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Collagen triple-helix repeat containing 1 (CTHRC1) protein in rheumatoid arthritis patients: Relation to disease clinical, radiographic and ultrasound scores

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ABSTRACT

Aim of the work: to study the relationship between collagen triple helix repeat containing 1 (CTHRC1) protein serum levels and disease activity, patients' well-being, as well as ultrasonographic and radiological scores in patients with rheumatoid arthritis (RA).

Patients and methods: The work included 70 RA patients and 70 age and gender matched controls. The disease activity score (DAS28) and health assessment questionnaire (HAQ) were assessed. Modified Larsen's score was used to score the hands and feet digital radiographs and musculoskeletal ultrasound (MSUS) examination using ultrasound-7 score was carried out. Serum CTHRC1 levels were measured by ELISA.

Results: Patients were 62 females and 8 males (F: M 7.8:1), their mean age was 42.2 ± 17.7 years and median disease duration 15 years. The median CTHRC1 serum levels were significantly higher in patients (453 ng/dl; 158–688 ng/dl) than control (99 ng/dl; 67–179 ng/dl) ($p < 0.001$). CTHRC1 was significantly increased in those with high activity ($p < 0.001$).CTHRC1 levels significantly correlated with DAS28 ($r = 0.87, p < 0.001$), CRP ($r = 0.43, p < 0.001$) and total ultrasound-7 score ($r = 0.27, p = 0.03$). Only total US7 score ($p = 0.003$) and CTHRC1 ($p < 0.001$) were significant predictors of activity. Serum CTHRC1 could significantly differentiate between patients and controls at cut off 179 ng/ml; sensitivity 95.7 % and specificity 100 % ($p < 0.001$) and between patients active and in remission at cut off 324 ng/ml; sensitivity 92.2 % and specificity 94.7 % ($p < 0.001$).

Conclusions: Patients with RA have significantly elevated serum levels of CTHRC1. In the process of structural bone ultrasonographic abnormalities as well as disease activity in RA patients, elevated CTHRC1 levels play a key role.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder involving mainly the synovial joints.Repeated disease activity flares can eventually lead to irreversible damage to joints and bones, ultimately leading to disability [1]. Early diagnosis and management of RA targeted at reducing disease activity is crucial for preventing or delaying the onset of erosive disease. This "treat-to-target" strategy depends on early patient identification and regular monitoring of disease activity to guide and optimize treatment in order to attain remission or low disease activity [2]. Early RA diagnosis and clinical evaluation of disease activity are still challenging tasks [3]. There is mounting proof that there are several molecularly distinct RA subtypes, each with its own unique disease processes, and that RA diversity reflects genetic and biological variances [3,4].

Despite the growing recognition of disease heterogeneity, clinical practice lacks biomarkers for stratifying RA patients. Rheumatoid factor (RF) and anti citrullinated protein antibodies (ACPA) are

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keysin the diagnosis of RA [5]. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), joint tenderness and swelling are additional classification criteria [6]. Biomarkers that can distinguish patients from healthy participants early in the disease process and that may reliably assess disease status are few [5]. Optimizing the rheumatology clinical practice in Egypt to develop tailored and targeted therapies is warranted [7]. Many biomarkers have been studied in Egyptian RA patients and were found to be promising in the assessment of disease activity [8–10], or associated metabolic disorders [11] and making them potential therapeutic targets.

Musculoskeletal ultrasound (MSUS) allows for the clear visualization of the morphological, structural, and perfusional changes brought on by RA synovitis at the level of the joint and tendons [12]. The utility of US in diagnosing and predicting joint and tendon problems varies depending on the clinical situation. It may confirm or forecast the definitive diagnosis in the very early stages of the disease or detect subclinical synovitis in established conditions [13].

The collagen triple helix repeat containing 1 protein (CTHRC1) is highly expressed in growing cartilage, bone, and other tissues in embryos and neonates [14]. Increased levels of the CTHRC1 have recently been linked to the severity of adjuvant-induced arthritis [15]. The question of whether CTHRC1 could be used as a marker for RA diagnosis and monitoring of disease activity in patients was previously raised by its expression in pannus, its relation to cartilage damage association with disease severity [6]. A strong link between serum CTRHC1 levels and the severity of RA has been reported [16].To the best of the authors' knowledge, no previous studies evaluated the relationship of CTHRC1 level with RA ultrasound features.

