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Article

Association between Serum Matrix Metalloproteinase-3 and Disease Activity in Rheumatoid Arthritis"

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Abstract: Background: Rheumatoid arthritis is a systemic disease with an autoimmune basis, which presents with inflammation mostly targeting the synovial joints with resultant degenerative changes and impaired functions. MMP-3 (matrix-metalloproteinase-3) is one member of the metalloproteinases family that plays a significant role in the pathogenesis of rheumatoid arthritis via degradation of cartilage and bone as well as activation of other enzymes like pro-MMP-1 and pro-MMP-9. Aim: The purpose of the present research is to assess the potential use of MMP-3 as a diagnostic biomarker for differentiating between the active and inactive states of RA. Methods: Levels of MMP-3 were quantitatively determined via ELISA method among 80 RA cases with equal division between active and inactive forms of the disease. Results: Most patients (61.25%) were aged between 40 and 59 years, and females outnumbered males at a ratio of 4.3:1. Serum MMP-3 was markedly higher in patients with active RA (607.686 ± 195.963 pg/ml) than in those with inactive disease (297.511 ± 130.653 pg/ml). Neither age nor gender showed a significant correlation with MMP-3 levels; nevertheless, MMP-3 tended to rise with longer disease duration and fall with extended treatment periods. Conclusion: The serum MMP-3 is a useful marker in diagnosing RA and assessing its activity and treatment response.

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Keywords: Arthritis, Rheumatoid, MMP-3, Autoimmune inflammatory disease, Synovial joints.

1. Introduction

A chronic systemic autoimmune inflammatory disorder, rheumatoid arthritis (RA) affects multiple organs and tissues, with the synovial joints being primarily involved, ultimately leading to marked functional disability and joint damage. Globally, relatively stable prevalence rates of RA have been reported, ranging between 0.5% and 1.0%. Women are affected more frequently than men, with disease rates notably higher among females, with an approximate female to male ratio of 3:1 [1], [2]. Furthermore, the occurrence of the disease increases gradually with age; it occurs in about 5% of females and 2% of males by the age of 70 years [3].

A strong link has also been noted between HLA-DR4 and adult seropositive RA [4]. In contrast, HLA-DR1 is noted to be of greater importance in Indian and Israeli series, while HLA-DW15 has significance among Japanese patients [3]. Smoking is considered the primary environmental trigger for RA [5]–[7]. In those testing positive for anti-citrullinated peptide antibodies ($ACPA^+$ RA) and in male patients, this association tends to be particularly stronger, in whom smoking-derived chemicals are known to activate peptidylarginine deiminase type 2 [8].

The zinc-containing endopeptidase family known as matrix metalloproteinases (MMPs, matrixins) includes both secreted and membrane-bound enzymes, which all naturally have the capacity to break down every extracellular matrix component [9] . Matrix metalloproteinases are deeply implicated in both normal physiological functions and pathological conditions. Under physiological circumstances, MMPs participate in processes including processes such as wound repair, cell migration, neurite outgrowth, angiogenesis, bone elongation, Mammary gland maturation, hair follicle development, uterine involution, antigen processing and presentation, ovulation, menstruation, sperm maturation, enamel development, and embryo implantation. On the other hand, dysregulated MMP activity is connected to a variety of pathological states, like arthritis, fibrosis, tumor growth and invasion, Infertility, cirrhosis, multiple sclerosis, glaucoma, lupus, scleroderma, aortic aneurysms, and many other illnesses [10].

