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Evaluation of Some Biochemical Factors Associated with Rheumatoid Arthritis

Tabarak Siraj Ibrahim[1] and Bushra Faris Hasan[2*]
[1,2]Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad, Iraq.
*Corresponding Author.

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Abstract

Rheumatoid arthritis (RA) is a systemic disease that causes chronic inflammation, primarily affecting the synovial joints in the hands and feet. Laboratory investigations, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile, and matrix metalloproteinase-1 (MMP-1), evaluate the body's inflammation level. Rheumatoid arthritis is generally progressive, causing fatigue and weakening of the muscle joints. Despite recent treatment improvements, there is no known cure for RA. The study aims to find the role of chemokine MMP-1 as a biomarker in serum samples of 80 patients with RA and 40 healthy subjects. The mean of MMP-1 was significantly higher in patients with RA compared to the control group (MMP-1: 3.27 ± 0.10 ng/mL vs. 1.40 ± 0.11 ng/mL, respectively). The results demonstrated a statistically significant distinction between the two groups. The binary logistic regression analysis revealed that MMP-1 had a statistically significant association with the occurrence of RA. Additionally, it was shown that MMP-1 had an area under the curve of 0.939 in people diagnosed with RA. Both of these experiments provided evidence of this result. According to the findings of the study, there is a possibility that MMP-1 has a role in the pathogenesis of RA since it was shown that patients with RA had higher levels of serum MMP-1, CRP, ESR, and lipid profile when compared to the control group. In conclusion, serum MMP-1 serves as a reliable diagnostic marker, accurately distinguishing individuals with active RA from control subjects.

Keywords: C-reactive protein, Lipid profile, Matrix metalloproteinase-1, Rheumatoid arthritis, Rheumatoid factor.

1. Introduction

Rheumatoid arthritis (RA) is an inflammatory disease that affects the entire body, causing long-term inflammation of the synovial membrane and gradual degradation of the joints. This condition ultimately leads to a decline in physical ability, work-related limitations, and a reduced overall quality of life (1). The global incidence of RA remains inadequately characterized due to the lack of comprehensive epidemiological studies conducted across different geographical regions. Nevertheless, it has been suggested that the occurrence of RA is approximately 3 times more common in women compared to men (2–4).

Inflammatory arthritis, which often affects the tiny joints in the hands and feet, is its primary symptom. It is characterized by symmetric, polyarticular pain and swelling. On the other hand, it is a systemic disease linked to numerous concomitant diseases and extra-articular symptoms. Inflammatory synovitis develops as a result of the interaction between specific environmental exposures and genetic factors (5,6). Before a condition can be labeled as RA, the illness process typically starts years before clinically apparent arthritis. It presents as a continuum that begins with asymptomatic immune dysfunction and proceeds through several stages (7). The trajectory of joint erosion is characterized by unpredictability and may persist despite the implementation of measures to control inflammation actively (8).

Nevertheless, RA is regarded as a disease with the possibility of a cure, particularly when diagnosed in its initial phases and managed with suitable treatment (9). The disease activity indicators commonly used lack specificity in the context of arthritis. Novel biomarkers have been established to forecast the occurrence of structural damage and disease progression in RA (10). There is a proposal suggesting that the pathophysiologic mechanisms behind synovial inflammation and articular erosion may exhibit distinct differences (11).

Matrix metalloproteinases (MMPs) are a collective of extracellular enzymes. During the state of normal equilibrium, they play a significant part in the process of tissue remodeling. However, in pathological conditions, they contribute to the detrimental process of tissue destruction (12). The MMP-1 plays significant functions in the process of bone and cartilage breakdown and disintegration (13). The production of these substances occurs within the inflamed joint by synovial fibroblasts and chondrocytes, and their activation is a consequence of cytokine-mediated stimulation (14). Subsequently, they are released into the bloodstream. Consequently, these substances have the potential to serve as a direct indicator of joint inflammation and damage in rheumatic diseases, particularly RA (15).

Matrix metalloproteinase-1 is a variety of proteins that break down the majority of extracellular matrix enzymes during organ formation, growth, and tissue turnover. The MMP-1 expression and activity in adult tissues are usually very low but are significantly increased in various immune-mediated conditions, such as inflammatory disorders, that may lead to tissue destruction. It has been abundantly clear in recent years that genetic and epigenetic variables contribute to the development of RA **(**16**)**, which is generally progressive and reduces physical functionality, leading to fatigue and weakened joints **(**2,17**)**. However, the exact causes of RA are still not understood **(**18**)**.