The purpose of this study is to ascertain whether CTHRC1 can be utilized to diagnose RA and track patient disease activity. The aim of this work has been extended to further assess the relationship between its level and ultrasonography and radiographic characteristics of RA.

2. Patients and methods

In this study, 70 RA patients meeting the American College of Rheumatology/European league against rheumatism (ACR/EULAR) classification criteria [2] were recruited from the Rheumatology outpatient clinic of Benha University Hospital's, Qalubiya, Egypt. 70 healthy age and sex matched individuals were considered as control. Patients <18 years, with other chronic inflammatory disorders, diabetes mellitus, chronic renal and liver diseases or those who were pregnant or lactating were excluded. All subjects provided written informed consent according to the Helsinki declaration and the study was approved by the ethical board of the Faculty of Medicine, Benha University (no. RC2-7-2020).

Every patient had a comprehensive clinical assessment and detailed history recording. ESR, CRP, RF and ACPA were assessed. The disease activity score (DAS28) was calculated and categorized into remission (score $\leq$ 2.6), low ($\geq$2.6-$\leq$3.2), moderate (>3.2-$\leq$ 5.1) and high (>5.1) activity [17]. Functional impairment was assessed using the Stanford health assessment questionnaire (HAQ) [18]. Hands and feet plain radiographs (posterior view) were taken, and the modified Larsen score (0–160) was used to assess joint damage [19].

*Musculoskeletal ultrasound assessment (MSUS):*It was performed using Logiq P9 US equipment (12–15 MHz) with linear array transducer by both grey scale (GSUS) and power Doppler (PDUS) (7.7 MHz) on palmar and dorsal sides.The German US7 score [20] evaluates the wrist, 2nd, 3rd and 5th metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints both hands. MSUS evaluation included synovitis, tenosynovitis, and erosions [21]. GSUS [22] and PDUS [23] were used to measure synovitis (effusion and/or synovial hypertrophy) semi-quantitatively (0–3). Tenosynovitis was assessed using a yes/no scale in both the GSUS and PDUS [8] and erosion in the GSUS [20].

Serum levels of CTHRC1 are measured using Enzyme-linked Immunosorbent Assay (ELISA) human Kit for Collagen Triple Helix Repeat Containing Protein1 (CTHRC1) (SEN690Hu, Cloud-Clone, USA) according to manufacturer instructions. Detection range: 1.56–100 ng/mL.

Statistical analysis: Statistical Package for Social Science (SPSS) (version 25.0) was used. As a test of normality, the Kolmogorov-Smirnov test was considered. For comparison of variables, the Student T, Mann-Whitney and Kruskal-Wallis tests were used. Correlation analysis was used to assess how strongly-two quantitative variables were related. The receiver operating characteristic (ROC) curve was developed to assess the diagnostic potential of CTHRC1.Regression analysis was used to predict risk factors. P-values were two-tailed and significance was set at $p < 0.05$.

3. Results

The study included 70 patients; 62 (88.6 %) females and 8 (11.4 %) males (F: M 7.8:1). Their mean age was 42.2 ± 17.7 years and median disease duration was 15 years. The 70 controlswere matched for gender: 61 females and 9 males (F: M 6.8:1) ($p = 0.8$) and age (42.5 ± 8.7 years) ($p = 0.85$). The body mass index (BMI) was comparable between patients and control (27.2 ± 5 *vs* 27.6 ± 5.4; $p = 0.63$).Table 1 shows patients' clinical, laboratory, radiographic and musculoskeletal ultrasonographic features as

Table 1
Rheumatoid arthritis patients clinical, laboratory, radiographic and musculoskeletal ultrasonographic features and medications received.

