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ORIGINAL ARTICLE

Role of matrix metalloproteinase-3 (MMP-3) and magnetic resonance imaging of sacroiliitis in assessing disease activity in ankylosing spondylitis

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Abstract The objective of this study is to evaluate the role of MMP-3 and MRI in assessing disease activity in sacroiliac joints of AS patients in comparison to the conventional measures Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Serum MMP-3 was measured in 30 patients who fulfilled the modified New York criteria for AS and in ten healthy volunteers. AS patients were categorized into those having high or low MMP-3 according to a cut-off value = 7.1 ng/ml. MRI of the sacroiliac joints (SIJs) was performed on all patients. SIJs were evaluated for enhancement and subchondral bone marrow edema. Results of MMP-3 and findings on MRI were correlated with multiple clinical parameters including BASDAI, ESR and CRP. Serum MMP-3 was significantly elevated in AS patients with active disease. Elevated MMP-3 levels were significantly associated with high BASDAI ($P = 0.046$), but not with ESR or CRP. MRI showed bone marrow edema and enhancement of SIJs in 19/30 patients with one patient showing enhancement only. These MRI findings were not correlated with MMP-3, BASDAI, CRP or ESR. In conclusion, serum MMP-3 is an objective measure reflecting clinical disease activity in AS. Bone marrow edema and enhancement detected by MRI of SIJs is another objective measure of disease activity, but are not correlated with MMP-3 or the conventional parameters as BASDAI, ESR, or CRP. Although both MMP-3 and MRI can reflect disease activity in AS they seem to be unrelated, perhaps each is reflecting a different aspect of disease activity. MMP-3 and MRI should be considered together with BASDAI in assessing disease activity and in guiding the available recommendations for initiation of biologics in AS.

Keywords Ankylosing spondylitis · Disease activity · BASDAI · MMP-3 · MRI

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Introduction

Over the past few years both clinicians and patients awareness of ankylosing spondylitis (AS) and its outcomes has increased owing to the availability of new treatments, such as the tumor necrosis factor-alpha (TNF-) inhibitors, as well as recent imaging modalities [1]. Because of the high cost of these drugs, it is important to generate an accurate method to measure disease activity to ensure that a particular patient will have a favorable response to the drugs.

The available Assessment of SpondyloArthritis International Society (ASAS) recommendations for treatment of AS patients with TNF-blockers depend on Bath AS Disease Activity Index (BASDAI) of four or more as the gold

standard indicator of active disease and hence the start of biologics [2]. BASDAI is a completely subjective tool, depending on patient response to a six-item questionnaire, which will vary depending on understanding, culture, education, pain threshold and patient functional disability [3]. In addition, although the BASDAI is regarded as a marker of inflammatory activity, this index has shown poor correlation with other serological markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) which are commonly used as measures of disease activity in many rheumatologic diseases [4]. The poor diagnostic value of ESR and CRP levels has led to investigating the role of a number of candidate biomarkers to measure disease activity in AS.

Recent studies measured matrix metalloproteinases (MMPs) to explore these biomarkers as useful tools for assessing disease activity more accurately in AS.

MMPs play an important role in the degradation and remodeling of the extracellular matrix, which is a pathological feature of chronic arthritis [5]. MMPs are zinc-dependent endopeptidases, essential in normal biological functions, and participate in many pathological conditions [6, 7]. MMPs are produced by fibroblasts, macrophages, synovial cells, endothelial cells, neutrophils and chondrocytes in response to proinflammatory cytokines such as interleukin-1 and TNF [8]. Of the MMP family, MMP-3 (stromelysin 1) hydrolyses a number of extracellular matrix components, including aggrecan, fibronectin, laminin and collagens and also activates several pro-MMPs, such as pro-MMP-1 and pro-MMP-9 [9].

Measuring MMP and tissue inhibitors of metalloproteinase (TIMP) has gained recent interest in different rheumatic diseases [5]. MMP-3 has been lately of outstanding interest in spondyloarthropathies (SpA) especially ankylosing spondylitis. Several new researches proved MMP-3 to be a sensitive and reproducible biomarker of disease activity in AS. MMP-3 is significantly increased in patients with active disease [10]. Changes in serum MMP-3 levels were evaluated following different TNF-therapy [11]. TNF-antagonist therapy induces a significant decrease in MMP-3 levels, together with decreases in conventional variables (ESR, CRP, and BASDAI). MMP-3 is a promising biomarker for disease activity in AS but its clinical implications are still under investigation [12].

Another parameter of disease activity in AS is the radiologic activity. The course of spinal inflammation associated with AS can be demonstrated by magnetic resonance imaging (MRI) [13, 14]. This new imaging technique is achieving a more central role to confirm diagnostic suspicion, thus enabled the earlier diagnosis of inflammatory back pain and has been recently included in the ASAS criteria for diagnosis of spondyloarthropathies (SpA) [15]. Furthermore, MRI is the most sensitive imaging modality for detection of active inflammation in spine and sacroiliac joints (SIJs) [16] and a significant reduction in spinal inflammation has been shown with MRI after treatment with anti-TNF-agents [17]. Hence, it is another objective tool for detection of disease activity. However, the exact link between clinical disease activity (BASDAI) and spinal inflammation as seen on MRI has not been well defined and many patients with low BASDAI will still show activity on MRI.