Belonging to the matrix metalloproteinase family, matrix metalloproteinase-3 (MMP-3), also known as stromelysin-1, is synthesized by articular synovial cells also fibroblasts, and chondroblasts. Within human articular cartilage, it represents the main metalloproteinase that is synthesized [11]. MMP- 3 is expressed in healthy people but to a much lesser extent as it is considered to contribute to physiological, continuous remodeling processes in cartilage and bone tissue. Overexpression of MMP-3 has been documented in RA patients, leading to markedly elevated concentrations within the synovial fluid. Accordingly, these patients have noticeably higher serum MMP-3 levels, which correspond to the quantity of MMP-3 found in the synovial fluid [12]. (MMP-3) is playing a crucial part in RA joint destruction [13], [14]. This is attributed to its wide substrate range, which encompasses gelatin, ovostatin, collagens III–V and IX, entactin, aggrecan, plasminogen, decorin, perlecan, casein, osteonectin, laminin, MBP, elastin, IL-1β, MMP-7, MMP-8, MMP-9, MMP-13, and MMP-2/TIMP-2 [15]. MMP-3 is additionally capable of activating other degradative enzymes, most notably procollagenase (proMMP-1) and progelatinase B (proMMP-9) [14].

Accordingly, MMP-3 represents a promising serological marker capable of identifying patients at high risk of developing imminent bone erosion. Moreover, given its direct involvement in the process of joint destruction, MMP-3 may also be utilized to monitor disease activity and therapeutic response. This can, in turn, help the clinicians in the formulation and modification of an individualized treatment strategy since high levels of MMP-3 point toward patients who, regardless of the stage of the disease, require aggressive therapy.

2. Methods

Subjects: This study followed a cross-sectional design and was carried out at Baghdad Teaching Hospital, Medical City, Rheumatology Consultation Clinic. A total of 80 RA patients were enrolled (15 men, 65 women; age range 18–77 years), and were equally allocated into two groups of 40 patients each, classified as either active or inactive RA according to DAS28 and ESR criteria. For each participant, clinical data were collected through history taking, physical examination, and laboratory investigations.

Materials: MMP-3 levels in serum were measured using an ELISA kit (CUSABIO™, China).

Specimen collection, storage, and handling:

1. Venous blood samples were collected under aseptic conditions to minimize hemolysis.
2. Samples were left to coagulate at room temperature for two hours.
3. Serum was obtained by centrifugation at 1000 ×g for 15 minutes.
4. Only visually clear, non-hemolyzed sera were included; hemolyzed specimens were excluded from analysis.

5. Serum samples were stored at −20°C until analysis.

Identification of MMP-3 by ELISA:

The test relies on the quantitative sandwich enzyme immunoassay technique. The wells in the microplate are coated with a monoclonal antibody specific for MMP3. The samples and standard preparations are added to enable capture. The wells are then washed and a biotinylated antibody added, followed by an avidin conjugate HRP solution and finally a substrate solution to develop a color intensity proportional to the MMP3 present.

Statistical Analysis: The data collected was entered into a computer-based database with expert statistical input. The data analysis used SPSS v18 (Chicago, IL, USA). The association of discrete data was measured using chi-squared and t-tests. Regression analysis procedures evaluated association with MMP-3. A value of <0.05 was used to measure levels of significance, and 95% CI used to determine MMP-3 levels regarding disease activity.

3. Results

Age and sex distribution is illustrated in table (1) which showed that 61.25% of current study patients were seen in age group 40-59 years old. No significant correlation was found between activity of disease in both sexes in regarding to age. Furthermore, most patients with RA, whether active or not were female, and the female: male ratio in active RA was 4.7:1, in inactive RA was 4:1, while the ratio in general, regardless of activity, was 4.3:1. (Table 1) (Figure 1).

Table 1. Age distribution of patients in relation to sex and disease activity.

Age (years)	males		females		Odds ratio	P value	Total No. (%)
	Active RA	Inactive RA	Active RA	Inactive RA			
20-29	1	-	1	4	9.00	o.24	6 (7.5)
30-39	1	3	4	2	0.166	0.21	10(12.5)
40-49	3	2	9	10	1.66	0.61	24 (30)
50-59	-	1	15	9	0.2	0.34	25 (31.25)
60-69	1	2	4	7	0.87	0.92	14 (17.5)
> 70	1	-	-	-	3.00	0.67	1 (1.25)
Total	7	8	33	32	0.84	0.77	80 (100)

