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Matrix Metalloproteinase 7 in Rheumatoid Arthritis Patients with Interstitial Lung Disease

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ABSTRACT

The study aim: The purpose of this study is to measure the matrix metalloproteinase 7 (MMP7) in rheumatoid arthritis (RA) patients with interstitial lung disease (ILD) and to assess for any correlation with RA-disease activity. **Research design:** A cross sectional study. **Sample**: a purposive sample included 40 rheumatoid arthritis patients from Ain Shams University Hospitals Inpatient Department of Rheumatology and Outpatient Clinic. **The results revealed** that serum (S) MMP7 was significantly higher among RA patients with interstitial lung disease than patients without. **Conclusion:** The study documented that S.MMP7 may be used as a screening test for detection of interstitial lung disease in patients with rheumatoid arthritis. **The study recommended**: Measurement of serum MMP7 level to RA patients may be used as screening test for detection of ILD

Keywords: RA: Rheumatoid arthritis. MMP7: Matrix metalloproteinase 7. ILD: Interstitial lung disease

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that most commonly affects the joints, causing progressive, symmetric, erosive destruction of cartilage and bone, which is usually associated with autoantibody production. Although joint disease is the main presentation, there are a number of extra-articular manifestations including subcutaneous nodule formation, vasculitis, inflammatory eye disease and lung disease. Of these manifestations, lung disease is a major contributor to morbidity and mortality [1].

Among the most significant factors contributing to this excess mortality is interstitial lung disease (ILD), the most common subtype of lung involvement in RA. In fact, the risk of death among individuals with clinically evident RA-associated ILD is 3 times higher than that among RA patients without ILD. Recent studies have further demonstrated that even though overall mortality rates in RA are declining, the rate of death due to RA-ILD has increased significantly [2].

The mechanism of pulmonary fibrosis occurring in ILD is not well understood. Patients with rheumatoid arthritis typically have circulating autoantibodies, the most common being rheumatoid factor and anti-cyclic citrullinated peptide (CCP). These antibodies may be present in the serum for several years before clinical disease onset. Both rheumatoid factor and anti-CCP have been linked to the development of ILD. There is growing evidence that rheumatoid arthritis begins in the lungs, a theory supported by a subgroup of patients who are anti-CCP positive with lung disease but have no articular manifestations [3]. The matrix metalloproteinases (MMPs) are thought to be key enzymes involved in remodeling of the extracellular matrix (ECM) in physiological and pathological situations (e.g. arthritis, cancer, atherosclerosis, and periodontal disease) [4].

Recent reports indicate that matrix metalloproteinase-7 (MMP-7) is a potential diagnostic and prognostic marker of interstitial pulmonary fibrosis (IPF). MMP-7 has been shown to be upregulated in the lungs in IPF, particularly in alveolar macrophages and hyperplastic epithelial cells. Bronchoalveolar lavage fluid (BALF) and serum levels of MMP-7 are significantly higher in patients with IPF compared with those in healthy subjects. Elevated levels of serum MMP-7 are associated with impaired lung function and poorer survival in IPF patients [5].

AIM OF THE WORK

The purpose of this study was to measure the (MMP7) in RA patients with ILD and to assess for any correlation with RA-disease activity.

PATIENTS AND METHODS

1Study design and sample:

This study was cross sectional study included 40 RA patients fulfilling the American College of Rheumatology and European League against Rheumatism (ACR / EULAR) 2010 classification criteria [1] Patients were selected from Ain Shams University Hospitals Outpatient Rheumatology Clinic and Inpatient Rheumatology Department.

The study was approved by the Ethics Board of Ain Shams University.

The patients were divided into 2 groups:

Group (1): 20 RA patients with ILD.

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Group (2): 20 RA patients without ILD or chest symptoms.

An oral consent was taken from all patients participated in this study

2- Methods of the study

All patients were subjected to the following:

A- Complete medical history

Detailed medical history was taken including articular and extra articular (age, sex, disease duration, morning stiffness, joint involvement, smoking, habits of medical importance).

Detailed respiratory manifestations as (dyspnea, cough, chest pain, others)

B- Clinical examination:

General and local rheumatological examination.

Local chest examination (inspection, palpation, percussion, auscultation)

Assessment of RA disease activity using **DAS 28 ESR** score [6]**.**

DAS 28 score include 28 joints including shoulders, elbows, wrists, metacarpophalangeal, and proximal interphalangeal of both hands, thumb interphalangeal joints and knees. DAS 28 score includes tender joint count (0:28), swollen joint count (0:28) and ESR level, general health assessment.

DAS28=0.56*√(tender joints) + 0.28*√(swollen joints) + 0.70*Ln(ESR) + 0.014*VAS

Data Management and Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 20).** Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

i. Descriptive statistics

1. Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non parametricnumerical data.
2. Frequency and percentage of non-numerical data.

ii. Analytical statistics

1. **Student T** Test was used to assess the statistical significance of the difference between two study group means.
2. **Mann Whitney Test (U test)** was used to assess the statistical significance of the difference of anon parametric variable between two study groups.
3. **Chi-Square test** was used to examine the relationship between two qualitative variables
4. **Fisher's exact test:** was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells
5. **Correlation analysis (using Pearson's method):** To assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.

- r= 0-0.19 is regarded as very weak correlation
- r=0.2-0.39 as weak correlation
- r=0.40-0.59 as moderate correlation
- r=0.6-0.79 as strong correlation
- r= 0.8-1 as very strong correlation

P-value refers to level of significance as follows:

-P value >0.05 = insignificant.

