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ORIGINAL ARTICLE

Metallothionein-1 Serum Level in Ankylosing Spondylitis Patients: Correlation with Disease Activity

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ABSTRACT

Background: Elevated Serum Metallothionein-1 (MT-1) levels have been described in a large spectrum of acute and chronic inflammatory diseases, so measuring MT-1 levels in the serum of Ankylosing Spondylitis (AS) could provide additional information about the diseases and better long-term outcome. This work aimed to investigate the role of Serum MT-1 in evaluation of disease activity in AS patients.

Methods: This is a matched case control work that was conducted on sixty individuals categorized into two equal groups, Group I: 30 patients with AS, Group II: 30 apparently healthy volunteers serving as a control group. All patients undergone clinical examination, assessment of disease activity in addition to the laboratory investigations, serum MT-1 was assessed by enzyme linked immunosorbent assay (ELISA).

Results: The median of Serum MT-1 was significantly higher among the AS group (P<0.001).

Significant positive correlations were revealed between serum MT-1 with Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS-CRP) grade (r=0.441, P=0.02), Erythrocyte Sedimentation Rate (ESR) (r=0.486, P=0.006) as well as CRP (r=0.513, P=0.004). Serum MT-1 had the highest sensitivity (93.33%) and specificity (90%) at cut-off point (23.42) among AS patients with area under the curve was (0.886) to discriminate healthy subjects from AS patients. It also had the highest sensitivity (96.3%) and specificity (66.67%) at cut-off point (40.35) among AS patients with area under the curve was (0.840) to discriminate highly active AS patients from moderately active AS patients.

Conclusion: Serum Metallothionein-1 could serve as a valuable biomarker for Ankylosing Spondylitis disease activity.

Keywords: Serum Metallothionein-1, Activity, Ankylosing Spondylitis.

INTRODUCTION

Ankylosing spondylitis is chronic inflammatory arthritis primarily affecting the axial skeleton. It is characterized by inflammation that begins in the spinal and peripheral joints and progressively involves the entheses, as well as extra-articular systems such as the intestines, heart, lungs, and eyes. The disease tends to worsen over time [1].

Metallothionein (MT) constitute a family of low molecular weight (<10 Kilodalton), cysteine-rich proteins. In humans, MTs are categorized into four subfamilies: MT-1, MT-2, MT-3, and MT-4 [2].

Reactive nitrogen species (RNS) as well as the reactive oxygen species (ROS) are the free radicals that MTs mainly scavenge. They bind xenobiotic heavy metals including cadmium, mercury, silver, and arsenic to their cysteine residues, which make up around 30% of their amino acid composition, and physiological heavy metals like zinc, copper, and selenium to the same extent. This interaction reduces oxidative stress, maintains intracellular heavy

metal concentrations, and thus contributes to the regulation of both metabolism and immunity [3].

Patients with AS exhibit significantly elevated serum levels of TNF-α, IL-6, and IL-17 compared to healthy individuals. Notably, earlier studies have demonstrated a positive relation between serum MT-1 levels and the proinflammatory cytokines (IL-17, IL-6, as well as TNF-α,) in AS patients [2].

MTs have since been recognized as multifaceted effectors in immune homeostasis regulation. Cancer, viral diseases, abnormalities of the central nervous system, autoimmune diseases, inflammatory bowel diseases, and other ailments have been extensively demonstrated through experimental investigations using MT-deficient human samples to demonstrate the crucial regulatory roles of MT isoforms. Extensive research has focused on MT1 in recent decades because of its widespread expression in almost all organs and its substantial role in homeostasis [4].

APCs, such as macrophages and dendritic cells (DCs), mediate the immune response by presenting antigens and bridging the gap between the innate and adaptive systems. Various immune-related illnesses can be triggered by dysregulation of APC activities. The immunosuppressive effects of MT1 on DCs have been shown in previous research. Increased MT1 levels are a hallmark of IL-10-expressing DCs; these cells are critical for the development of regulatory T-cell phenotypes and the expansion of Foxp3+ T cells. In contrast to DCs that produce IL-10, which are stimulated with either dexamethasone or ZnCl2, DC membranes have elevated MT1 expression that is ZnCl2-dependent rather than impacted by dexamethasone [5].