Although MMP-3 and MRI have been recently highlighted as objective tools in assessing disease activity in AS, yet the association between MMP-3 and disease activity and inflammation detected by MRI is not well studied. In this study, we are investigating the relation between recent objective measures of AS disease activity (MMP-3 and MRI) and conventional ones (BASDAI, ESR and CRP).

Objective

To evaluate the role of MMP-3 and MRI of SIJs in assessing disease activity in AS patients in comparison to the conventional measures: BASDAI, ESR and CRP.

Materials and methods

This research was approved by the Alexandria University Ethical Committee. The study was conducted on 30 AS patients, who visited the rheumatology outpatient clinic in Alexandria main university hospital and fulfilled the 1984 Modified New York criteria [18] for the diagnosis of AS. The control group included ten healthy volunteers of matched age and sex. All patients were examined by the same researcher after giving a written informed consent. Patients were evaluated clinically and disease measurements were carried out and included.

- BASDAI, a six-item patient self-administered questionnaire. Each item was scored on a 0–10 numerical rating scale (NRS) [3, 19].
- The patient's global assessment of disease activity (BASGI) (0–10 NRS) [20].
- Bath AS Functional Index (BASFI), a ten-item (0–10 NRS) self-administered questionnaire that assesses functional disability [21].
- The Bath AS Metrology Index (BASMI) for evaluation of the axial status, which consists of five measurements: tragus to wall distance, cervical rotation, lumbar side flexion, lumbar flexion and intermalleolar distance [22].

Exclusion criteria

Only AS patients with axial disease were included, whereas AS with arthritis in at least one peripheral joint were

excluded from the study. Patients with ongoing or previous therapy with TNF-α inhibitors or other biological agents and patients with technical contraindications to MRI such as cardiac pacemakers and similar devices were also excluded.

MRI technique

All patients were imaged using the closed-configuration Philips Gyroscan Intera 1.5T MRI machine located at the Department of Radiodiagnosis, Main University Hospital of Alexandria. Sacroiliac joints were evaluated for enhancement (ENH) and subchondral bone marrow edema (BME). Radiologic activity in sacroiliac joints was defined according to the ASAS definitions for active lesions on MRI of SIJs [23].

Patients were scanned in the supine position using a body coil. A coronal oblique scan plane parallel to the length of the sacrum was chosen. Two slabs were employed—one transverse, positioned cranially to the region of interest to diminish flow artifacts, and one frontally through the bowel and anterior abdominal wall, to diminish motion artifacts from breathing and bowel movements. The following sequences were used [24]:

1. Coronal and axial oblique T1 weighted turbo-spin-echo (TSE) TE 14 ms, TR 892 ms, matrix 256 × 256, FOV 320 mm, NSA 3 and slice thickness 4 mm with 0.4 mm interspaces.
2. Coronal and axial oblique short time inversion recovery (STIR) TE 55 ms, TR 2,500 ms, matrix 256 × 256, FOV 320 mm, NSA 2 and slice thickness 4 mm with 0.8 mm interspaces.
3. Coronal and axial oblique T2 FS TE 100 ms, TR 3,500 ms, matrix 256 × 256, FOV 320 mm, NSA 2 and slice thickness 4 mm with 0.8 mm interspaces.
4. Coronal and axial oblique T1 weighted TSE with fat suppression (FS) before and after IV administration of gadolinium diethylenetriaminepentate, 0.1 mmol/kg body weight.

Biomarker assay

ESR was measured using Westegreen method and the serum CRP using CRP kit (Electalab-Italy) in all patients and controls, with normal values being less than 10 mm/h and less than 6 mg/l, respectively [25].

Serum samples were obtained and stored at −20°C until assays for MMP-3 were performed.

The MMP-3 ELISA kit measures total MMP-3 including pro-MMP-3, active MMP-3, and MMP-3/TIMP complexes [26]. Serum MMP-3 was measured by ELISA (Icon Central Laboratories, Farmingdale, NY, USA). The MMP-3 assay employed recognizes natural total human MMP-3 but not MMP-3 bound to 2-macroglobulin. The range of the assay is 11–165 ng/ml, with sensitivity of 0.3 ng/ml. Individual samples were diluted 1:5 and assayed in duplicate.

Clinical measurements, blood sampling, and MRI of SIJs were performed on the same day for every patient.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS ver.17 Chicago, IL, USA).

The distributions of quantitative variables were tested for normality using Kolmogorov–Smirnov test which revealed abnormal distribution of the data. Thus, non-parametric statistics were applied. Quantitative data were described using median, minimum and maximum. Mann–Whitney was used to test quantitative independent variables. Correlations between two quantitative variables were assessed using Spearman's rho test.

Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Fisher's exact correction was applied when more than 20% of the cells have expected count less than 5.

Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level. It is quoted as two-tailed probabilities.

