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Serum Levels of Tripartite Motif-containing Protein 72 (TRIM72) in Iraqi Rheumatoid Arthritis Patients and Its Relevance to the Disease Activity State

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ABSTRACT

Background & Objective: Uncontrolled active rheumatoid arthritis patients have a progressive disability, pain, swelling problems, and stiffness that often lead to systemic complications, early death, socioeconomic costs, and comorbidity. The objectives of this study were to measure the serum levels of Tripartite motif-containing protein 72 in Iraqi patients with rheumatoid arthritis and healthy individuals, assessment of the efficiency of Tripartite motif-containing protein 72, determine their essential serum rates in association with disease activity, sociodemographic and clinical specifications of the diseases.

Materials & Methods: In this case-control study, 117 Iraqi patients with rheumatoid arthritis were investigated according to the 2010 American College of Rheumatology / European League Against Rheumatism from December 2020 to March 2022. The patients were divided into two groups. Group 1 were the RA patients with active disease, Group 2 were the RA patients with inactive disease, and healthy subjects served as the control group.

Results: Serum levels of Tripartite motif-containing protein 72 in the active RA groups (101.92±160.18 Pg/mL) were significantly higher as compared with the inactive RA group (64.58±54.34 Pg/mL) and the control group (41.06 ±32.48 Pg/mL) (P<0.005). Tripartite motif-containing protein 72 could not discriminate between RA and the controls (since its AUC ≥0.689).

Conclusion: There was a positive relationship between DAS-28ESR and Tripartite motif-containing protein 72 levels, which induces bone erosion. The serum Tripartite motif-containing protein 72 level showed a significant elevation in rheumatoid arthritis patients compared with healthy controls. Tripartite motif-containing protein 72 had a poor discriminative ability between RA and the control group.

Keywords: Disease Activity Score 28, Rheumatoid Arthritis, Tripartite Motif-containing Protein 72

Introduction

Rheumatoid arthritis is a chronic inflammatory systemic and autoimmune disorder characterized by Synovial hyperplasia and inflammation of synovial joints. The inflammation of synovial joints transformed the synovium into an invasive pannus. These transforms causes the infiltration and activation of macrophages, plasma cells, and memory T cells and permanently destroys cartilage and bone (1). Therefore, uncontrolled active rheumatoid arthritis patients suffer from progressive disability, pain, swelling problems, and stiffness that often lead to systemic complications, early death, socioeconomic costs, disability, and comorbidity (2, 3). It is estimated that rheumatoid arthritis influences about 0.24% of the world's population (4).

The presence of a conserved N-terminal RBCC module that is made up of a fascinating new gene (RING) domain, one or two BBoxes (B1/B2), and a coiled-coil (CC) domain distinguishes the tripartite motif (TRIM) proteins from other members of the huge protein family (5). More than eighty kinds of the TRIM family have been found in humans so far (6, 7). Alterations of functions of TRIM proteins were connected to diverse diseases, including cardiovascular problems, infections, neuropsychiatric disorders, cancers, and diabetes mellitus (8-11). The potential of TRIM family members for drug development is based on E3 ubiquitin ligase activities (12).

The tripartite motif family protein 72 (TRIM72, also called mitsugumin 53 MG53) is one of the tripartite motif (TRIM) family members. TRIM72 includes the typical tripartite motif with 477 amino acid residues (13, 14). Mitsugumin 53 (MG53) has the potential to become a promising pharmaceutical therapeutic for recovery

purposes. Multi-organ injury recovery can also be achieved using the MG53 protein as a pharmaceutical therapeutic (15, 16). TRIM72 is basic for layer repair and wound mending after myocardial damage (17, 18). TRIM72 balances a hypoxic tumor microenvironment (TME) and plays tumor-suppressive parts in breast cancer progression. Thus, TRIM72 may be a helpful target in breast cancer (19).

The objectives of the present research were to estimate rates of serum Tripartite motif-containing protein 72 in Iraqi patients with rheumatoid arthritis and healthy individuals, assess the efficiency of Tripartite motif-containing protein 72, determine their essential serum rates in association with disease activity, sociodemographic and clinical specifications of the diseases.