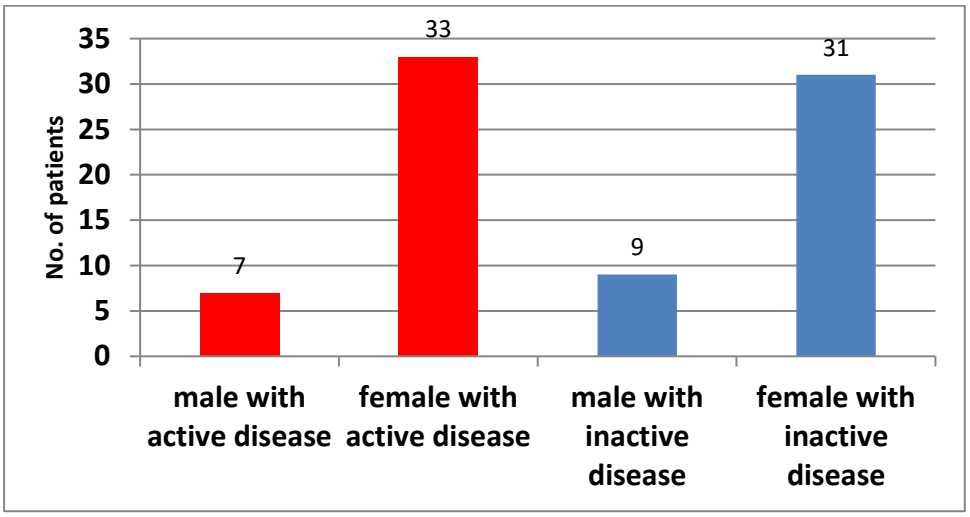

Figure 1. Frequency distribution of patients according to sex and disease activity.

Quantitative analyses of serum MMP-3 concentration using unpaired t-test in regard to disease activity showed a highly significant correlation; as in table (2).

Table 2. Correlation between MMP-3 and activity of the disease.

	MMP-3 mean ± SD (pg/ml)	*Standard Error*	*Confidence Interval*	*P- value*
Active disease (n=40)	607.686 ± 195.963	37.24	236.036-384.313	<0.001*
In active disease (n=40)	297.511 ± 130.653			

*** Very highly significant value**

Matrix metalloproteinase-3was not affected by sex. This is shown in table (3).

Table 3. Relationship between MMP-3 and sex.

Sex	**NO.**	**MMP-3 X* ± SD *(Pg/ml)***
Female	65	448.3 ± 227.7
Male	15	471.1 ± 233.1

*** Mean**

SD(standard deviation)

Matrix metalloproteinase-3 was not significantly affected by age. This is shown in figure (2).

