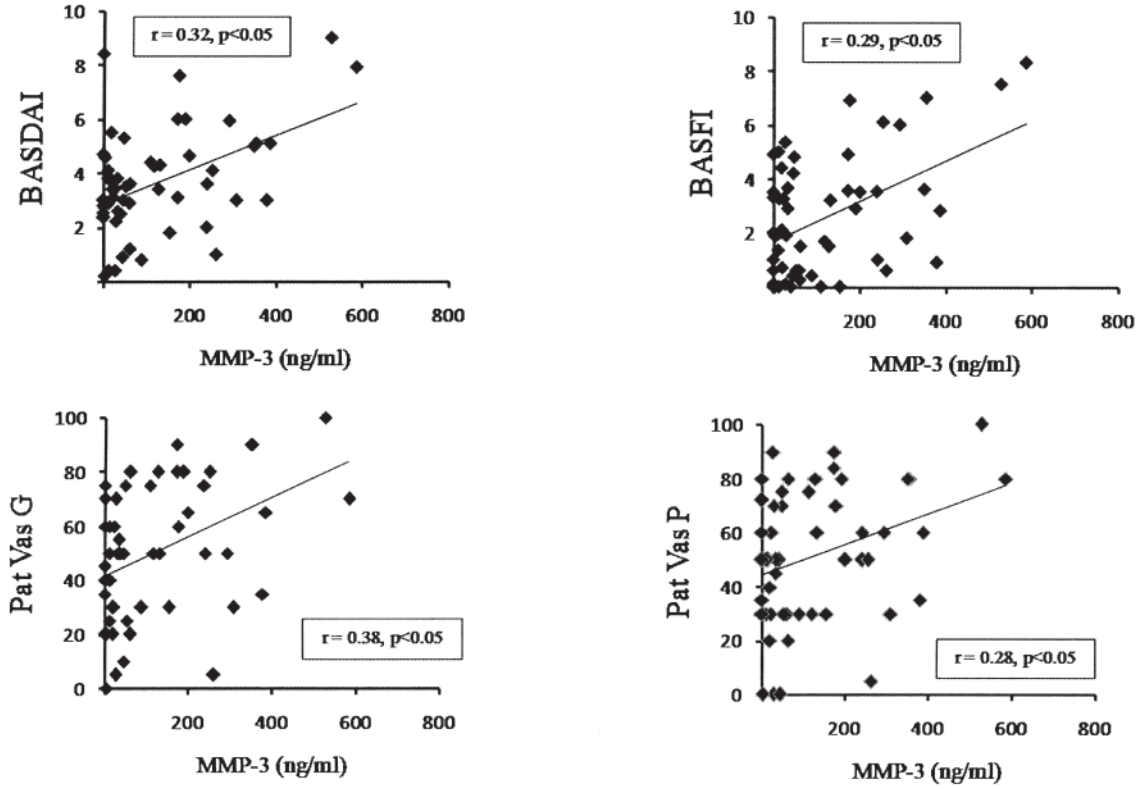

Figure 2. Scatterplot showing correlation of matrix metalloproteinase-3 (MMP-3; ng/ml) with disease activity measures: Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), patient VAS for global disease activity (PatVAS G), and patient VAS for pain (PatVAS P). Correlation coefficient was calculated using Spearman's rank correlation and is shown as r. The 95% CI were 0.05–0.54 for BASDAI, 0.02–0.52 for BASFI, 0.12–0.59 for PatVAS G, and 0.01–0.51 for PatVAS P.

arthritis. In previous studies from our group, synovial fluid levels of MMP-3 were shown to be significantly elevated in patients with inflammatory arthritis as compared to osteoarthritis[18]. Studies in rheumatoid arthritis (RA), AS, and JIA have shown that although concentrations of MMP-3 are several hundred-fold higher in the synovial fluid in comparison to serum levels, they correlate strongly with serum MMP-3 and both are good markers of joint inflammation[11,15,20].

Our study showed lack of correlation between serum levels of MMP-3 and enthesitis. Further, the levels of MMP-3 in patients with only enthesitis were lower than the patients with coexistent arthritis or only arthritis. This observation is consistent with a previous study in AS demonstrating significantly elevated MMP-3 levels in AS patients with peripheral arthritis as compared to those with only axial disease[14,20].

TIMP-1, the inhibitor of MMP-3, is produced in response to inflammation. The molar ratio of MMP-3/TIMP-1 has been shown to correlate with disease activity in patients with RA and AS[9,14]. However, in our study, the molar ratio of MMP-3/TIMP-1 had a weaker association with markers of disease activity as compared to those seen with MMP-3 levels.