Materials and Methods

2.1. Patients

Baghdad Teaching Hospital / Medical City provides services to various Iraqi populations, including rural, urban, and inner-city areas from a few governorates. Therefore, this case-control study was carried out at Baghdad Teaching Hospital / Medical City and the Department of Biochemistry, Medicine College, Baghdad University, Baghdad, Iraq. The subjects were admitted to hospital from December 2020 to March 2022. All patients were examined and treated by specialists.

In this study, 117 Iraqi patients with rheumatoid arthritis were tested according to the reexamined 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) Classification Criteria for RA (20).

The patients were divided into two groups according to EULAR response criteria (21), which were centered on the activity score as decided by the DAS28 (22). Group 1, RA patients with active disease state score including 62 samples; Group 2, RA patients with inactive disease including 55 samples; and healthy subjects (n=58) served as the control group who underwent routine physical examinations with no underlying rheumatoid arthritis, diabetes mellitus, autoimmune diseases, pregnancy, lupus, and other complications.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were 2010 ACR/EULAR RA classification criteria, affirmation of RA, age (≥30) years, disease duration up to 2 years, Remission-to-high Disease Activity Score in 28 joints (DAS28), erythrocyte sedimentation rate (ESR), present results recorded of kidney function tests, serum urea and creatinine, hepatic function tests, Aspartate Aminotransferase and Alanine Aminotransferase to be within the normal range. The exclusion criteria were as follows: joint surgery within 6 months, lupus, osteoarthritis, psoriatic arthritis, Sjogren's syndrome, Gout, infectious arthritis, scleroderma, spondyloarthropathies, ankylosing spondylitis, and polymyalgia rheumatica, age (≤30), history of hypertension, diabetes, pregnancy, congestive heart failure, or concomitant renal, hepatic, cardiac, or infectious processes. All patients signed a consent form. The research procedure was affirmed by the Logical and Moral Committee in Medicine College, Baghdad University, and the Rheumatology Medical Department at Baghdad Educating Healing Center (No: 819; Date: 25/10/2020). The research was conducted in accordance with the standards of the Helsinki Declaration.

2.3. Data Collection

Data on demographic characteristics, disease span, age, recent lab data, weight, WBC, ESR, data about patients, sore and swollen joints, and visual analog scale ratings were gathered. This was done through patient interviews using a patient information record designed for this study.

2.4. Blood Sample Preparation and Collection

Eight to ten milliliters of peripheral venous blood were obtained from each patient group and divided into two parts. The primary one (6-8 mL) was carried to a plain tube, which was permitted to clot for 30 minutes. Subsequently, the serum was separated by centrifugation at 2500 rpm for 10 minutes and stored at –20˚C until the examined biochemical parameters were carried out. The second blood part (2-3 mL) was added into a citrate tube and sent to the Laboratory of Baghdad Teaching Hospital for ESR and hematological investigations. Serum TRIM-72 (CUSABIO, China., Cat.No. CSB-EL024511HU) concentrations were assessed by the enzyme-linked immunosorbent test based on the producer's references.

2.5. Statistical Analysis

The statistical analysis was done using IBM SPSS for Windows version 26.0 program (IBM Corp., Armonk, NY, USA). The mean and standard deviation (SD) were used for the present data. One-way analysis of variance (ANOVA) was used to compare the statistical differences between the groups. The comparisons between the two groups were analyzed by independent sample t-test. Pearson's correlation was used to evaluate how the different biomarkers were related. Finally, the sensitivity, specificity, area under the curve, cut of value, and accuracy utility were explored with receiver operating characteristic (ROC) curve analysis. A P-value below 0.05 was considered statistically significant.