There are more than one hundred different varieties of arthritis, and many of the issues that affect the joints are similar; thus, there are many varied symptoms. This makes it challenging to differentiate between the diseases. Laboratory investigations for RA include blood tests that evaluate the body's level of inflammation, such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid profile, and MMPs **(**3,19**)**.

The MMPs have been identified as key contributors to the development of RA (20). The upregulation of MMP-1, MMP-3, MMP-9, and MMP-13 expression in RA synovial fibroblasts (RASFs) suggests that MMPs have a significant impact on the degradation of cartilage in the joints affected by RA (21). The MMP-1, also known as collagenase 1, and MMP-13, also known as collagenase 3, are enzymes that specifically cleave collagen. On the other hand, MMP-3, also referred to as stromelysin 1, and MMP-9, also known as gelatinase B, are enzymes that primarily target proteoglycans composed of aggrecan. The deterioration of proteoglycans located on the surface, coupled with the breakdown of collagen fibrils in the deep zone, collectively contributes to the degradation of articular cartilage (22). The MMPs may therefore have a unique function in the joint degradation process in RA (23). The

effective management of RA requires a comprehensive understanding of the regulatory mechanisms that activate MMP genes in RASFs, which may significantly contribute to knowledge of the pathological processes and facilitate the development of novel therapeutic approaches for this illness (24).

This study aims to evaluate serum MMP-1 and certain biochemical factors in patients with RA and to investigate their correlation with disease activity among Iraqi patients.

2. Materials and Methods

The current study included 120 subjects divided into two groups: 80 patients with RA were enrolled in the study (74 females and 6 males). The patients' ages ranged from 24 to 74 years. Additionally, forty control subjects were individuals whose ages ranged from 20 to 60 years, and their gender (33 females and 7 males), during the period from March 2023 to June 2023. This study was conducted at the Medical City Hospital. Before participating in the study, each individual gave their informed consent. The National Center for the Development of Humans and the Medical City's approval of the study. Each subject underwent subsequent laboratory tests, including MMP-1, CRP, ESR, rheumatoid factor (RF), and lipid profile [(cholesterol triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein (VLDL)].

2.1. Inclusion and exclusion criteria

This study included patients with RA aged 24 to 74 years. The RA patients were found to have another autoimmune disease, gout, osteoarthritis, polycystic ovary syndrome, disabilities, and cancer, and pregnant women were excluded from the current work.

Six milliliters of blood were collected from each individual. After the blood was put into gel tubes and left to coagulate for 30 minutes at room temperature, each sample was centrifuged for 5 minutes at 3000 × g. After that, the serum was separated into Eppendorf tubes and stored at -20°C for MMP-1, CRP, RF, and the lipid profile, among others.

The quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique was used to measure the levels of MMP-1, CRP, RF, and lipid profile in serum using Pepro Tec kits from the USA, according to the manufacturer's instructions. Anti-MMP-1, CRP, RF, and lipid profile antibody (the arresting antibody) were coated in the wells of a 12x8-well plate. A serum or standard was then added to the relevant wells. An antibody for detecting bioavailable anti-human chemokines was added. After the wells had been cleaned, avidin and horseradish peroxidase (HRP) were added. Once the wells have been cleaned to remove. The substrate solution and the unstructured avidin-enzyme reagent interact, changing color before ceasing. The color change was measured spectrophotometrically at a wavelength of 450 nm ± 10 nm.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 26, was employed to assess the influence of different factors on the study's parameters. Data were expressed as mean ± standard error (SE), and a t-test was employed in this specific inquiry to make statistically significant comparisons between various means. The Pearson's method was used to determine the correlation (r-coefficient) between MMP-1 and other parameters. A p-value less than 0.05 was considered statistically significant. Additionally, receiver operating characteristic (ROC) analysis was used to determine the sensitivity and specificity of the markers, while multivariate cluster analysis was also used. The chi-square test was used to investigate the possible association between baseline characteristics (BMI and sex) and the distribution of the analyzed groups.

3. Results

The results indicated that there was no statistically significant correlation at the predetermined significance level of 0.05. In contrast, the results for age, smoking, and menopause suggest a highly significant increase in the patient group compared to the control group ($p < 0.05$), as shown in **Table (1)**.