Item mean ± SD, median (range) or n(%)	RA patients (n = 70)
Age (years)	42.2 ± 17.7
Gender F:M	62:8
Disease duration (years)	15 (2–20)
VAS	5 (1–9)
TJC	6 (2–24)
SJC	4 (0–21)
DAS28	3 (1.1–5.6)
Modified Larsen score	23 (2–96)
HAQ	1 (0.1–2.7)
Hemoglobin (g\dL)	10.8 (8.5–13.1)
ESR (mm/h)	55 (25–100)
CRP(mg/ml)	27 (5–86)
RF positivity	57 (81.4)
RF titre (IU/ml)	64 (32–120)
ACPA positivity	65 (92.9)
ACPA titre (IU)	42 (0.5–100)
CTHRC1 (ng/dl)	453 (158–688)
MSUS	
Synovitis GS	13 (2–27)
Synovitis PD	19 (0–36)
Tenosynovitis GS	3 (0–7)
Tenosynovitis PD	7 (1–18)
Erosions	4 (0–14)
Total US7score	49 (7–88)
Medications	
Steroids	18 (25.7)
Methotrexate	53 (75.7)
Hydroxychloroquine	64 (1.4)
Leflunomide	13 (18.6)
Etanrecept	10 (14.3)
Adalimumab	5 (7.1)

RA: rheumatoid arthritis, DAS28: disease activity score, TJC: tender joint count, SJC: swelling joint count, HAQ: health assessment questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, ACPA: anti citrullinated protein antibodies, CTHRC1: collagen triple helix repeat containing 1 protein, MSUS: musculoskeletal ultrasounds, GS: gray scale, PD: power Doppler.

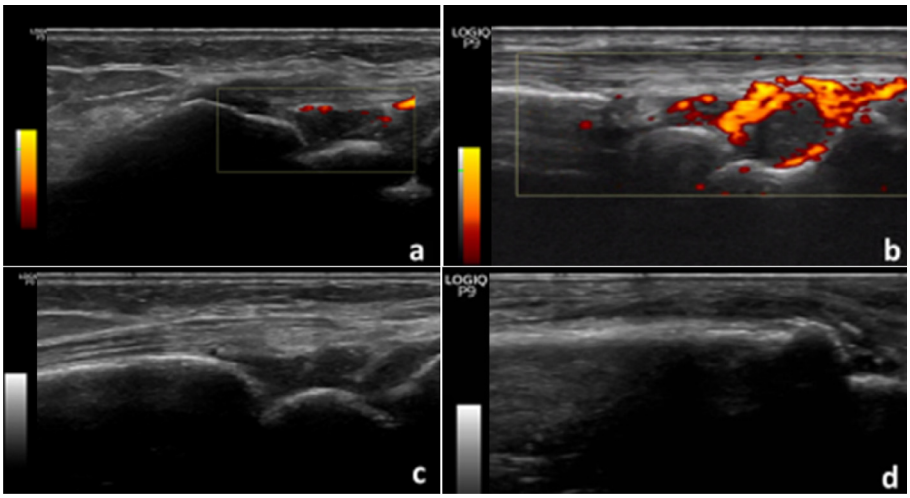

Fig. 1. (a and b) Power Doppler ultrasonography showing variable grades of increasedvascularity within the hypertrophied synovium at the wrist joint denoting synovitis in a rheumatoid arthritis patient. (c):Dorsal longitudinal grey scan of wrist joint showing joint cavity enlargement due to hypoechoic synovial fluid as well as hyperechoic synovial thickening. (d): Dorsal longitudinal scan of 2nd metacarpophalangeal (MCP) joint showing synovial hypertrophy along with effusion.

Table 2
Correlation of collagen triple-helix repeat containing 1 protein (CTHRC1) with parameters in rheumatoid arthritis (RA) patients.

Parameterr (p)	CTHRC1 in RA patients (n = 70)	
TJC	0.02	(0.88)
SJC	0.46	**(<0.001)**
DAS28	0.87	**(<0.001)**
HAQ	0.03	(0.81)
Modified Larsen score	0.06	(0.64)
CRP	0.43	**(<0.001)**
MSUS		
Synovitis GS	0.54	**(<0.001)**
Synovitis PD	0.06	(0.61)
Tenosynovitis GS	0.25	**(0.04)**
Tenosynovitis PD	0.3	**(0.01)**
Erosions	−0.03	(0.78)
TotalUS7score	0.27	**(0.03)**

CTHRC1: collagen triple helix repeat containing 1 protein, RA: rheumatoid arthritis, TJC: tender joint count, SJC: swollen joint count, DAS28: disease activity score, HAQ: health assessment questionnaire, CRP: C-reactive protein, MSUS: musculoskeletal ultrasounds, GS: gray scale, PD: power Doppler. Bold values are significant at $p < 0.05$.