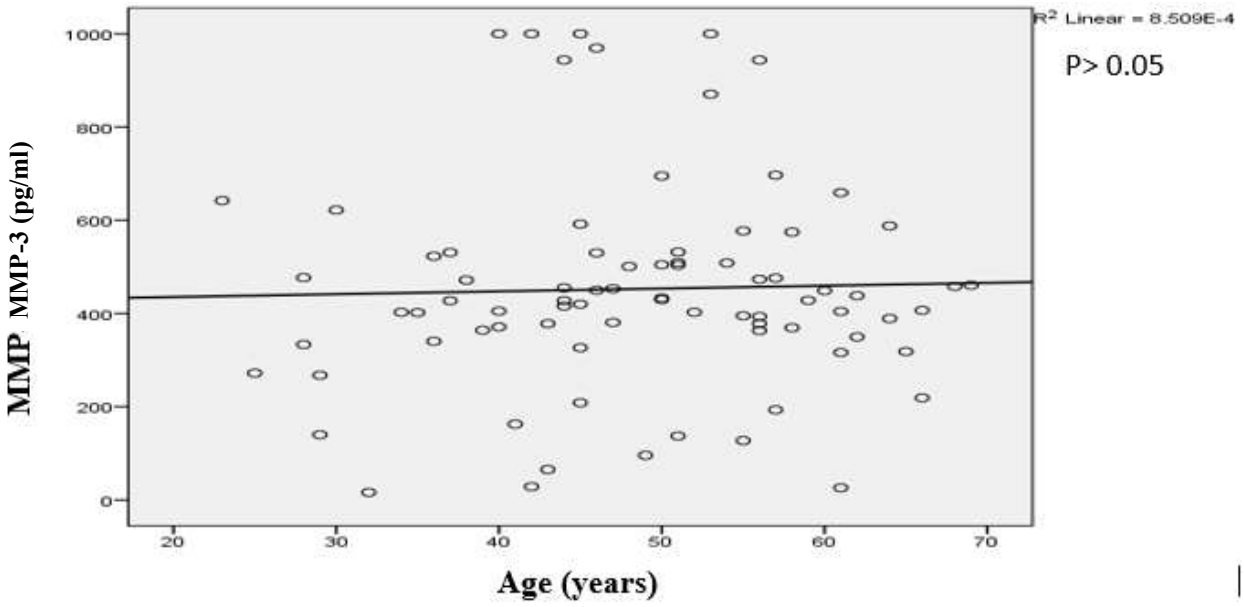

Figure 2. Regression line blotted among MMP-3and age.

MMP-3(Matrix-metalloproteinase-3), R^2 (linear regression coefficient

The duration of illness significantly affect uprising of MMP-3 level. This is shown in figure (3).

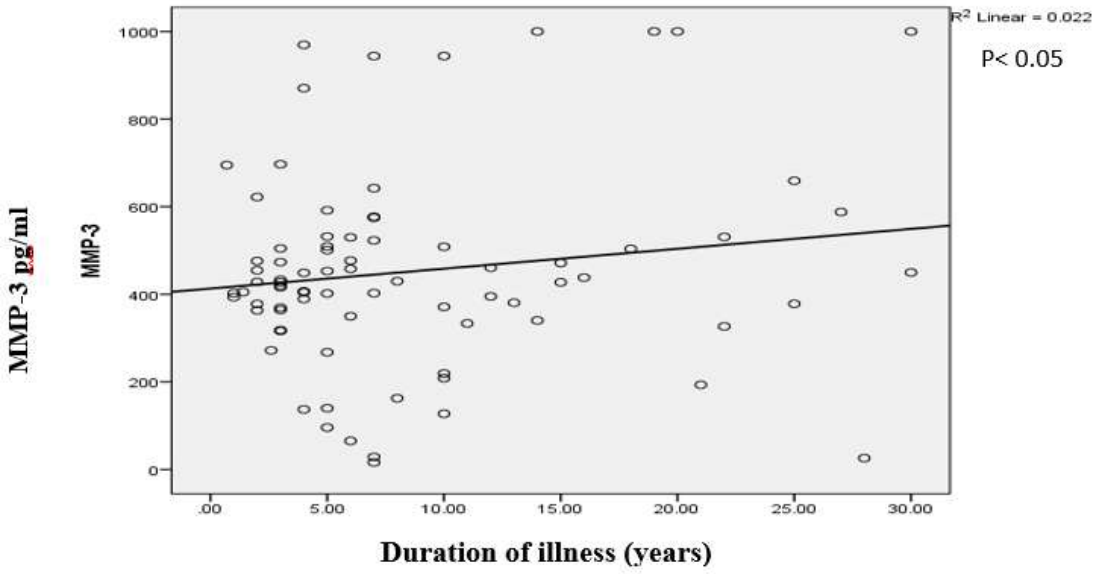

Figure 3. Regression line blotted among MMP-3 and duration of illness (years)

MMP-3(Matrix-metalloproteinase-3), R^2 (linear regression coefficient)

The duration of treatment significantly affect MMP-3 level. This is shown in figure (4).