Table 1. Groups distribution according to the baseline characteristics

Parameters		RA Patients (n = 80) No. (%)	Control (n = 40) No. (%)	*p*-value
Age (Years)	≤ 50	39 (48.8%)	31 (77.5%)	0.0001*
	> 50	41 (51.2%)	9 (22.5%)	
BMI (kg/m^2)	Healthy weight (18.5-24.9)	14 (17.5%)	13 (32.5%)	0.078
	Overweight (25-29.9)	27 (33.8%)	17 (42.5%)	
	Obese (30-34.9)	24 (30%)	7 (17.5%)	
	Extremely Obese (>35)	13 (16.3%)	3 (7.5%)	
Gender	Female	74 (92.5%)	33 (82.5%)	0.098
	Male	6 (7.5%)	7 (17.5%)	
Smoking	Yes	-	2 (5%)	0.044*
	No	80 (100%)	38 (95%)	
Menopause	POST	32 (40%)	8 (20%)	0.0001*
	PRE	43 (53.8%)	25 (65.5%)	

*Significant difference at $p < 0.05$ level.

Serum MMP-1, CRP, and RF levels revealed significant increases in RA patients compared to the controls. The median ESR level in RA was substantially higher than that in the control group, as shown in **Table (2**). The results show that there was a significant increase in the serum lipid profile in RA patients compared to the control, except for serum HDL-C, which showed a significant decrease in RA patients compared to the control (**Table 3**). The correlation between MMP-1 and other parameters in RA patients is demonstrated in **Table (4).**

Table 2. Serum level of MMP-1, CRP, RF, and ESR between RA patients and control**.**

Parameters	Mean ± SE		*p*-value
	RA Patients (n = 80)	Control (n = 40)	
MMP-1 (ng/mL)	3.27±0.10	1.40±0.11	< 0.0001
CRP (ng/mL)	2443.09±17.33	1272.41±35.24	< 0.0001
RF(ng/mL)	0.93±0.13	0.35±0.034	< 0.0001
ESR (mm/hr)	33.82±2.53	15.54±1.14	< 0.0001

*Significant difference between two independent means using Students-t-test at 0.05 level. MMP-1= matrix metalloproteinase-1; CRP=C-reactive protein; RF= rheumatoid factor; ESR= erythrocyte sedimentation rate; RA= rheumatoid arthritis.

Table 3. Serum lipid profile in RA patients and control

Parameters	Mean ± SE		p-value
	RA Patients (n = 80)	Control (n = 40)	
Cholesterol (mg/dL)	196.63±4.29	105.83±3.32	0.0001*
TG (mg/dL)	210.11±1.59	168.35±3.56	0.0001*
HDL-C (mg/dL)	33.15±0.59	42.75±0.54	0.0001*
LDL-C (mg/dL)	121.45±4.14	29.43±2.95	0.0001*
VLDL-C (mg/dL)	42.02±0.31	33.67±0.71	0.0001*

Data were presented as Mean ± SE.*Significant difference between two independent means using Students-t-test at 0.05 level.

The correlation between MMP-1 and other parameters in RA patients is demonstrated in **Table (4**).

Table 4. Correlation between MMP-1 and other parameters in RA patients

		MMP-1 (ng/mL)
		RA Patients
Age (years)	**r**	-0.082
	p	0.468
BMI (kg/m^2)	**r**	0.105
	p	0.354
Cholesterol (mg/dL)	**r**	0.223*
	p	0.047
TG (mg/dL)	**r**	-0.027
	p	0.810
HDL-C (mg/dL)	**r**	0.197
	p	0.080
LDL-C (mg/dL)	**r**	0.206
	p	0.067
VLDL-C (mg/dL)	**r**	-0.027
	p	0.810
CRP (pg/mL)	**r**	-0.007
	p	0.949
ESR (mm/H)	**r**	-0.036
	p	0.753
RF (ng/mL)	**r**	-0.160
	p	0.156

*Correlation is significant at the 0.05 level.

The ROC analysis revealed that the level of MMP-1 in serum could discriminate among RA patients with a sensitivity of 0.963 and a specificity of 0.150 (area under curve = 0.939), as shown in **Figure (1**).

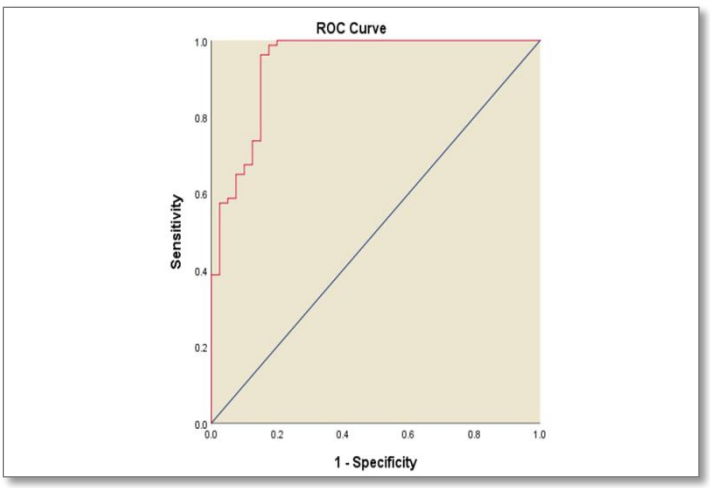

Figure 1. The ROC curve for MMP-1 in RA patients

4. Discussion

The current data indicates the predictive value of MMP-1 as an RA biomarker, which is more pronounced in malignant lesions. The most notable finding in this study is the higher levels of serum MMP-1, CRP, ESR, and lipid profiles in patients with RA compared to the control group.