well as received medications. GS and PD findings are presented in Fig. 1. The median CTHRC1 serum levels were significantly higher in patients (453 ng/dl; 158–688 ng/dl) than in control (99 ng/dl; 67–179 ng/dl) ($p < 0.001$). CTHRC1was significantly lower in patients in remission (198; 158–456 ng/dl, n = 18) compared to those with low (405; 198–576 ng/ml, n = 19), moderate (501; 343–678 ng/ml, n = 26) and high (668; 640–688 ng/ml, n = 7) activity ($p < 0.001$).

Serum CTHRC1 significantly correlated with DAS28, CRP, SJC, synovitis GS, tenosynovitis GS and PD as well as total US7score (Table 2). Ordinal regression analysis was conducted for the possible predictive factors of activity in RA patients, using age, gender, BMI, duration, CRP, ESR, RF, CCP, total US7 score, and CTHRC1 as confounders. On univariate analysis, higher CRP, US7 score and CTHRC1 were associated with a risk of higher DAS28. Only a higher total US7 score and CTHRC1 were significant predictors of activityon multivariate analysis (Table 3).

Serum CTHRC1 could significantly differentiate between patients and controls at a cut off value of 179 ng/ml; area under the curve (AUC) 0.998, 95 %CI 0.994–1, sensitivity 95.7 % and specificity 100 % ($p < 0.001$) and between patients active and in remission at a cut off value of 324 ng/ml; area under the curve (AUC) 0.952, 95 %CI 0.902–1, sensitivity 92.2 % and specificity 94.7 % ($p < 0.001$) (Fig. 2).

4. Discussion

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that affects 1 % of individuals globally, according to the

Table 3
Regression analysis for the possible predictive factors of disease activity in rheumatoid arthritis patients.

Parameter	Disease activity in RA patients (n = 70)							
	Univariable				Multivariable			
	p	OR	(95 %CI)		p	OR	(95 %CI)	
Age	0.87	0.99	(0.96-	1.03)				
Gender	0.58	1.31	(0.51-	3.35)				
BMI	0.25	1.03	(0.98-	1.09)				
Disease duration	0.45	0.98	(0.94-	1.03)				
ESR	0.16	0.99	(0.97-	1.004)				
CRP	**0.001**	1.03	(1.01-	1.04)	0.12	1.02	(0.99-	1.04)
RF	0.44	1.004	(0.99-	1.02)				
ACPA	0.26	1.004	(0.99-	1.01)				
Total US7 score	**0.001**	1.03	(1.01-	1.04)	**0.003**	1.03	(1.01-	1.05)
CTHRC1	**<0.001**	1.01	(1.01-	1.01)	**<0.001**	1.01	(1.006-	1.013)

RA: rheumatoid arthritis, BMI: Body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, ACPA: anti citrullinated protein antibodies, CTHRC1: collagen triple helix repeat containing 1 protein. Bold values are significant at $p < 0.05$.