Results

Thirty AS patients and ten matched healthy controls were enrolled in the study. The patients constituted 27 men and 3 women, with mean age of 29.1 ± 9.84 years, and mean age at disease onset of 18.8 ± 7.94 years. HLA-B27 was positive in 21 of patients. The clinical and laboratory measures of AS patients are shown in Table 1.

The mean CRP level was statistically higher in AS patients (17.88 ± 15.25 mg/l) than in controls (1.64 ± 0.80 mg/l) ($P = 0.000$). Also, the mean ESR level was statistically higher in patients (40.21 ± 22.1 mg/l) than in controls (8.15 ± 2.3 mg/l) ($P = 0.000$).

The correlation matrix between clinical and serological parameters is shown in Table 2. CRP and ESR were statistically correlated with each other (rho = 0.460, $P = 0.041$) but not with BASDAI or the other clinical parameters. BASDAI was closely correlated with both BASFI (rho = 0.364, $P = 0.034$) and BASGI (rho = 0.608, $P = 0.000$), but not with BASMI (rho = 0.085, $P = 0.631$).

Patients were divided into two subgroups, those with clinically active disease if BASDAI ≥ 4 and those with clinically inactive disease when BASDAI < 4. The number of AS patients in each subgroup was 21 and 9, respectively. Clinical and laboratory parameters were compared between

Table 1 The clinical and laboratory findings in AS patients

Variable	Mean	Standard deviation (SD)	Median	Range	Minimum	Maximum
Occiput-wall (cm)	6.53	9.194	0.00	29.00	0.00	29.00
Chest expansion (cm)	2.55	2.060	2.25	10.00	0.50	10.50
Schober index (cm)	8.79	5.658	11.00	16.00	0.50	16.50
BASDAI	5.12	1.801	5.50	6.10	1.60	7.70
BASFI	5.34	2.321	5.50	8.60	1.40	10.00
BASMI	5.20	3.044	5.50	10.00	0.00	10.00
BASGI	6.48	2.023	6.50	9.00	1.00	10.00
ESR (mm/h)	35.80	18.471	32.00	94.00	3.00	97.00
CRP (mg/l)	17.88	15.254	18.00	58.30	0.50	58.80
MMP-3 (ng/ml)	13.96	15.036	7.37	59.50	2.50	62.00

Table 2 Correlations between clinical and serological parameters in AS patients

	BASFI	BASMI	BASGI	ESR	CRP	BME score	ENH score
BASDAI							
rho	0.364	0.085	0.608	0.133	0.138	0.119	0.041
P value	0.034	0.631	0.000	0.588	0.443	0.537	0.833
BASFI							
rho		0.662	0.186	0.313	0.303	−0.267	−0.251
P value		0.000	0.293	0.191	0.086	0.161	0.190
BASMI							
rho			0.254	0.222	0.279	−0.513	−0.544
P value			0.147	0.361	0.116	0.004	0.002
BASGI							
rho				−0.161	−0.181	−0.181	−0.253
P value				0.510	0.313	0.348	0.185
ESR							
rho					0.460	0.256	0.297
P value					0.041	0.290	0.217
CRP							
rho						−0.103	−0.058
P value						0.589	0.759
BME score							
rho							0.907
P value							0.000

these subgroups. The only parameter which showed statistical difference was the BASGI, being higher in the active subgroup ($P = 0.001$) (Table 3).

Serum MMP-3

The mean MMP-3 levels were numerically but not statistically higher in AS patients compared to controls, with mean levels of 13.96 ± 15.03 and 8.73 ± 9.09 ng/ml, respectively ($P = 0.223$) (Table 1). Patients were categorized into those having high or low MMP-3 according to a cut-off value based on the median (=7.1 ng/ml). According to this cut-off value, 16 patients (53.3%) had high MMP-3 levels (mean value 24.81 ± 17.6) and 14 patients (46.7%) had low MMP-3 levels (mean value 3.85 ± 1.1).

Relationship between MMP-3, clinical and laboratory parameters

Fourteen patients (66.7%) with clinically active disease (BASDAI ≥ 4) and 22.2% (2 patients) of those with inactive disease (BASDAI < 4) had high MMP-3 levels. Thus, high MMP3 was significantly associated with high BASDAI among AS patients ($P = 0.046$).

Table 3 Clinical and serological differences between clinically active and inactive AS patients

