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Assessment of Plasma Level of CTHRC-I in Patients with Rheumatoid Arthritis

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Abstract

Background Rheumatoid arthritis (RA) is a chronic progressive, autoimmune disease that affects about 1.5% of the community. New markers are needed for early diagnosis of RA as seronegativity in early RA remains a major limitation of both anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF).

Objective To measure the plasma levels of the collagen triple helix, repeat containing-1 (CTHRC-1) protein in RA patients.

Methods 103 RA patients (56 new diagnostic without treatment group and 47 patients on treatment were included in this study according to American College of Rheumatology (ACR) criteria, in addition to 25 subjects as healthy control group. CTHRC-1 level was measured by using Immunoassay System in plasma samples.

Results The mean and SD of CTHRC1 was (49.10±6.51 ng/ml) in RA patients was significantly higher than its mean in healthy controls (6.20±2.81 ng/ml), (p value =0.002). The distribution of CTHRC1 was insignificantly associated with patient treated or not (P value 1.000, 0.273) respectively, or were the patients had positive or negative RF (P value 0.118, 1.000) respectively.

Conclusion Using the Immunoassay System for CTHRC-1 quantification, CTHRC1 could be used as a plasma marker that can aid in the diagnosis of RA although it has no association with seropositivity with RF or treatment.

Keywords Collagen triple helix repeat containing-1, rheumatoid arthritis, serum rheumatoid factor, anti-CCP

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List of abbreviations: Anti-CCP = Anti cyclic citrullinated peptide, CRP = C-reactive protein, CTHRC1 = Collagen triple helix repeat containing 1 protein, ESR = Erythrocyte sedimentation rate, RA = Rheumatoid arthritis, RF = Rheumatoid factor

Introduction

The collagen triple helix repeat containing 1 protein (CTHRC1) is a veiled modulator of signaling, which is a key controller of joint remodeling, it promotes cell proliferation and immigration [(1)]. CTHRC1 that showed expression in murine investigational arthritis is increased in the synovium. These monoclonal antibodies have very little cross-reactivity with the skeletal isoforms [(2)]. CTHRC1 very sensitive and specific indicator of myocardial damage [(3)]; their assays have been beset by some analytical problems [(4)]. Others suggest that this CTHRC1 is not affected by rheumatoid factor (RF) [(1)].

This study aimed to evaluate the benefit of plasma CTHRC1 as a marker that help in diagnosis of rheumatoid arthritis disease (RA) disease and could be a marker for difference between seropositive and seronegative RA, and their correlation with other markers.

Methods

Data were collected during the period from March 2020 to September 2020. This study included (103) RA patients of less than 1 year duration that were classified to new diagnostic without treatment group (56 patients) and early treated group (47 patients), in addition to (25 healthy control group). Their ages were > 18 years. All recruited patients were seen in Rheumatology Outpatients Clinic in Teaching Baghdad Hospital in Baghdad. The diagnosis of RA was according to the American College of Rheumatology criteria for RA [(5)]. Venous blood specimens (5 ml) were collected from each subject; 3 ml of each sample for serum. Serum CTHRC1 was detected by using the Immunoassay System (VEDALAB Inc, 28091 cat. number, France). The RF IgG concentrations in both healthy controls and patients were measured on the Immunoassay System (Chorus Inc, 86038 cat. number, Italy), (Chorus Anti-CCP device, 86094 cat. number, Italy) of Anti-CCP kit and (AGAPPE, 52009002 cat. number, Switzerland) of CRP kit.

Statistical analysis

Statistical analysis was performed using the SPSS 10 statistical pack up. Mean and standard deviation (SD) were used to express variables. Unpaired t-test was used to compare the difference in mean between two continuous variables, differences were considered statistically significant at $P<0.05$. For comparing more than two groups, the one-way ANOVA method was used to determine if there is statistical significance across the groups or not. Receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic utility of marker as estimated by the area under the curve (AUC). [(6)].

Results

Demographical and serological data of study groups

Table (1) shows demographical characteristics of patients and controls. There was no significant difference in mean age between patients and controls (42.22±11.23, 36.4±11.15 years) respectively; p value =0.126). While there was significant difference in the sex distribution, although majority of patients and controls were females but males were more in patients than in control (p value =0.030). In patients, 29.1% have positive family history of RA which significant different from controls were none of them have (p value =0.040).

Table 1. Demographical and serological data of study groups

Parameters		Patients (No. = 103)	Control (No. = 25)	P value
Age (Yrs)	Mean±SD	42.22± 11.23	36.40±11.15	0.126
Sex No. (%)	Female	77 (74.8)	22 (88.0)	0.030
	Male	26 (25.2)	3 (12.0)	
Disease Duration (Months) No. (%)	(1-6)	46 (44.7)	---	0.003
	(7-12)	57 (55.3)		
Family History No.	No	73 (70.9)	25 (100)	0.04
	Yes	30 (29.1)	0 (0.0)	
	Negative	36 (35.0)	25 (100)	

Serological data were illustrated in table 2 were the difference between patients and controls were highly significant as majority of RA patients had elevated ESR (79.62%), positive CRP (86.4%), positive Anti-CCP (91.3%), and (65.0%) of them had positive RF while only 8% of controls has elevated ESR, and none of them had positive CRP, Anti-CCP or RF (p value 0.001, <0.001, 0.001 and 0.001) respectively.