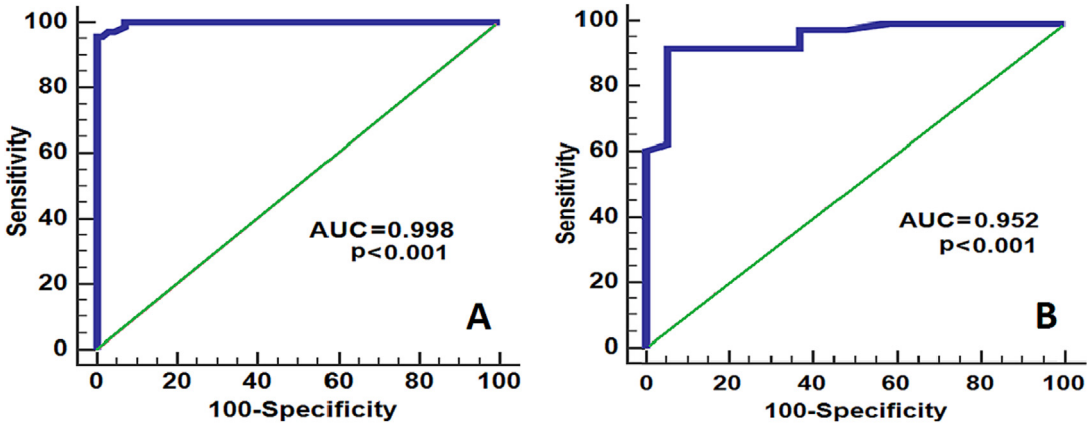

Fig. 2. Validity of collagen triple-helix repeat containing 1 protein (CTHRC1) level for discrimination between (A) rheumatoid arthritis (RA) patients and controls at cut of 179 ng/ml (B) active (n = 52) cases and those in remission (n = 18) at cut of 324 ng/ml.

World Health Organization [22]. There is a deficiency in the availability of precise and simple-to-measure biomarkers for the diagnosis of RA and for the detection of patients with high disease activity who are more likely to develop erosive, joint-destructive disease [23]. CTHRC1 is a secreted glycoprotein reported to regulate collagen deposition and to be linked to the Transforming growth factor β/Bone morphogenetic protein and the Wnt/planar cell polarity pathways. It was found to be highly expressed in multiple human cancer types [24].The information at hand points to CTHRC1 as a potential novel RA diagnostic and prognostic biomarker. The precise significance of CTHRC1 in the pathogenesis of RA, including its role in the synovium and the emergence of bone erosion, will require further research [25]. However, promising novel therapeutic agents for osteoporosis promote osteogenesis and inhibit osteoclastogenesis by transferring CTHRC1 and osteoprotegrin [26].

In this study, patients' mean serum CTHRC1 levels were noticeably greater than those of controls. This is in line with a number of previous studies [15,16,27,28].With a cutoff value of >179 ng/ml and sensitivity of 95.7 %, specificity of 100 %, and excellent accuracy AUC, the diagnostic performance of CTHRC1 for differentiating between RA patients and controls can considerably predict disease. The present study beat *Myngbay et al.* [27] and *Hu and associates* [28], whose findings suggested that CTRHC1 was capable of differentiating between RA and controls with sensitivity of 62 %, 84.5 %, and specificity of 86 %, 75.6 %, respectively. However, *Selim et al.* showed comparableresults, with a sensitivity and specificity of 98.3 % and 100 %, respectively [16]. CTHRC1 may therefore be useful as a simple serum biomarker to assist in RA diagnosis [29].

In terms of disease activity, current results revealed a highly significant relation between CTHRC1 serum levels and each of DAS38, SJC and CRP. This goes in line with the study of *Myngbay et al.* [15], whoreported that CTHRC1 levels significantly correlated with DAS38, SJC and CRP but not with TJC. Similarly, *Selim et al.* [16] detected a correlation between CTHRC1serum levels and disease activity; DAS28 and CRP levels. CTHRC1 could significantly distinguish between active and remitted cases at a cut off value of 324 ng/ml with sensitivity 92.2 % and specificity 94.7 % suggesting the potential benefit of using serum CTHRC1 levels to monitor RA disease activity.

Regarding radiographic severity, a non-significant relationship between serum CTHRC1 levels and the modified Larsen's score was found.We are aware of no past studies that have looked at this relation.CTHRC1 is a secreted Wnt signaling modulator, which is a key regulator of joint remodeling [30] and enhances cell proliferation and migration [21]. As a potential marker for RA diagnosis and activity monitoring, CTHRC1 expression pattern in pannus, its main role in fibroblast-like synoviocytes cartilage degradation and its link with disease severity have been emphasized [15].

In terms of MSUS evaluation, the current study found a significant relation between serum CTHRC1 levels and US7 score components including synovitis GS, tenosynovitis GS/PD and total US7 score. This is consistent with disease activity and the ability of CTHRC1 levels to detect early structural changes on MSUS examination that traditional radiographs cannot detect. To the best of our knowledge, no prior research has examined such relationship.

More research on this topic with a larger sample size is needed to elucidate the role of CTRHC1 in the progression of cartilage and bone erosions in the joints of RA patients.Further larger scale longitudinal studies are recommended.

In conclusion, CTHRC1 serum levels have the potential to be used as a diagnostic biomarker for RA. CTHRC1 is linked to disease activity as well as structural musculoskeletal ultrasonographic joint changes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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