	BASDAI ≥ 4 (no. = 21)		BASDAI < 4 (no. = 9)		*Z**	*P* value
	Mean ± SD	Median (min.–max.)	Mean ± SD	Median (min.–max.)		
Age	30.0 ± 10.1	28 (17–51)	27.1 ± 9.47	24 (18–48)	−0.839	0.402
Occiput-wall	7.85 ± 9.99	1 (0–29)	3.44 ± 6.42	0 (0–17)	−1.179	0.238
Chest expansion	2.61 ± 2.40	2 (0.5–10.5)	2.38 ± 0.96	2.5 (1–4)	−0.692	0.489
Schober index	7.85 ± 5.7	10.5 (0.5–16.5)	11 ± 5.19	12 (1–16)	−1.613	0.107
BASFI	5.92 ± 2.14	5.6 (2.4–10)	3.97 ± 2.25	2.8 (1.4–7.7)	−1.857	0.063
BASMI	5.81 ± 2.87	6 (0–10)	3.78 ± 3.11	4 (0–8)	−1.392	0.164
BASGI	7.29 ± 1.34	7.5 (5–10)	4.6 ± 2.18	6 (1–7)	−3.208	0.001
ESR	34.1 ± 17.21	32 (3–90)	39.77 ± 21.68	32 (27–98)	−0.358	0.720
CRP	20.4 ± 17.03	22.9 (0.50–58.8)	12.32 ± 8.62	16.7 (2.3–21.8)	−1.108	0.268

*Z** stands for Mann–Whitney test

Table 4 The clinical and serological differences between AS patients with high and those with low MMP-3 levels

	AS with low MMP-3		AS with high MMP-3		*Z**	*P* value
	Mean ± SD	Median (min.–max.)	Mean ± SD	Median (min.–max.)		
BASMI	3.64 ± 2.76	4.00 (0.00–8.00)	6.56 ± 2.65	6.50 (2.00–10.00)	−2.473	0.013
BASGI	5.89 ± 2.54	6.25 (1.00–10.00)	7.00 ± 1.30	7.00 (5.00–9.00)	−1.149	0.250
BASFI	4.32 ± 2.01	5.05 (1.40–7.70)	6.22 ± 2.26	5.75 (3.40–10.00)	−1.935	0.053
CRP	9.66 ± 10.34	3.80 (1.00–32.40)	17.58 ± 17.69	10.50 (0.50–58.80)	−1.068	0.286
ESR	34.43 ± 20.36	32.00 (3.00–97.00)	37.00 ± 17.23	32.00 (5.00–90.00)	−0.921	0.357

*Z** stands for Mann–Whitney test

The clinical and laboratory differences between AS patients with high and those with low MMP-3 levels were compared (Table 4). Patients with elevated MMP-3 had statistically higher BASMI ($P = 0.013$) and BASFI ($P = 0.053$) than patients with low MMP-3. There was no statistical difference between both subgroups as regards to the BASGI, CRP or ESR.

Findings on MRI of SIJs (Fig. 1)

MRI signs of chronicity (erosions and joint space narrowing) were detected in all patients. Of them, 17 patients (56.7%) were shown to have ankylosis. Radiologic activity in SIJs was defined according to the ASAS definitions for active lesions on MRI of SIJs. Findings on MRI of SIJs were scored into three grades: 1 (mild), 2 (moderate) and 3 (severe) according to the intensity of BME and ENH. A single score was obtained for each patient. Only those with moderate and severe grades were considered as positive for the presence of active disease. BME (suggestive of active disease) was detected in SIJs of 19/30 (63.3%) AS patients. These findings were bilateral in 18 patients and unilateral in 1 patient only. 15 patients (50%) had grade 2 BME and 4 (13.3%) had grade 3, whereas post-gadolinium ENH was detected in the 19 AS patients having BME, with one patient showing bilateral ENH in the absence of BME. ENH was grade 2 in 6 patients (20%) and grade 3 in 14 (46.7%).

Relationship between MRI activity, clinical and laboratory parameters

MRI features of inflammation were detected more frequently in clinically active than inactive AS patients without reaching statistical significance. BME was detected in 63.2% of active AS patients, and 36.8% of inactive patients ($P = 0.419$), whereas ENH was detected in 60% of active AS patients, and 40% of inactive patients ($P = 0.179$). At the same time, 81.8% of AS without detectable BME were clinically active and 90% without ENH were also active with BASDAI ≥ 4.

As regards the association between the MRI activity and MMP-3 levels, there was no statistically significant relation. BME was detected in 52.63% of AS with high MMP-3 levels compared to 47.37% of patients with low MMP-3 ($P = 0.919$), whereas ENH was present equally in AS with high and low MMP-3 levels (50% each) with $P = 0.709$ (Table 5).