Recent studies have explored the association between serum MT-1 levels and disease activity in AS, seeking to determine its potential as a biomarker for disease monitoring. Elevated MT-1 levels may reflect an adaptive physiological response to counteract inflammation-induced oxidative stress, whereas reduced levels could indicate a compromised protective mechanism, potentially contributing to increased tissue damage and progression of joint ankylosis. However, findings on this correlation remain inconsistent; while some studies suggest a direct relationship between higher MT-1 levels and greater disease severity, others propose that early disease stages may trigger a compensatory rise in MT-1 expression. Gaining deeper insight into MT-1's role in AS pathophysiology could pave the way for novel therapeutic strategies focused on reducing oxidative stress and fine-tuning immune regulation to decelerate disease progression [5].

To the best of our knowledge, this is the first study of its kind to be conducted at Zagazig University Hospitals. Given that genetic, environmental, and ethnic factors can influence the pathogenesis and clinical expression of ankylosing spondylitis, it is essential to investigate biomarkers of disease activity within different populations. Therefore, this study aimed to evaluate the role of serum Metallothionein-1 in assessing disease activity among Egyptian patients with ankylosing spondylitis attending Zagazig University Hospitals.

METHODS

This is a matched case control study that was conducted on in the departments of Rheumatology & Rehabilitation and Clinical Pathology at Zagazig University Hospitals on sixty individuals categorized into two equal groups, Group I (AS group): 30 patients, 17 (56.7%) were males and 13 (43.3%) were females. They ranged in age from 18 to 45 years, Group II (Control group): 30 apparently healthy volunteers serving as a control group.

The research ethics board of the Faculty of Medicine at Zagazig University gave its approval to the study, and all participants gave written informed consent. A component of the Code of Ethics for Research Involving Humans, the Declaration of Helsinki ensures that the study was carried out in compliance with its provisions. Before this study could begin, we obtained approval from the Institutional Review Board (IRB#: 10967-19-7-2023).

We included adult patients (aged 18 years and older) who had been diagnosed with ankylosing spondylitis (AS) according to the Modified New York criteria. These criteria required the presence of inflammatory-type low back pain, limitation of lumbar spine motion in both the sagittal and frontal planes, and reduced chest expansion. In addition, radiographic evidence of sacroiliitis was necessary defined as bilateral sacroiliitis of grade 2 or higher, or unilateral sacroiliitis of grade 3 or higher. A definitive diagnosis of AS was established when at least one clinical criterion was present along with the specified radiological findings [6]. Sacroiliitis had been graded on a scale from 0 to 4 as follows: grade 0 indicated normal findings; grade 1 represented suspicious changes; grade 2 showed minimal abnormality such as small localized areas of erosion or sclerosis without joint space alteration; grade 3 indicated definite abnormality with moderate to advanced sacroiliitis, including erosions, sclerosis, joint space widening or narrowing, or partial ankylosis; and grade 4 reflected severe abnormality with complete ankylosis of the sacroiliac joint.

We excluded all participants with Other spondylo-arthropathies such as: Inflammatory bowel disease, Reactive arthritis and psoriatic arthritis, any other autoimmune diseases as: Polymyositis, systemic sclerosis, rheumatoid arthritis, dermatomyositis, overlap syndrome and mixed connective tissue disease, Bechet disease, and vasculitis. Also, patients with liver diseases, malignancies, infection, or cardiovascular diseases as well as pregnancy were excluded.

Detailed history, involving onset, course and duration of the disease., General examination: for mucocutaneous, cardiac, chest and ophthalmic examinations. Local examination of locomotor system with assessment of range of motions.

Assessment of disease activity in AS patients: Patients were assessed by ASDAS-CRP score. The 3 cut-offs selected to separate these states were: Low disease activity was defined as 1.3 - $\leq$ 2.1, Moderate as <2.1 - $\leq$ 3.5 and High as ASDAS >3.5 [7].