Results

Table 1 shows the demographic and anthropometric properties of rheumatoid arthritis patients and the control group. Table 1 illustrates the mean±SD values of age and BMI of the three groups under study. The mean ages were 51.12±11.42 years, 50.20±10.69 years, and 51.52± 11.31 in the Inactive RA group, the active RA group, and the controls, respectively, with non-significant differences among the studied groups. The mean values of BMI did not differ significantly among the studied groups: Inactive RA (28.25±4.831 kg/m^2), active RA (27.97±4.68 kg/m2), and for controls (27.75±4.751 kg/m^2).

There were 41 females (74.54%), 14 males (25.45%) in the Inactive RA group, 49 females (79.03%), 13 males (20.96%) in the active group, and 40 females (68.96%), 18 males (31.03%) in the control group. There was no significant difference among the studied groups, while the smoker number was substantial differences among the studied groups.

Table 1. Demographic and anthropometric characteristics of the study groups

Characteristics	Control Groups N=58	Inactive RA disease Groups N=55	Active RA disease Groups N=62	P-value
Age(years)	51.52± 11.31	51.12±11.42	50.20±10.69	0.279
BMI (Kg/m²)	26.55±4.751	27.25±4.831	28.97±4.680	0.017
		Gender, no. (%)		
Female	40 (43.09%)	41 (40.86%)	49 (46.06%)	0.450
Male	18 (14.91%)	14 (14.14%)	13 (15.94%)	
female to male ratio	20: 9	82: 28	98: 26	
		Smoking number (%)		
Non-smoker	31 (37.78%)	44 (35.83%)	39 (40.39%)	0.008
Passive smoker	24 (15.58%)	6 (14.77%)	17 (16.65%)	
Smoker	3 (4.64%)	5 (4.40%)	6 (4.96%)	

Disease Activity Score and Used Medications of Rheumatoid Arthritis Patients

Table 2 highlights the results of tender joints count (TJC), swelling joints count (SJC), patient global assessment, evaluator global assessment DAS28, CDAI, ESR, and WBC C among rheumatoid arthritis patients, indicating a significant difference. Among the 117 RA patients, 43 patients were treated with conventional DMARDs (25 inactive RA groups and 18 active RA groups), 41 with biological DMARDs (20 inactive RA and 21 active RA), and with combination DMARDs (11 inactive RA and 23 active RA); this was statistically significant (P=0.077). Additionally, there were no significant differences in Tripartite motif-containing protein 72 in rheumatoid arthritis patients.

Table 2. Clinical, Laboratory Characteristics and Tripartite motif-containing protein 72 of rheumatoid arthritis patients

Parameter	Inactive RA disease Groups N=55	Active RA disease Groups N=62	P-value
Disease duration (years)	7.51±4.807	8.95±5.871	0.152
Number of tender joints	1±0.816	5.74±3.24	0.0001
Number of swollen joints	0.22±0.44	2.57±2.10	0.0001
Patient global assessment	1.857±1.864	5.34±1.98	0.0001
Evaluator global assessment	3±3.696	4.62±2.36	0.0001
CDAI	3.974± 0.462	16.622± 10.116	0.0001
DAS-28ESR	2.145± 0.183	4.270±1.166	0.0001
	Medications		
Using conventional DMARDs (Methotrexate)	25 (20.41)	18 (22.59	0.077
Using biological DMARDs (etanercept)	20 (19.46)	21 (21.54)	
Using combination DMARDs	11 (16.14)	23 (17.86)	
ESR (mm\hr)	12.27±5.704	32.34±26.983	0.001

Parameter	Inactive RA disease Groups N=55	Active RA disease Groups N=62	P-value
WBC 10^9\L	7.32±1.84	8.33±2.04	0.006
TRIM-72 (Pg\m)	64.58±54.3	101.92±160.18	0.102

Tripartite Motif-containing Protein 72

As shown in Table 3, the results of this study indicated a significant correlation regarding the mean serum levels of Tripartite motif-containing protein 72 among the study groups.