Table 2. Serological data of study groups

Parameters		Patients (No. = 103)	Control (No. = 25)	P value
ESR	Elevated	82 (79.62)	2 (8.0)	0.001
No. (%)	Normal	21 (20.40)	23 (92.0)	
CRP	Positive	89 (86.4)	0 (0.0)	<0.001
No. (%)	Negative	14 (13.6)	25 (100)	
Anti-CCP	Positive	94 (91.3)	0 (0.0)	0.001
No. (%)	Negative	09 (08.7)	25 (100)	
RF	Positive	67 (65.0)	0 (0.0)	0.001
No. (%)	Negative	36 (35.0)	25 (100)	

ESR: Normal value for female =0-20 mm/h, Normal value for male = 0-9 mm/h, CRP: Positive value (more than 6 mg/l) in serum

The mean and SD of CTHRC1 was (49.10±6.51 ng/ml) in RA patients and (6.20±2.81 ng/ml) in healthy control group, the difference was significant (p value =0.002) (Table 3).

Table 3. Comparison of Collagen triple helix repeat containing 1 protein (CTHRC1) between patients and controls

Parameter		Patients (No. = 103)	Control (No. = 25)	P value
CTHRC1 (ng/ml)	Mean±SD	49.10±6.51	6.20±2.81	0.002

Distribution of CTHRC1 marker according treatment and seropositivity of RF

Table (4) shows association of "CTHRC1" marker with treatment of patients and their seropositivity for RF patients. It showed that there is no significant association of CTHRC1 distribution whether the patients were treated or not (P value 1.000, 0.273) respectively, or were the patients had positive or negative RF (P value 0.118, 1.000) respectively.

Table 4. CTHRC1 marker distribution according to RF Patients (treated and Untreated (positive and negative) with comparisons significant

RF Groups	CTHRC1	No. & %	Treatment		Total	P value
			Untreated Patients	Treated Patients		
RF ±ve	Positive	No.	2 (33.3)	8 (80.0)	10 (62.5)	0.118 NS
	Negative	No.	4 (66.7)	2 (20.0)	6 (37.5)	
	Total	No.	6 (100)	10 (100)	16 (100)	
RF-ve	Positive	No.	3 (50.0)	0 (0.0)	3 (42.9)	1.000 NS
	Negative	No.	3 (50.0)	1 (100)	4 (57.1)	
	Total	No.	6 (100)	1 (100)	7 (100)	
P value			1.000 NS	0.273 NS		

NS: Non-significant at P>0.05

Discussion

There is an unmet need for specific and easy-to-measure biomarkers to diagnose RA patients and distinguish patients with high disease activity who are at increased hazard of developing erosive, joint destructive disease.

The present study revealed that prevalence of RA was more in female patients than male patients similar to result in 2014 showed (75.25% vs 24.75%, respectively) [(7)]. Few studies have shown opposite result more frequent in men than in women (72% versus 55%, respectively) [(8)].

In present study, the percentage of patients had 7-12 months of disease duration more than the 1-6 months of patients' groups, while study reported the patients fulfilling the American College of Rheumatology (ACR) criteria at presentation, 53% with disease duration of ≤3 months, compared with 94% of patients who presented with disease duration of >12 weeks, therefore, the strongest predictor of persistent disease was a disease duration of >3 months [(9)]. Although family history of RA is an old concept [(10)], present data appeared patients had family history less than those with no family history of RA. Somers and his colleagues reported a high rate of RA in female offspring with a maternal history of RA [(11)].

Early diagnosis of RA is important for preventing joint damage via treatment. For patients having typical symptoms, the disease could be easily diagnosed, often in the first year of disease onset. For many patients with atypical symptoms, it could take more time to diagnose. Consequently, specific and sensitive serological tests are required for diagnosis. Furthermore, ESR and CRP with high positive results, although they are nonspecific for the diagnosis of RA, but they are important assisting markers for the diagnosis of RA. Simultaneous finding of RF, Anti-CCP, CRP and ESR is helpful for the confirmed diagnosis of RA [(12)]. Patients that had positive RF and Anti-CCP more than with negative test results, recently the new criteria for diagnosis of RA have been introduced in addition to Anti-CCP, together with RF [(13)]. Thus, these parameters could be used as specific serologic markers for RA. It is showed that Anti-CCP have the power to predict the development of RA in patients with early arthritis, and the possibility of future onset of RA in certain high-risk populations [(14)].

The most important finding of this study was that concentrations of high sensitivity, CTHRC1 were higher in patients with RA compared to controls. The difference remained statistically significant after adjustment for demographic characteristics (P=0.002). Other results reported that patients with seropositive RA do not have falsely elevated CTHRC1 levels [(1)].

Current study found that neither seropositivity for RF nor treatment of patients have significant effect on CTHRC1. This finding agree with a study that reported no significant

association between CTHRC1 level and inflammatory markers, acute phase reactants. This suggests that active inflammation may not be the primary driver of CTHRC1 elevation in RA [15].

In conclusion, CTHRC1 may be plasma marker that can aid in the diagnosis of RA.

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Author contribution

Dr. Alwan: collection of data, interpretation and writing of manuscript. Abdul-Ridha and Ali: final revision of the manuscript.

Conflict of interest

Authors declare no conflict of interest.

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