Laboratory Investigations included: Complete blood count (CBC) was done on Sysmex XN 2000 Hematology analyzer (Sysmex, Kobe, Japan), Erythrocyte sedimentation rate (ESR) on vision B ESR Analyzer (YHLO Biotech Co, Shenzhen, China), C-reactive protein (CRP) and Rheumatoid Factor on Cobas 6000 c501 Modular Analyzer (Roche, Germany), Liver and kidney function tests were done by Cobas 8000 Modular Analyzer Series/c702 (Roche Diagnostics, Germany), Complete urine analysis and Serum Metallothionein-1 (MT-1) by ELISA in which the kit was with Catalog No. DLR-MT1-Hu (WUXI DONGLIN SCI&TECH DEVELOPMENT CO.,LTD).

STATISTICAL ANALYSIS

Data analysis was conducted using IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation or median with interquartile range (IQR), depending on data distribution. Spearman's rank correlation test was applied for ordinal or non-normally distributed variables, while the Mann-Whitney U test was used for group comparisons based on median values. Receiver Operating Characteristic (ROC) analysis determined cutoff values for ultrasonography cross-sectional regions. Statistical significance was set at $p \leq 0.05$.

RESULTS

Group I (AS group) included 30 patients. The disease duration among AS patients ranged from 6 months to 17 years with mean ± SD of 6.85 ± 5.19 (Table 1).

According to the clinical data in our study, the most frequent rheumatological symptom detected were low back pain and sacroiliitis that were detected among all of the patients of this group (100%), followed by enthesitis among (76.7%) of patients, cervical pain in (60%) of patients, peripheral arthritis in (53.3%) of patients, while uveitis was detected in only (10%) of the patients (Table1).

The ASDAS-CRP score was between 1.2 and 4.82 with mean ± SD of 2.49 ± 1.10. As regards ASDAS grading, (33.3%) of the patients had

moderate disease activity, while (23.3%) had high and low activity and (20%) were in remission. (Table 2).

The median of Serum Metallothionein-1 was significantly higher among the AS group (P<0.001) (Table 3). A significant positive relation was observed between serum MT-1 levels and ASDAS-CRP (r = 0.441, p = 0.02), ESR (r = 0.486, p = 0.006), and CRP (r = 0.513, p = 0.004) (Table 4).

Significant association between serum metallothionein-1 and ASDAS-CRP grade was observed as median of metallotionein-1 level was higher among patients with higher disease activity *(P<0.001)* (Table 5).

We conducted Receiver operation Curve (ROC) analysis to determine the optimal cutoff value to discriminate AS patients from the control group. Analysis showed that serum metallothionein-1 had highest sensitivity (93.33%) and specificity (90%) at cut-off point (23.42) among AS patients with area under the curve was (0.886) to discriminate healthy subjects from AS patients (Figure 1).

On conducting ROC analysis to determine the optimal cutoff value to discriminate highly active AS patients from moderately active AS patients, analysis showed that serum metallothionein-1 had highest sensitivity (96.3%) and specificity (66.67%) at cut-off point (40.35) among AS patients with area under the curve was (0.840). (Figure 2).

Table 1: Clinical data among the AS group.

Variables	**AS group (n=30)**
BMI *(kg/m^2)* *Mean ± SD* *Range*	 26.03 ± 3.56 (17.3 – 32.65)
Disease duration *(years)* *Mean ± SD* *Range*	 6.85 ± 5.19 (0.5 – 17)
Number of tender joints *Mean ± SD* *Range*	 4.6 ± 5.18 (0 – 20)
Number of swollen joints *Mean ± SD* *Range*	 0.23 ± 0.82 (0 – 4)
Cervical pain *(N. %)*	18 (60%)
Low back pain *(N. %)*	30 (100%)
Sacroiliitis *(N. %)*	30 (100%)
Peripheral arthritis *(N. %)*	16 (53.3%)
Enthesitis *(N. %)*	23 (76.7%)
Uveitis *(N. %)*	3 (10%)

BMI: Body Mass Index, AS: Ankylosing Spondylitis, SD: Standard Deviation, N.: Number, %: Percentage.