Table 3. Comparison of Tripartite motif-containing protein 72 between study groups

Parameter	Control Groups N=58	Inactive RA disease Groups N=55	Active RA disease Groups N=62	P-value
TRIM-72 (Pg\mL)	41.06±32.48	64.58±54.34	101.92±160.18	0.005

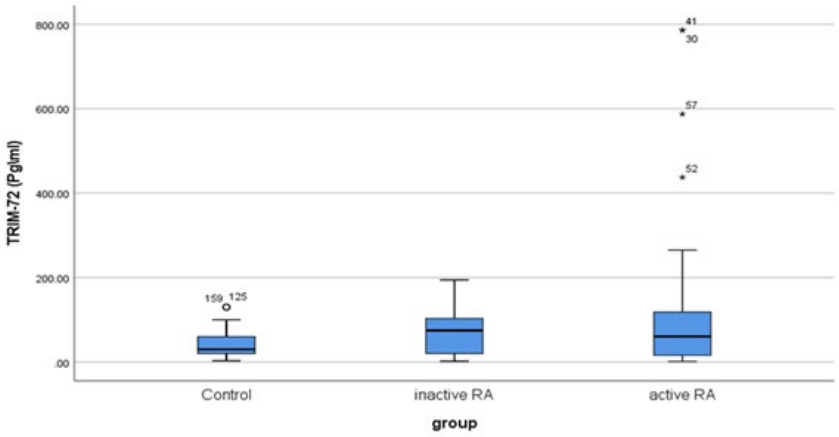

Figure 1. Box plot of Tripartite motif-containing protein 72 of all studied cases.

The Diagnostic Criteria of the Receiver Operator Curve of Tripartite Motif-containing Protein 72 Among Studied Cases

According to Table 4, Tripartite motif-containing protein 72 had a poor discriminative ability between RA and the control group. The validity parameter of Tripartite motif-containing protein 72 of studied cases showed a specificity of 80% and sensitivity of 61.7%. The serum TRIM-72 level at a cutoff value of 22.5 pg/mL is illustrated in Figure 2.

Table 4. ROC curve and validity parameter Tripartite motif-containing protein 72 of studied cases

TRIM-72 (Pg\mL)	
AUC	0.689
95% CI AUC	0.591- 0.787
P-value	0.001
Cut point	22.5
sensitivity	61.7%
specificity	80%
accuracy	70.43%
PPV	76.59%
NPV	66.17%

PPV- positive predictive value
NPV- negative predictive value

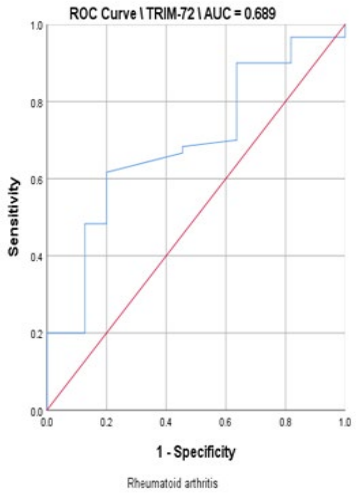

Figure 2. The receiver operator curve (ROC) for Tripartite motif-containing protein 72 of studied cases showing the cut-off, Sensitivity, Specificity, and Area under curve.

Correlation Coefficient Between Clinical and Characteristic Features and Lab parameters with Tripartite Motif-containing Protein 72 of Patients with Rheumatoid Arthritis

Table 5 and Figures 3-5 showed the correlation between characteristic, clinical, and lab features with Tripartite motif-containing protein 72. In RA persons, there was a direct significant correlation between Tripartite motif-containing protein 72 with CDAI, DAS-28 ESR, and BMI.

Table 5. Correlation between characteristic features, clinical features, and Lab with Tripartite motif-containing protein 72 of patients with rheumatoid arthritis

Variables	Tripartite motif-containing protein 72	
	β	P-value
Age (years)	-0.073	0.435
Gender	-0.158	0.126
BMI (kg\m^2)	0.190*	0.040
Disease duration (years)	-0.108	0.247
Number of tender joints	-0.027	0.810
Number of swollen joints	-0.182	0.115
Patient Global assessment	-0.067	0.553
Evaluator global assessment	-0.068	0.547
CDAI	0.202*	0.029
DAS-28 ESR	0.219*	0.018
ESR (mm\hr)	0.006	0.945
WBC 10^9\L	0.047	0.617

β- correlation coefficient
P<0.05 was considered significant.