-P value < 0.05 = significant.

-P value < 0.01 = highly significant.

Independent t-test, ANOVA (analysis of variance) was used in relation analysis

6. **The ROC Curve** (**Receiver Operating Characteristic)** provides a useful way to evaluate the Sensitivity and specificity for quantitative Diagnostic measures that categorize cases into one of two groups.

RESULTS

Table (1) Serum MMP7 level among the 40 studied RA patients

Parameter	Range	Mean±SD
Serum MMP7 level	92.70-381.3	201.51±85.79

Serum MMP7 level ranged from 92.70-381.3 with means of (201.51±85.79), these levels are higher than normal range (0.16-10 ng/ml).

Table (2): Comparison between RA patients with and without ILD regarding mean serum MMP7 level

	RA pts without ILD (20)		RA pts with ILD (20)		t test	
	Mean	±SD	Mean	±SD	p value	sig.
S.MMP7	127.05	26.98	275.97	52.05	<0.001	HS

This table showed that the mean serum MMP-7 marker level was significantly higher among RA patients with ILD (p<0.001), which may suggest that it has a role in the pathogenesis of ILD.

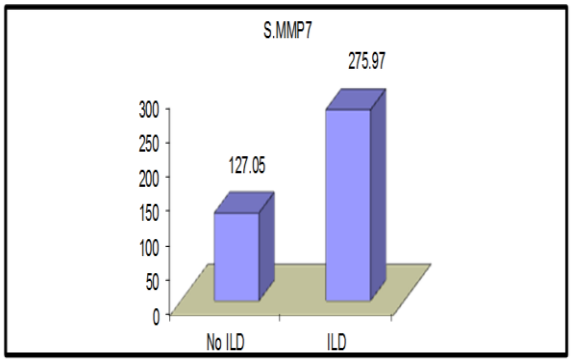

Fig (1): S.MMP7 among both studied RA groups (with and without ILD)

Correlative data

Table (3): Correlation between serum level of MMP7 and demographic, clinical, and laboratory data among the studied RA patients (with and without ILD): (N=40)

Parameter	S. MMP7 in RA patients	
	RA patients (n=40)	
	R	p value
Morning stiffness	0.835**	**<0.001**
SJC	0.186	0.251
TJC	-0.411	0.072
DAS 28 ESR	-0.155	0.515
ESR(mm/hr)	0.292	0.068

This table showed that there were statistically significant positive correlations between morning stiffness, with mean S. MMP7 level. There was no other significant correlation regarding disease activity detected by DAS score or other parameters.

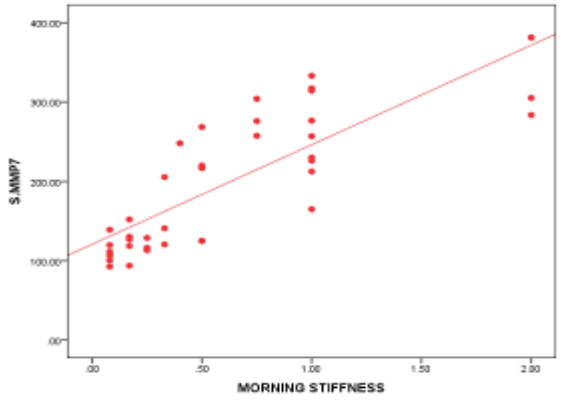

Fig (2): Correlation between serum MMP7with morning stiffness within the studied 40 RA patients

DISCUSSION

This study was a cross sectional study that included 40 RA patients fulfilling the American College of Rheumatology and European League against Rheumatism (ACR / EULAR) 2010 classification criteria [7]. Patients were selected from Ain Shams University Hospitals Outpatient Rheumatology Clinic and Inpatient Rheumatology Department.

Our 40 studied RA patients were divided into 2 groups: Group 1: RA patients without ILD which included 20 patients, Group 2: RA patients with ILD which included 20 patients.

Comparison between RA patients with and without ILD as regards serum MMP 7 showed that there was a highly significant difference between both groups ($p<0.001$) being higher in patients with ILD, coming in accordance with **chen *et al.*** study [8] who reported significant difference between both groups regarding the level of MMP7 ($p=0.001$) being higher among ILD patients.

On correlating serum MMP7 with joint affection, disease activity as measured by DAS score, among the studied RA patients (with and without ILD), it was found that, the S.MMP7 level showed positive correlation with duration of morning stiffness ($p <0.001$). While there was no significant correlation regarding other clinical parameters including DAS score. This was in agreement with **moinzadeh *et al.*** [9] who found highly significant positive correlation regarding morning stiffness ($p=0.031$).

SUMMARY AND CONCLUSION

In conclusion our study showed that S. MMP7 can be used as a screening test for detection of interstitial lung disease in patients with rheumatoid arthritis,

In our study, serum MMP7 level was higher in RA patients with ILD than patients without, but there were no statically significant relation regarding clinical and laboratory assessment of disease activity. So MMP7 might be specific to lung diseases.

RECOMMENDATIONS

Rheumatoid Arthritis patients should be followed up carefully by good history taking, prompt clinical examination and the required specific investigations in each follow up visit, Interstitial lung diseases is a common extra articular manifestation that increase the morbidity among RA patients.

RA patients with pulmonary manifestations (dry cough, exertional dyspnea, wheezy chest) should undergo further evaluation for detection of ILD.

Serum MMP7 may be used as screening test of RA patients for detection of ILD.

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