Table 2: Clinical indices among the AS group

Variables	**AS group (n=30)**
ASDAS-CRP *Mean ± SD* *Range*	 2.49 ± 1.10 (1.20– 4.82)
ASDAS grade *(N. %)* – Remission – Low activity – Moderate activity – High activity	 6 (20%) 7 (23.3%) 10 (33.3%) 7 (23.3%)

AS: Ankylosing Spondylitis, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein, SD: Standard Deviation, N.: Number, %: Percentage.

Table 3: Serum Metallothionein-1 levels among AS group and control group

Variables	**AS group (n=30)**	**Control (n=30)**	**P Value**
Median (IQR) *Range*	53.01 (40.9) (34.21 – 207.4)	11.7 (10) (2.39 – 23.4)	**<0.001**[1]

*[1]Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05

Table 4: Correlation between Metallothionein-1 levels and different variables among AS group

Variable	**Metallothionein-1**	
	r	***P***
BMI	-0.075	0.695
Disease duration	0.296	0.113
NTJ	0.099	0.602
NSJ	0.216	0.252
ESR	0.486	**0.006**
CRP	0.513	**0.004**
ASDAS-CRP	0.933	**<0.001**

*Spearman correlation, Non-significant: P >0.05, Significant: P ≤0.05, Highly significant: P<0.001, BMI: Body Mass Index, NTJ: Number of Tender Joints, NSJ: Number of Swollen Joints, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein.

Table 5: Association of serum Metallothionein-1 level with clinical data among AS patients

Variables		**Serum Metallothionein-1** *Median (IQR)*	**P Value**
Sex	Male	53 (98.6)	0.41[1]
	Female	52.2 (16.8)	
Cervical pain	Absent	49.5 (22.3)	0.57[1]
	Present	58.2 (42.9)	
Peripheral arthritis	Absent	49 (73.1)	0.84[1]
	Present	54.3 (14.1)	
Uveitis	Absent	53.9 (44.2)	0.19[1]
	Present	40.6 (11.5)	
Pelvic compression test	Negative	48.6 (109.6)	0.78[1]
	Positive	53.9 (39.4)	
Pelvic distraction test	Negative	54.3 (53.4)	0.36[1]
	Positive	51.3 (36.8)	
Sacral compression test	Negative	48.6 (24.2)	0.53[1]
	Positive	53.9 (44.9)	
Ganslen test	Negative	56.4 (63.5)	0.29[1]
	Positive	49 (24.7)	
Faber test	Negative	56.4 (53.6)	0.34[1]
	Positive	49.5 (34.2)	
ASDAS-CRP grade	Remission	38.3 (4.95)	**<0.001**[2]
	Low	47.6 (5.45)	
	High	58.2 (12.23)	
	Very high	164 (48)	

*[1]Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05 , MT-1: Metallothionein-1, IQR: Interquartile Range, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein, PCT: Pelvic Compression Test, PDT: Pelvic Distraction Test, SCT: Sacral Compression Test, GT: Ganslen Test, FABER: Flexion, Abduction, and External Rotation Test, P: P-value.

Figure 1: ROC curve analysis of serum Metallothionein-1 to discriminate between AS patients and healthy controls.