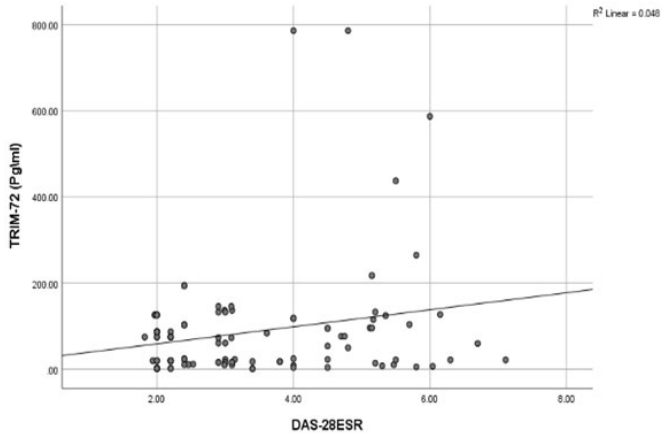

Figure 3. **The histogram of the relationship between Tripartite motif-containing protein 72 with DAS-28 in RA patients**

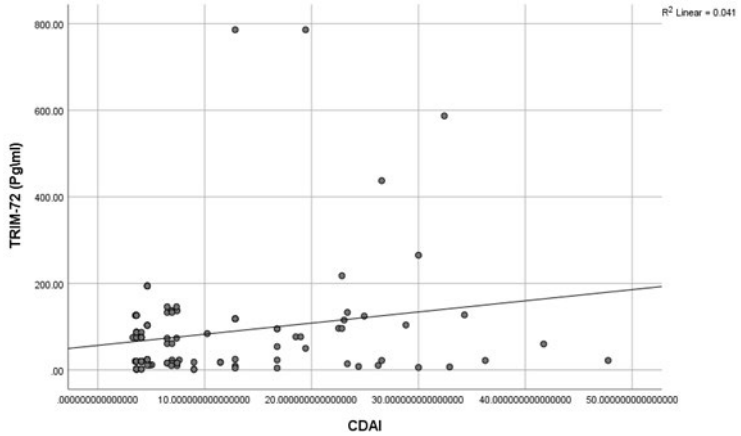

Figure 4. **The histogram of the relationship between Tripartite motif-containing protein 72 with CDAI in RA patients**

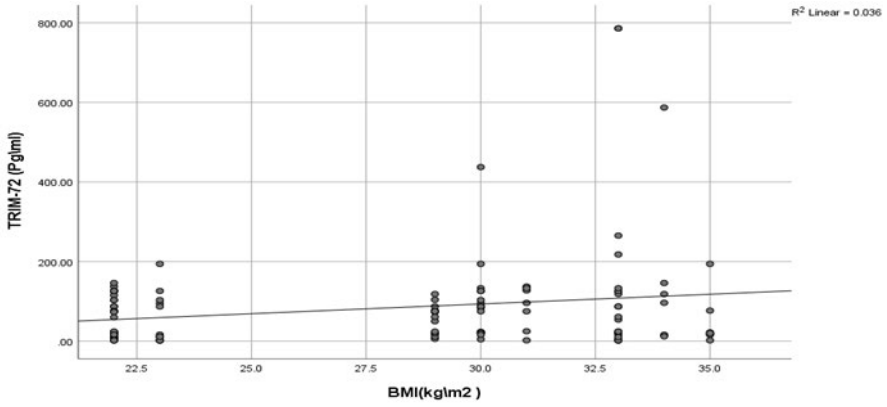

Figure 5. **The histogram of the relationship between Tripartite motif-containing protein 72 with BMI in RA patients**

Discussion

Rheumatoid Arthritis is an autoimmune disease that begins with a misfortune of tolerance to altered self-antigens and immune system abnormalities, inevitably driving to synovitis and cartilage and bone debasement. Abnormalities in such peripheral and vital tolerance components could cause immune cells to respond to self-antigens, causing broad inflammation and tissue damage in immune system diseases **(23)**.