In the longitudinal analysis, change in MMP-3 level closely reflected change in disease activity, suggesting that MMP-3 is a sensitive marker of disease activity. MMP3 performed marginally better than ESR as a measure of disease activity, especially in patients with peripheral arthritis. This could be partly related to the short half-life of MMP-3 and the direct pathogenic role of MMP-3 in joint inflammation, thus reflecting ongoing joint inflammation better[8,20].

Our study has limitations, i.e., inclusion of patients with long disease duration and receiving drugs, use of unvalidated measures like BASDAI and BASFI, limited followup data, and lack of data on radiological damage. Longitudinal studies in RA and AS had demonstrated good correlation of MMP-3 levels with structural damage[21,22,23,24].

Thus the data suggest that MMP3 levels correlate with various measures of disease activity in ERA and may be a potential biomarker in ERA. Further study of the effect of treatment on levels of MMP3 in patients with ERA may establish its role as a biomarker.

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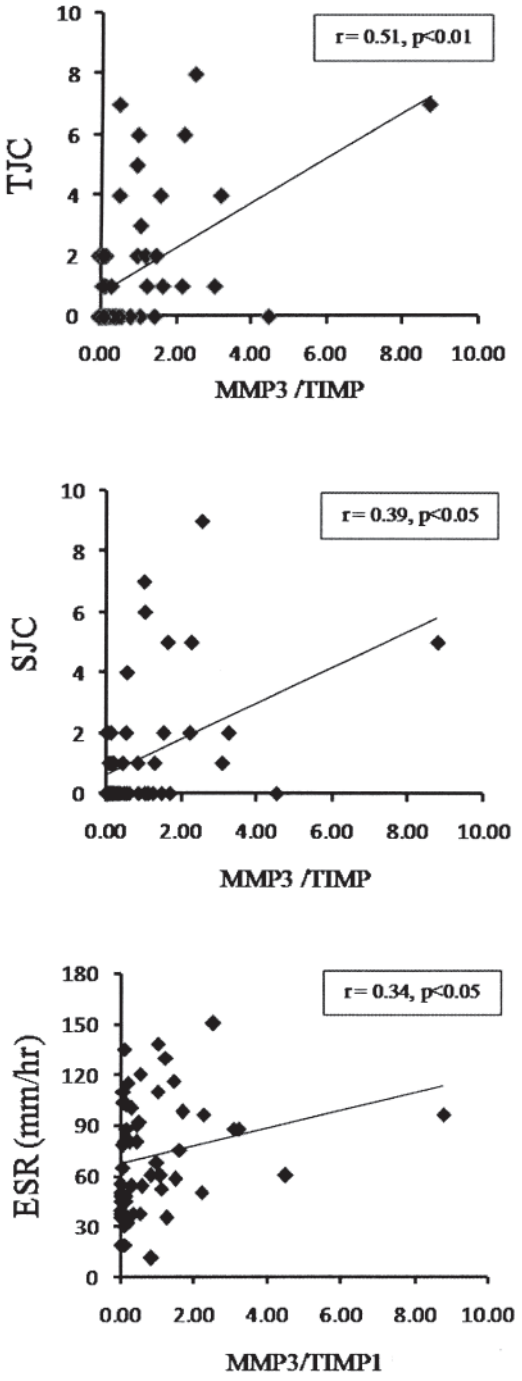

Figure 3. Scatterplot showing correlation of MMP-3/TIMP-1 ratio with tender joint count (TJC), swollen joint count (SJC), and erythrocyte sedimentation rate (ESR). Correlation coefficient was calculated using Spearman's rank correlation and is shown as r. The 95% CI were 0.28–0.68 for TJC, 0.14–0.59 for SJC, and 0.08–0.56 for ESR.

Table 3. Disease activity at inclusion and at followup in 24 patients.

Feature	Median (IQR) at Baseline	Median (IQR) at Followup
Tender joint count	0 (0–2)	0 (0–1)
Swollen joint count	0 (0–2)	0.0 (0–0)*
MASES	1 (0–1.75)	0 (0–1.3)*
BASDAI	3.5 (2.6–5)	2.7 (1.5–4.4)
BASFI	1.9 (0.6–4.2)	0.6 (0–4.5)
BASMI	1.8 (1.6–2.4)	1.8 (1.4–2.3)
Physician global assessment (0–100)	55 (40–63.8)	30 (10–60)*
Patient global assessment (0–100)	50 (31.3–75)	35 (10–67.5)
Patient pain (0–100)	50 (31.3–74.3)	40 (11.3–70)
ESR, mm/h	65 (45–96)	48 (31–80)*
MMP-3 ng/ml	33.8 (< 6.25–223.7)	6.34 (< 6.25–86.1)*
TIMP-1 ng/ml	200.6 (105.1–287.6)	209.7 (78.8–250.8)
MMP-3/TIMP 1	0.18 (0.003–1.72)	0.11 (0–0.36)

* $p < 0.05$. BASMI: Bath Ankylosing Spondylitis Metrology Index; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinase; for other definitions see Table 2.