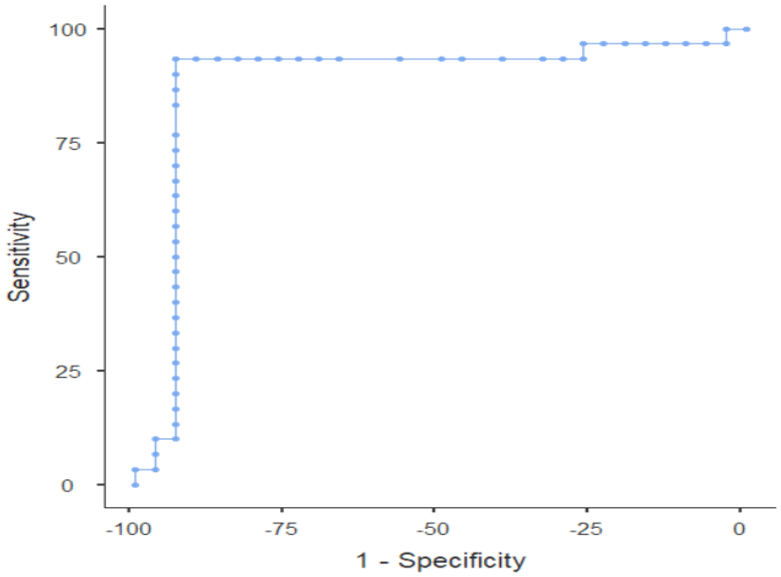
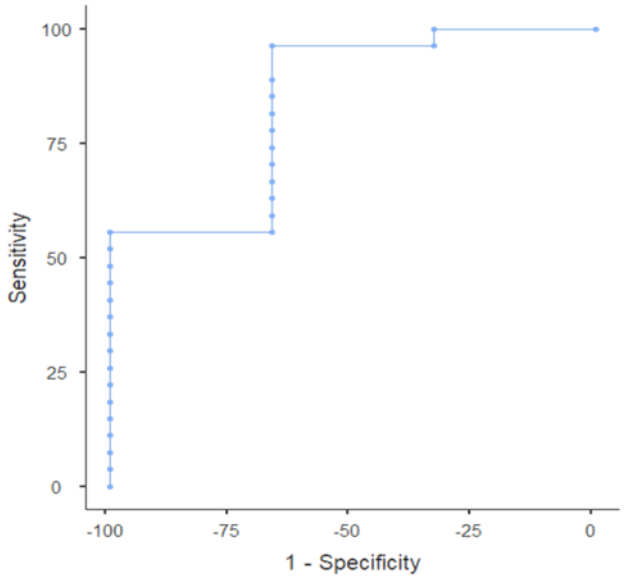


Figure 2: ROC curve analysis of serum Metallothionein-1 to discriminate between highly active and moderately active AS patients.



*[1]Mann-Whitney U test, Non-significant: P >0.05, Significant: P ≤0.05, MT-1

DISCUSSION

A kind of spondyloarthritis (SpA), ankylosing spondylitis is defined by immune-mediated inflammatory arthritis that mostly impacts the axial skeleton and sacroiliac joints. It is a chronic condition. Inflammation and the consequent creation of new bone at both the axial and peripheral entheseal sites are hallmarks of the disease. Spinal fusion, syndesmophytes, and enthesophytes all have a role in the development of AS, which in turn causes disability, functional restrictions, and chronic pain [8].

Various inflammatory markers produced by cells including monocytes/macrophages, fibroblast-like synoviocytes, and dendritic cells play critical roles in promoting and sustaining joint inflammation. Consequently, there remains an ongoing need to identify more effective diagnostic biomarkers for AS [9].

Metallothioneins (MTs) have been identified as key regulators in immune suppression processes. Specifically, MTs inhibit cytotoxic T-cell function and facilitate the regulatory T-cells proliferation. Additionally, MTs participate in both innate and adaptive immunity by acting as chemo-attractants for natural killer cells, macrophages, and subsets of dendritic cells [10].

In the present study comparing patients with AS (group I) versus healthy control patients (group II), there wasn't any significant difference regarding to age and gender ($p>0.05$)**.** These results align with the findings of Habata et al. [11], who compared a group of AS patients to a healthy control group and found no significant differences regarding age as well as gender.

Using whole-spine sagittal T2-weighted MRI, their study assessed the relationship between spinal inflammation, structural abnormalities, mobility, and DD. Following propensity score matching of 219 axial SpA patients with controls from the general population (selected from an initial cohort of 304 axial SpA patients and 967 general population participants), they reported a mean BMI of 24.2 ± 4.4 and a disease duration of 32.2 ± 13.0 years.