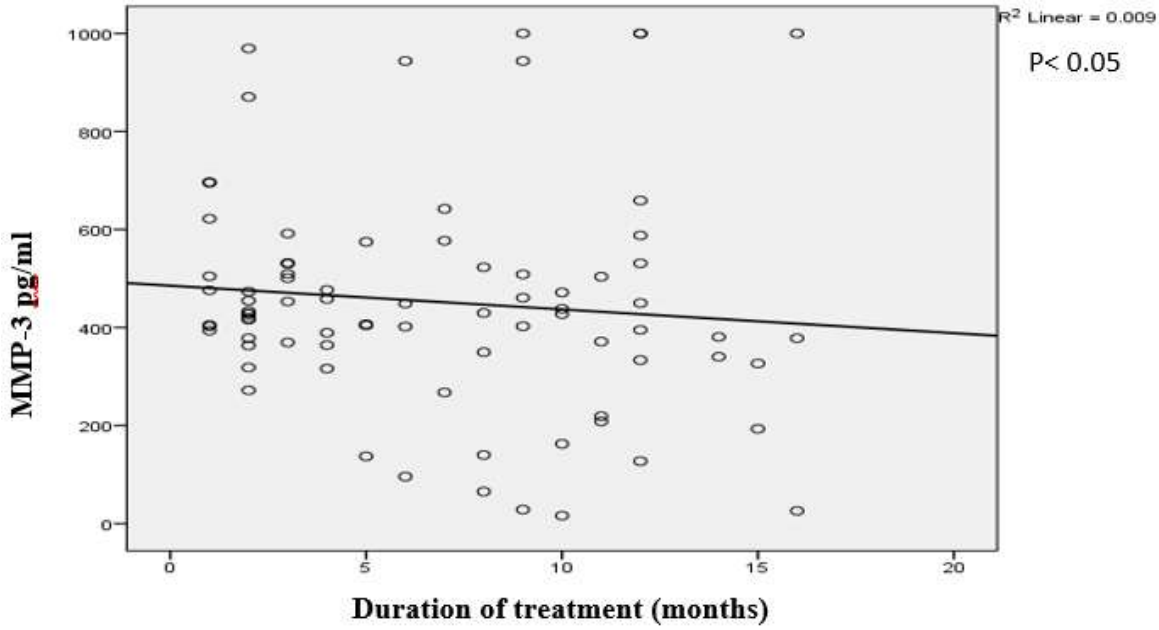

Figure 4. Regression line blotted among MMP-3and duration of treatment.
MMP-3(Matrix-metalloproteinase-3), R^2 (linear regression coefficient)

4. Discussion

In this study, most patients with rheumatoid arthritis (61.25%) were within the age range of 40–59 years. This finding is in agreement with findings reported in previous Iraqi studies [16]–[18] in addition to findings reported in studies conducted abroad [19]–[22].These studies demonstrated that Most patients with rheumatoid arthritis were over 40 years of age. Rheumatoid arthritis tends to develop after the age of 40 as a result of the cumulative effect of multiple factors that contribute to immune depression, including stress, the activation of autoreactive lymphocytes that interact with self-antigens may result from thymic involution and prolonged or increased exposure to various antigens, including smoking, drugs, and chemicals [23].

The current study showed that the female to male ratio was 4.3:1and this was in agreement with many other studies as that conducted by Al-Rawi ZS, Symmons D, AL-Ubaidi A H, and Abdul-Wahid KM which showed a ratio of 5:1, 2.7:1, 6.5:1,and 3.5:1, , respectively [16], [17], [18], [24]. The observed female predominance in rheumatoid arthritis could be attributed to hormonal factors, particularly estrogen, which promotes T-helper cell function while inhibiting T-suppressor cell activity. Additionally, estrogen receptors are expressed on memory T-cells as well as on synovial cells [25], [26]. Estrogen alters immune responses through binding a cytoplasmic receptors in cells that contain hormone receptors leading to the activation or, in some instances, repression of gene expression. Furthermore, The detection of prolactin receptors on human peripheral T and B cells provides evidence that this hormone may influence the regulation of immune responses. Consequently, prolactin may bias immune cells toward TH1-dominated responses, which could explain the greater tendency of women to mount TH1-like rather than TH2-like immune responses. The former is a pro-inflammatory reaction, and it potentiates the autoimmune disease process [27].