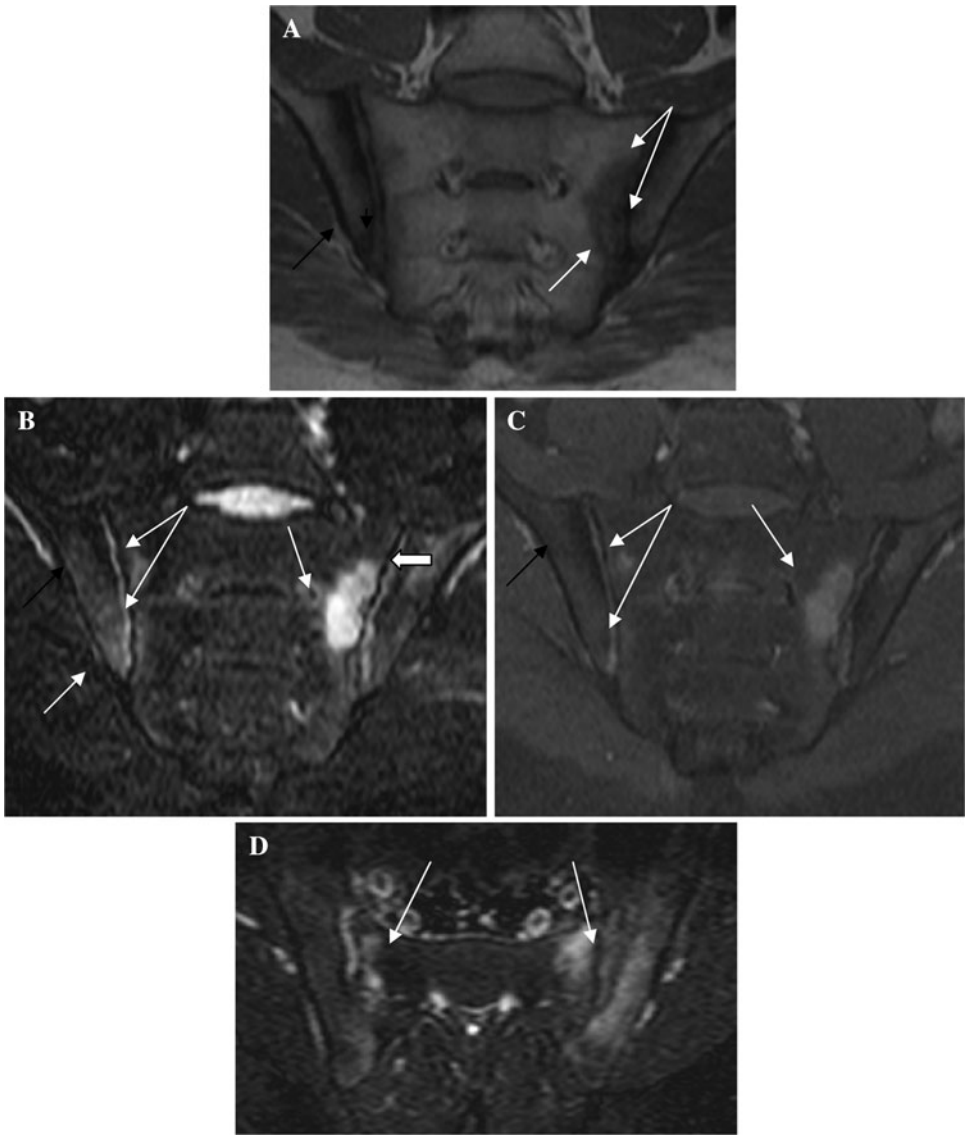

Fig. 1 Multiple sacral and ilial areas of hypointensity signals (*arrows*) were noted on **a** coronal oblique T1-weighted image that became hyperintense on **b** coronal oblique STIR and homogenously enhancing on **c** coronal oblique T1 FS post-contrast weighted image denoting active inflammation. Sclerosis was seen as subchondral hypointensity signal in all sequences (*black arrows*). Axial oblique STIR WI confirmed that the inflammation was in the synovial part of the joint (**d**)

MRI features of activity were not related to CRP. BME was detected in 72.7% of AS with positive CRP compared to 89.5% of patients with negative CRP ($P = 0.327$), whereas ENH was present in 70% of AS with positive CRP and 90% with negative CRP ($P = 0.300$) (Table 5).

MRI scores of BME and ENH were also assessed for correlation to the different variables. Both parameters were significantly correlated to each other ($P = 0.000$) and each was highly correlated with BASMI ($P = 0.004$ and 0.002, respectively). BME and ENH were not statistically correlated to CRP, ESR, BASDAI or any other clinical variable (Table 2).

Discussion

Accurate assessment of AS disease activity has become very important in clinical practice. Owing to the availability of anti-TNF drugs as a treatment in AS, it is important to generate an accurate method to measure disease activity to ensure that a particular patient will have a favorable response to these costly drugs. Actually, there is no standard method to assess disease activity in AS patients due to the lack of comprehensive relation between laboratory, imaging and clinical findings [27, 28]. Thus, physicians and patients may judge the disease activity on different bases [29].

The measurement of acute-phase reactants (APR) can be a powerful assessment tool for monitoring many inflammatory diseases. In AS only 50–70% of patients with active disease have an increased level of CRP and a raised ESR, and measurement of the levels of these APR has been suggested to have limited value in determining disease activity [30, 31].