This study found that RA patients had higher serum MMP-1 levels than controls, which may

indicate the presence of the disease and its progression. The RA can develop from a moderate, non-destructive type to a serious, rapidly degenerative joint condition. It could be used to estimate RA progression and identify the best course of therapy. Previous research had relevant results, and such chemokines have been linked to the development of RA. There has been little research on the effects of serum MMP-1 on RA, and most studies have been conducted in vitro and human models (25-27). It has been suggested that their serum levels correlate with levels produced by the synovium and thus reflect the level of inflammation and activity of rheumatoid synovitis. The pathophysiologic mechanisms of joint inflammation and bony erosion may be partially independent; each might be determined by a principal cytokine or protease in different disease conditions. This could be explained by the abundant expression of MMP-1 by articular synovial cells, fibroblasts, and chondrocytes in inflamed rheumatoid synovium, which is then released into the bloodstream. Therefore, their serum concentrations can be considered alternative non-invasive biomarkers of RA activity in clinical practice (27).

Rheumatoid arthritis patients also had a higher BMI in the obese and extremely obese groups, as presented in **Table (1**). In contrast to the current study, Abd-Allah et al. (28) found no link between the MMP1 polymorphism and RA susceptibility in patients from Brazil, Spain, and Korea. The ROC curve study for MMP-1 has the best AUC as an RA marker. However, one study found no statistically significant change in MMP-1 levels between the RA and control groups (28). According to this study, blood MMP-1 levels predict clinical remission of RA better than CRP levels. Patients with RA who haven't been treated and have persistent systemic inflammation have different lipoprotein and apolipoprotein profiles, which may make them more likely to develop atherosclerosis (29). Moreover, RA patients have a continuous trend of reduced levels of HDL cholesterol in comparison to controls who are matched in terms of age and sex (30). However, the findings regarding total cholesterol and LDL-C levels are more varied. Several studies have reported notable increases in these parameters compared to the control group, while other investigations have not found similar results (31). The different lipid factors that increase the risk in people with RA have significantly higher ratios of apolipoprotein B to A1, total cholesterol to HDL cholesterol, and LDL to HDL cholesterol (32).

The mean ± SE of CRP levels in patients and controls was 2443.09 ± 17.33 (1272.41 ± 35.24 pg/mL), respectively. The findings revealed a significantly higher CRP level in patients with RA compared to the control group ($p < 0.01$), as presented in **Table (2)**. This suggests that CRP can be used as a potential biomarker for RA and may indicate the presence and severity of the disease (33).The mean ± SE of ESR in patients and controls was 33.82 ± 2.53 and 15.54 ± 1.14 mm/h, respectively. The findings revealed a significant increase in ESR among RA patients compared to the control group, with a p-value of less than 0.01 ($p < 0.01$), as presented in **Table (2)**. This suggests that ESR can be used as a potential biomarker for RA and may indicate the presence and severity of the disease. Monitoring ESR levels in RA patients can help assess disease progression and guide treatment decisions (34).

The mean ± SE of RF levels in patients and controls were 0.93 ± 0.13 ng/mL and 0.35 ± 0.34 ng/mL, respectively. The results demonstrate a significant rise in RF levels in patients with RA compared to the control group, with a p-value of less than 0.01, as shown in **Table (2)**. RF levels can serve as a potential biomarker for RA and may indicate the disease's presence and severity. Monitoring RF levels can help assess disease progression and guide treatment decisions in RA patients. Elevated RF levels in RA patients may be associated with the inflammatory process and disease activity in these patients (33, 34).

5. Conclusion

Serum MMP-1 levels were considerably related to RA. This might indicate its role in the pathophysiology of RA. As a result, it may be helpful in treating RA. Furthermore, MMP-1 has excellent diagnostic performance with high accuracy in distinguishing between individuals with RA and healthy controls.

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Conflict of Interest

There are no conflicts of interest.

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None.

Ethical Clearance

The scientific committee in the College of Sciences for Women at the University of Baghdad and the Medical City Hospital approved this study. A verbal agreement was obtained from each person included in the survey on March 29, 2023.

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