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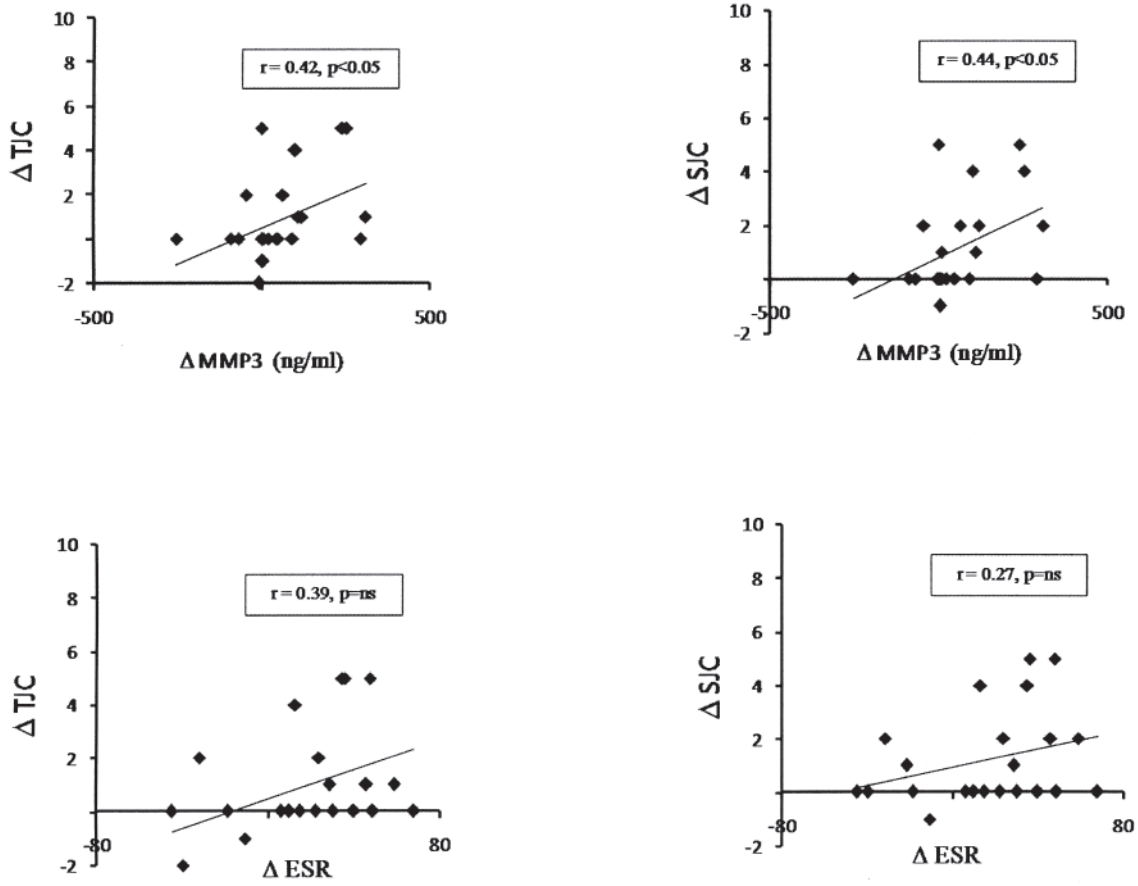

Figure 4. Scatterplot showing correlation of change in MMP-3 (ΔMMP-3; ng/ml) with change in tender joint count (ΔTJC), swollen joint count (ΔSJC), and of change in erythrocyte sedimentation rate (ΔESR) with ΔTJC and ΔSJC. Correlation coefficient was calculated using Spearman's rank correlation and is shown as r. The 95% CI were 0.02 to 0.70 for ΔTJC vs ΔMMP3, 0.05 to 0.71 for ΔSJC vs ΔMMP3, –0.01 to 0.68 for ΔTJC vs ΔESR, and –0.15 to 0.61 for ΔSJC vs ΔESR.

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