Results obtained in the present study showed non-significant differences in BMI among the three studied groups (Table 1). These results confirmed the results of Xia Feng *et al.* **(24)**, who reported no statistically

significant associations between BMI or BMI categories and RA.

The average ratio of females to males affected with RA in the current study was 2.9:1 in the inactive group and 3.8:1 in the active group. It has long been speculated that there are female-specific factors that enhance the risk for RA, like hormonal changes and the hormonal role in developing RA **(25-26)**. It has been proposed that estrogen, androgen, and prolactin play a role in susceptibility to autoimmune diseases **(27)**.

One of the most important factors that have been distinctly related to increased risk for RA among females is the existence of polycystic ovary syndrome, potentially pre-eclampsia, early menopause, as well as a change in incidence in females towards more elderly patients, indicating that pathogenesis includes hormonal factors **(28-32)**. The sex hormone role is not simple; sex hormones can have significant effects on the cells that are known to be involved in RA. Therefore, complex interactions between hormones may affect disease susceptibility.

The number of smokers showed significant differences among study groups (P=0.008) (Table 1). Several studies have suggested that cigarette smoking is related to an increased risk of developing RA **(33-35)**. Also, several studies have reported that smoking interacts with HLA-DRB1 in increasing the risk of anti-cyclic citrullinated peptide antibody (ACPA) positive but not ACPA negative **(36-38)**.

The exact pathophysiological effects of smoking on RA remain unclear; however, several mechanisms have been suggested. It has been shown that components of cigarette smoke influence synovial inflammation, which has a reversed effect when a smoker stops smoking. Furthermore, in nonsmokers, RA remission rates have been reported to be lower in smokers **(39, 40)**.

The present study demonstrated that Tripartite motif-containing protein 72 was significantly higher in the active RA disease group, compared with the inactive RA group and control group (P<0.005) (Table 1). It could be the 1st study to illustrate the relationship between TRIM72 and RA, but the mechanism remains unclear.

TRIM-72 has been mentioned as a crucial element of the cell membrane repair device **(41)** and also TRIM72 was pre-recognized as a skeletal and cardiac muscle-specific protein **(42)**.

A ROC curve analysis assessed the Tripartite motif consisting of protein 72 (Table 4 and Figure 2). The best cut-off value of TRIM-72 between all cases was 22.5 pg\mL with the optimal combination of sensitivity and specificity for 61.7% and 80%, respectively; the area under the curve was 0.689 in discriminating between RA and controls.

The current research was outlined to estimate the conceivable correlation of TRIM72 with demographic, anthropometric features, clinical features, and biochemical markers in studied cases. Studying Tripartite motif-containing protein 72 in RA patients showed a positive significant correlation with CDAI, DAS-28 ESR, and BMI (Table 5 and Figures 3-5), linking the TRIM-72 with specific disease activity. Many TRIM proteins play a role in rheumatoid arthritis. For example, TRIM32 is associated with inflammation via its regulation of NF-κB signaling in rheumatoid arthritis **(43)**.

Conclusion

The serum Tripartite motif-containing protein 72 level showed a significant elevation in rheumatoid arthritis patients compared with healthy controls. Poor discriminative value of Tripartite motif-containing protein 72 was shown between rheumatoid arthritis patients and the control group. More studies are needed on Tripartite motif-containing protein 72 to be used as a biomarker to detect early RA.

Authors' Contributions:

MQA conceived and designed the study, conducted research, provided research materials, and collected and organized data. ZRA analyzed and interpreted data. FG wrote the initial and final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Ethical approval

The study protocol was approved by the Scientific and Ethical Committee in the College of Medicine, University of Baghdad, and the Rheumatology Medical Department at Baghdad Teaching Hospital (No: 819; Date: 25/10/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflict of Interest

The authors declared no conflict of interest.

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