In our data, ESR and CRP levels were significantly elevated in AS patients than in controls ($P = 0.000$). In

Table 5 Relation between MRI activity and clinical and laboratory parameters

Variables	BME		Test *P* value	ENH		Test *P* value
	Present 19	Absent 11		Present 20	Absent 10	
	No. (%)	No. (%)		No. (%)	No. (%)	
MMP-3						
Low	9 (47.37)	5 (45.45)	0.010 (0.919)	10 (50)	4 (40)	0.268 (0.709)
High	10 (52.63)	6 (54.55)		10 (50)	6 (60)	
BASDAI						
<4	7 (36.8)	2 (18.2)	1.155 (0.410)	8 (40)	1 (10)	2.857 (0.204)
≥4	12 (63.2)	9 (81.8)		12 (60)	9 (90)	
CRP						
−ve	2 (10.5)	3 (27.3)	1.407 (0.327)	2 (10.0)	3 (30.0)	1.920 (0.300)
+ve	17 (89.5)	8 (72.7)		18 (90.0)	7 (70.0)	
ESR						
−ve	1 (5.3)	1 (9.1)	0.164 (0.685)	1 (5.0)	1 (10.0)	0.268 (1.000)
+ve	18 (94.7)	10 (90.9)		19 (95.0)	9 (90.0)	

addition, CRP levels were elevated in AS patients with clinically active disease compared to those with inactive disease as measured by BASDAI, but the differences were statistically insignificant ($P = 0.268$). These findings were consistent with Ozgocmen et al. [32] when they categorized 27 AS patients into active and inactive groups based on BASDAI. Although we found ESR and CRP to be statistically correlated, yet ESR was not elevated in clinically active cases. In agreement with others, correlations between BASDAI, ESR and CRP were not observed [12, 32].

Since disease activity in AS patients is not well reflected by ESR and CRP levels, these markers cannot be used as the only parameters for evaluating AS disease activity [31, 33].

In this study, serum level of the recently studied biomarker MMP-3 was measured in AS patients and in healthy controls. MMP-3 was elevated in AS patients compared to controls, but did not reach statistical significance ($P = 0.223$). Yang et al. also did not find statistical difference in serum MMP-3 levels between 41 AS patients and 28 healthy subjects [34].

When we categorized our AS patients into those with high and low MMP-3 levels according to the cut-off value of 7.1 ng/ml, it was found that elevated MMP-3 was significantly correlated with the clinical disease activity in AS patients, which is reflected by BASDAI ≥ 4 [35]. Elevated MMP-3 was related to BASMI, but not to BASFI or BASGI. In addition, MMP-3 was not related to ESR or CRP which is consistent with other studies [30, 36].

In agreement with previous studies [12, 30, 37], the presence of significant association between serum MMP-3 levels and BASDAI and the lack of this relation between BASDAI and APR would indicate that serum MMP-3 could be an objective parameter for measurement of disease activity and that it is more useful than ESR and CRP in evaluating disease activity in AS patients [12, 35].

During the past few years, the role of MRI in early detection of axial inflammation has been highlighted. More recently, it has been included in the new ASAS classification criteria for the early diagnosis of axial SpA [15]. Considering this central role and being an objective measure that reflects AS activity, it was worthy to study the relation between MRI features of activity and the other available parameters of disease activity.

In the present study, 19/30 AS patients were found to have BME with post-gadolinium ENH of SIJs and one patient showed ENH only. MRI signs of activity were significantly correlated with each other and with BASMI, but not with ESR or CRP. This goes with the results of others [38]. A study reported the finding of normal CRP in 29 SpA patients with MRI signs of SIJ inflammation, whereas others reported contradictory findings [39]. In a study by Jee et al. [40], BME but not ENH was correlated with CRP and ESR.

In addition, both MRI features of inflammation were not statistically related to BASDAI. The ten AS patients who were found to lack MRI features of inflammation were clinically active, which is consistent with previous results [36, 38, 41]. On the other hand, some studies found AS patients with MRI features of inflammation to have normal clinical examination [37]. These results confirm the lack of an association between MRI and BASDAI.

Despite the lack of correlation between MRI and the conventional variables in the present work, we cannot ignore the fact that MRI is the most sensitive modality to

detect active inflammation in the SIJs [42]. We may suspect that absence of correlation with other measures in the present work would rather add to the questions of inaccuracy of conventional parameters as measures of disease activity, especially that they already have well known drawbacks. APR have limited value in determining disease activity in AS [4], and previous studies have reported different and contradictory findings regarding the relation between APR and disease activity [12, 32, 36]. As for the BASDAI, though easy to apply, may not perform efficiently and is totally patient dependant. In order to overcome this inaccuracy of BASDAI, the ASAS has recently defined newer measures of disease activity in AS such as the mini-BASDAI [43] and ASDAS [44, 45]. The latter includes CRP or ESR in addition to some items of the BASDAI. These new measures are currently tested for their efficacy, but still they are mainly subjective.

An important issue is those AS patients who were found to lack MRI features of active inflammation in the presence of high BASDAI. Are they really indicated for biologics based on the current guidelines of ASAS for initiation of biologics in AS? Accordingly, which will the best predictor of anti-TNF-response, is it the presence of clinical or MRI activity or both? [46, 47] All these questions necessitate further studies to be answered.

Surprisingly, BME and ENH were not statistically related to MMP-3 levels. This was also reported in a study which found that MMP-3 levels were not correlated with inflammatory changes on MRI of SIJs [48]. The author proposed that this may be the result that MRI reflects direct inflammation, whereas MMP-3 reflects turnover of joint matrix components which is only indirectly related to inflammation.