The most frequent articular manifestations detected in our study were low back pain (100%) and sacroiliitis (100%) which was detected among all the AS patients' group, followed by enthesitis (76.7%), cervical pain (60%) then peripheral arthritis (53.3%) among patients, while uveitis was detected among only (10%) of the patients. These findings also were supported by **Ouardi et al.,** [14] as they found that low back pain was revealed in (98%), peripheral arthritis (67.5%), and uveitis (13.5%). Additionally, Abdelaziz et al. [12], in their comparative analysis of cases with ankylosing spondylitis and axial psoriatic arthritis, reported the presence of uveitis in 60.3%, peripheral arthritis in 39.7%, and enthesitis in 34.5% of cases.

In the current study, spinal mobility assessment of the AS group revealed that the modified Schöber test ranged from 2 to 4 cm with a median (IQR) of 3 (1) cm, and chest expansion ranged from 2 to 5 cm with median (IQR) of 4.25 (1.75) cm. These findings align with Abdelaziz et al. [13], who reported abnormal spinal mobility in AS patients with a mean ± SD modified Schöber test of 3.8 ± 0.9 cm and chest expansion of 2.9 ± 0.6 cm

Physical examination regarding sacroiliitis tests (Rt/Lt), showed that (83.3%) of AS patients had positive Pelvic compression, (73.3%) had positive pelvic distraction and (90%) had positive sacral compression. About (60%) of AS patients had positive FABER and (40%) had positive Gaenslen`s test. These results coincide with Abdelaziz et al. [12] who revealed that positive FABER test in 52 AS patients (89.7%) and positive Compression test in 52 AS patients (89.7%). [12].

Concerning disease activity scores in the AS group, ASDAS-CRP ranged from 1.20 to 4.82, with a mean ± SD of 2.49 ± 1.10. According to ASDAS grading, 33.3% of patients had moderate disease activity, while 23.3% had high activity, another 23.3% had low activity, and 20% were in remission. These results are consistent with Yoyssef and Elrefay [16], who reported an ASDAS-CRP mean ± SD of 3.91 ± 2.14. The relatively high percentage of patients

in remission and low activity (43.3%) is encouraging, but the 23.3% with high disease activity highlights the need for closer monitoring and potential treatment escalation to improve outcomes.

Concerning laboratory parameters in our study, acute phase reactants showed a statistically significant difference, with CRP and ESR levels significantly higher in the ankylosing spondylitis group compared to controls. This finding is consistent with the results reported by Georgiadis et al. [17].

In the current study, AS patients showed significant elevated serum levels of Metallothionein-1 compared to healthy individuals, with notable positive correlations observed between serum MT-1 and disease activity parameters, including ASDAS-CRP ($r = 0.933$, $p < 0.001$), CRP ($r = 0.513$, $p = 0.004$), and ESR ($r = 0.486$, $p = 0.006$). These findings align with those reported by Ma et al. [18], who similarly observed significant positive relation between MT-1 levels and AS-associated proinflammatory cytokines, as well as measures of disease activity, including ASDAS-CRP ($r = 0.478$, $p = 0.0001$), ESR ($r = 0.322$, $p = 0.0079$), as well as the CRP ($r = 0.513$, $p = 0.0006$). The stronger correlation between MT-1 and ASDAS-CRP in our study may indicate a more direct link between MT-1 and overall disease activity, reinforcing the potential of MT-1 as a biomarker for AS severity and inflammation.

This study has a few limitations. First, the relatively small sample size may limit the generalizability of the findings. Second, due to its cross-sectional design, the study cannot establish causality or assess changes in MT-1 levels over time. Despite these limitations, the findings offer valuable insight into the potential role of MT-1 in disease activity among AS patients.

CONCLUSION

In AS patients, serum Metallothionine-1 correlates with clinical and laboratory features, it was correlated with ASDAS-CRP score of AS activity. So, Serum Metallothionine-1 could serve as a promising marker for diagnosis of AS patients and assessment of disease activity.

CONFLICT OF INTEREST or FINANCIAL DISCLOSURE:

No potential conflict of interest to be reported by the authors.

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