Prior research has consistently demonstrated that serum MMP-3 concentrations are markedly higher in RA patients with active disease when compared to those with inactive disease. Keyszer G *et al.* reported that serum MMP-3 outperformed cytokine measurements and connective tissue turnover markers in reflecting clinical RA activity

[28]. Ribbens C *et al.* similarly found that active RA was associated with raised serum MMP-3, whereas levels remained within normal range in inactive patients lacking clinically detectable synovitis, leading the authors to conclude that serum MMP-3 closely mirrors the extent of synovial inflammation [29]. Furthermore, serum MMP-3 has been found to be linked to rheumatoid arthritis activity and also to predict functional and also radiographic outcomes during the initial untreated disease. This parameter is most useful in clinical practice in cases where the standard markers are not reliable, for example, in patients who have normal CRP values and non-erosive rheumatoid arthritis [20]. The association of MMP-3 with both disease activity and articular erosion severity highlights its direct role in joint inflammation and tissue breakdown. Accordingly, MMP-3 may serve as a supplementary biomarker for assessing RA activity and disease severity [11]. Besides, Tchetverikov I. et al. showed that high serum MMP-3 levels were detected in patients with severe RA compared to those with mild disease, suggesting its role as a predictor of further joint deterioration [30].

The current study did not reveal a correlation between serum MMP-3 concentrations and either the age or sex of the patients. Such results have been corroborated by Posthumus MD et al. and Ateş A et al, who observed a similar lack of significant variation in serum MMP-3 concentrations between male and female RA patients. This could be explained by the possibility that the significantly elevated MMP-3 production in affected individuals overshadows any slight sex-related differences. [14], [31].

Within the context of the current study, a positive relationship was observed between mean serum MMP-3 concentration and disease duration. This finding agrees with the literature, which has shown a well-established link between circulating MMP-3 levels and the length of disease in RA patients. Overall, those with long-standing disease demonstrated higher median serum MMP-3 compared to newly diagnosed patients, implying that MMP-3 concentrations may reflect the burden of intra-articular inflammatory tissue and could be influenced by how long the disease has been present. Thus, the synovial pannus of the affected joint has been identified as the predominant origin of MMP-3, whereby the progressive expansion of pannus tissue throughout the chronic course of the disease likely drives greater MMP-3 secretion into the synovial fluid and subsequently into systemic circulation [32].

In the present study, a sharp reduction was noted for mean serum levels of MMP-3 in relation to longer therapy using anti-TNF-alpha agents, such as etanercept; such findings have been supported by previous research. It has been shown that treatment with etanercept shows a marked relationship with reduction in serum MMP-3 concentrations alongside decreases in other inflammatory markers, supporting a potential contribution of this therapy to limiting the subsequent progression of joint damage [33]. Anti–tumor necrosis factor-α therapy demonstrates delay radiographic progression, highlighting its potential benefit in preventing long-term disability resulting from joint damage, in addition to reducing short-term disability associated with the symptoms of inflammatory arthritis [34]. After treatment of adult patients with RA with anti-tumor necrosis factor-α (etanercept) the clinical improvement including functional status and acute phase reactants is rapid and durable [35]. The pro-inflammatory cytokine TNF-α causes tissue destruction because it is a potent transcriptional inducer of MMP-3 therefore, their function must be tightly controlled. Substantial evidence now indicates that inhibition of TNF leads to marked improvements in patient outcomes in rheumatoid arthritis [36].

5. Conclusion

Serum levels of MMP-3 were found to be significant in patients suffering from active rheumatoid arthritis in comparison to those suffering from the inactive form of the disease. This indicates the strong association between MMP-3 and disease activity. These results also revealed that MMP-3 levels increase with the prolonged nature of the disease and

decrease with the prolongation of treatment, specifically anti-TNF-α. These results suggest the practical application of MMP-3 in assessing the response to treatment. No significant association of patient age and sex with MMP-3 levels was found. Hence, serum levels of MMP-3 can effectively be used as a marker to assess the response of rheumatoid arthritis patients to treatment.

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Competing interests statement The authors confirm the absence of any competing interests.

Ethics statement Ethical approval was secured from the Rheumatology Unit, Department of Medicine, Medical City, Baghdad Teaching Hospital. This research adhered to the principles of the Declaration of Helsinki. All participants signed informed consent forms before enrolling in the study.

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