Although there is lack of a significant consistent relation between the various measures of disease activity in AS among the different studies including this study, yet all of these measures were suppressed in response to TNF-inhibitors which prove that these parameters are linked somehow although the exact link is still unclear [32, 48, 49]. Some suggested that each parameter may be reflecting a different aspect of disease activity that leads to a different disease outcome, as it is recently suggested that elevated MMP-3 was found to be predictor of radiographic progression in AS [50].

From the current study, it is suggested that the newer objective measures (MRI and MMP-3) should start to take a more central role in the available ASAS recommendations for initiation of biologics in AS which depend mainly on BASDAI as the gold standard parameter of activity.

Conclusion

Serum MMP-3 is an objective measure reflecting clinical disease activity in AS. Bone marrow edema and enhancement detected by MRI of SIJs is another objective measure of disease activity, but is not correlated with MMP-3 or the conventional parameters as BASDAI, ESR, or CRP. Although both MMP-3 and MRI can reflect disease activity in AS they seem to be unrelated, perhaps each is reflecting a different aspect of disease activity. As single-variable parameters cover only part of the disease activity, MMP-3 and MRI should be considered together with BASDAI in assessing disease activity and in guiding the available ASAS recommendations for initiation, continuation and discontinuation of biologics in AS which depend on BASDAI as its gold standard.

Recommendations

To start having national guidelines for initiation of biologics in Egyptian AS patients based on the incorporation of multiple parameters including the newer disease activity measures as MMP-3 and MRI to be relevant to the economic impact of anti-TNF-therapy.

Conflict of interest The authors declare no conflicts of interest.

References

1. Sengupta R, Stone MA (2007) The assessment of ankylosing spondylitis in clinical practice. Nat Clin Pract Rheumatol 3(9):496–503
2. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B, Dougados M, Géher P, Inman RD, Khan MA, Kvien TK, Leirisalo-Repo M, Olivieri I, Pavelka K, Sieper J, Stucki G, Sturrock RD, van der Linden S, Wendling D, Böhm H, van Royen BJ, Braun J (2006) ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 65:442–452. doi:10.1136/ard.2005.041137
3. Garrett S, Jenkinson T, Kennedy G, BASDAI et al (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 21:2286–91
4. Yildirim K, Erdal A, Karatay S et al (2004) Relationship between some acute phase reactants and the Bath ankylosing Spondylitis Disease Activity Index in patients with ankylosing spondylitis. South Med J 97:350–353
5. Hembry RM, Bagga MR, Reynolds JJ et al (1995) Immunolocalisation studies on six matrix metalloproteinases and their inhibitors, TIMP-1 and TIMP-2, in synovia from patients with osteo- and rheumatoid arthritis. Ann Rheum Dis 54:25–32
6. Nagase H, Woessner JF Jr (1999) Matrix metalloproteinases. J Biol Chem 274:21491–21494
7. Visse R, Nagase H (2003) Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 92:827–839
8. MacNaul KL, Chartrain N, Lark M, Tocci MJ et al (1990) Discoordinate expression of stromelysin, collagenase, and tissue inhibitor of metalloproteinases-1 in rheumatoid human synovial fibroblasts. Synergistic effects of interleukin-1 and tumor necrosis factor-alpha on stromelysin expression. J Biol Chem 265:17238–17245

9. Nagase H (1997) Activation mechanisms of matrix metalloproteinases. Biol Chem 378:151–160
10. 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 61:161–166
11. Vandooren B, Kruithof E, Yu DT et al (2004) Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor alpha blockade in spondylarthropathy. Arthritis Rheum 50:2942–2953
12. Chen C, Lin K, Yu D et al (2006) Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity. Rheumatology 45:414–420
13. Lukas C, Braun J, van der Heijde D et al (2007) Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. J Rheumatol 34:862–70
14. Braun J, Bollow M, Eggens U, Konig H, Distler A, Sieper J (1994) Use of dynamic magnetic resonance imaging with fast imaging in the detection of early and advanced sacroiliitis in spondylarthropathy patients. Arthritis Rheum 37:1039–1045
15. Bennett AN, Marzo-Ortega H, Emery P et al (2009) Diagnosing axial spondyloarthropathy. The new Assessment in SpondyloArthritis International Society criteria: MRI entering centre stage. Ann Rheum Dis 68:765–767
16. Weber U, Maksymowych WP (2008) How does imaging help the clinician in the evaluation and management of spondyloarthritis? Skeletal Radiol 37:487–490
17. Braun J, Landewe R, Hermann KG, Han J et al (2006) Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo controlled magnetic resonance imaging study. Arthritis Rheum 54:1646–1652
18. van der Linden S, Valkenberg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 27:361–368
19. van Tubergan A, Debates I, Ryser L et al (2002) Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 47:242–248
20. Jones SD, Steiner A, Calin A et al (1996) The Bath ankylosing spondylitis patient global score (BAS-G). Br J Rheumatol 35:66–71
21. Calin A, Garrett S, Whitelock H et al (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 21:2281–2285
22. Jenkinson T, Mallorie P, Whitelock H et al (1994) Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 21:1694–1698
23. Dougados M, Hermann K-G, Landewé R et al (2009) The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 68:ii1–ii44
24. Docherty P, Mitchell MJ, MacMillan L et al (1992) Magnetic resonance imaging in the detection of sacroiliitis. J Rheumatol 19:393–401
25. Lewis SM (2001) Miscellaneous tests. In: Lewis SM, Bum BJ, Bates I (eds) Dacie and Lewis practical haematology, 9th edn. Churchill Livingstone, London, pp 527–531
26. Taylor DJ, Cheung NT, Dawes PT (1994) Increased serum proMMP-3 in inflammatory arthritides: a potential indicator of synovial inflammatory monokine activity. Ann Rheum Dis 53:768–772
27. Zochling J, Braun J (2005) Assessment of ankylosing spondylitis. Clin Exp Rheumatol 23:S133–S141
28. Calin A, Nakache JP, Geuguen A et al (1999) Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? Rheumatology 38:878–882
29. Spoorenberg A, van Tubergen A, Landewe R et al (2005) Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. Rheumatology 44:789–795
30. Spoorenberg A, van der Heijde D, de Klerk E, Dougados M et al (1999) Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. J Rheumatol 26:980–984
31. Sheehan NJ, Slavin BM, Donovan MP et al (1986) Lack of correlation between clinical disease activity and erythrocyte sedimentation rate, acute-phase proteins or protease inhibitors in ankylosing spondylitis. Br J Rheumatol 25:171–174
32. Ozgocmen S, Godekmerdan A, Ozkurt-Zengin F (2007) Acute-phase response clinical measures and disease activity in ankylosing spondylitis. Joint Bone Spine 74:249–253
33. Ruof J, Stucki G (1999) Validity aspects of erythrocyte sedimentation rate and C-reactive protein in ankylosing spondylitis: a literature review. J Rheumatol 26:966e70
34. Chunhua Y, Gu J, Rihl M et al (2004) Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. Arthritis Rheum 51:691–699
35. Wendling D, Cedoz J, Racadot E (2008) Serum levels of MMP-3 and cathepsin K in patients with ankylosing spondylitis: effect of TNFa antagonist therapy. Joint Bone Spine 75(5):559–562
36. Puhakka K, Jurik A, Schiottz-Christensenl B et al (2004) Magnetic resonance imaging of sacroiliitis in early seronegative spondylarthropathy. Abnormalities correlated to clinical and laboratory findings. Rheumatology 43:234–237
37. Woo J, Lee H, Sung I et al (2007) Changes of clinical response and bone biochemical markers in patients with ankylosing spondylitis taking etanercept. Rheumatology 34:1753–1759
38. Goh L, Suresh P, Gafoor A, Hughes P, Hickling P (2008) Disease activity in longstanding ankylosing spondylitis: a correlation of clinical and magnetic resonance imaging findings. Clin Rheumatol 27(4):449–455
39. Visvanathan S, Wagner C, Marini JC et al (2007) Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. Ann Rheum Dis 67:511–517. doi:10.1136/ard.2007.071605
40. Jee W, McCauley T, Lee S et al (2004) Sacroiliitis in patients with ankylosing spondylitis: association of MR findings with disease activity. Magn Reson Imaging 22:245–250
41. Jarrett SJ, Sivera F, Cawkwell LS, Marzo-Ortega H, McGonagle D, Hensor E, Coates L, O'Connor PJ, Fraser A, Conaghan PG, Emery P (2009) MRI and clinicalfindings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. Ann Rheum Dis 68:1466–1469. doi:10.1136/ard.2008.092213
42. Bredella MA, Steinbach LS, Morgan S, Ward M, Davis JC (2006) MRI of the sacroiliac joints in patients with moderate to severe ankylosing spondylitis. AJR 187:1420–1426
43. Song H, Rudwaleit M, Listing J et al (2009) Comparison of the BASDAI and the modified BASDAI (mini-BASDAI) in assessing disease activity in patients with ankylosing spondylitis without peripheral manifestations. Ann Rheum Dis. 68(11):1701–1707. doi:10.1136/ard.2008.099226
44. Lukas C, Landewé R, Sieper J et al (2009) Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 68:18–24. doi:10.1136/ard.2008.094870
45. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, Braun J, Landewé R, for the Assessment of

SpondyloArthritis international Society(ASAS) (2009) ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 68:1811–1818. doi:10.1136/ard.2008.100826

46. Rudwaleit M, Schwarzlose S, Hilgert ES et al (2008) MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 67:1276–1281
47. Lord P, Farragher T, Lunt M et al (2010) Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology. Biol Register Rheumatol 49(3):563–570
48. Maksymowych W, Rahman P, Shojania K et al (2008) Beneficial effects of adalimumab on biomarkers reflecting structural damage in patients with ankylosing spondylitis. Rheumatology 35:2030–2037
49. Maksymowych W, Poole A, Hiebert L et al (2005) Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. J Rheumatol 32:1911–1917
50. Maksymowych WP, Landewé R, Conner-Spady B et al (2007) Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis. Arthritis Rheum 56:1846–1853