2023, 20(3 Suppl.): 928-936
https://dx.doi.org/10.21123/bsj.2023.8036
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
Baghdad Science Journal

Estimation levels of CTHRC1and some cytokines in Iraqi patients with Rheumatoid Arthritis

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Received 01/11/2022, Revised 24/12/2022, Accepted 26/12/2022, Published 20/06/2023

Abstract

Collagen triple helix repeat containing-1 (CTHRC1) is an essential marker for Rheumatoid Arthritis (RA), but its relationship with pro-inflammatory, anti-inflammatory, and inflammatory markers has been scantily covered in extant literature. To evaluate the level of CTHRC1 protein in the sera of 100 RA patients and 25 control and compare levels of tumour necrosis factor alpha (TNF-α), interleukin 10 (IL-10), RA disease activity (DAS28), and inflammatory factors. Higher significant serum levels of CTHRC1 (29.367 ng/ml), TNF-α (63.488 pg/ml), and IL-10 (67.1 pg/ml) were found in patient sera as compared to that in control sera (CTHRC1 = 15.732 ng/ml, TNF-α = 33.788 pg/ml, and IL-10 = 25.122 pg/ml). There was no significant correlation between the level of serum CTHRC1 and DAS28 (r = 0.046, P = 0.650), while there were positive significant correlations between the levels of serum CTHRC1 and CRP (r = 0.372, P = 0.0001), ACPA (r = 0.254, P = 0.01), TNF-α (r = 0.202, P = 0.044), and IL-10 (r = 0.260, P = 0.0001). The level of CTHRC1 (> 25.385 ng/ml) in combination with the levels of CRP and ACPA provided a good indication of RA prediction with sensitivity = 71.0%, specificity = 100.0%, accuracy = 0.71%, positive predictive value (PPV) = 100.0%, and negative predictive value (NPV) = 46.3%. The study showed a significant correlation between the levels of CTHRC1 and TNF-α, and IL-10. These molecules may play a prominent role in the diagnostic and etiology of RA.

Keywords: ACPA, CTHRC1, IL-10, Rheumatoid Arthritis, TNF-α.

Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease, a chronic inflammatory disease characterized by painful joints and synovitis, and it affects about 1% of the population [1]. It is accompanied by multi-organ diseases in addition to stiffness, pain, and swelling of many joints. Joint destruction develops quickly after onset, leading to irreversible physical dysfunction and deformation of the influenced joints. A precise diagnosis and therapy are needed in the initial stages of the disease [2]. Despite the attempts to find biomarkers for RA diagnosis [3–5], there is still a deficiency of diagnostic and prognostic biomarkers for improved patient classification.

The two most remarkable auto-antibodies in RA are rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), which provide various clinical and pathophysiological data [6]. However, ACPA and RF are not present in 20–30 % of RA patients, and erosive RA may occur without these two markers [7].

Collagen triple helix repeat containing-1 (CTHRC1) is a newly found biomarker that may help with more accurate RA diagnosis and disease activity

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evaluation [8–11]. CTHRC1 levels are higher in patients with RA compared to that in control or people with other types of arthritis, such as osteoarthritis (OA) or reactive arthritis (ReA), or are detected at extremely low levels in the latter group [10,12]. These data show that CTHRC1 may improve RA differential diagnosis when combined with a wide panel of markers [10,12]. Moreover, accumulating data suggest that CTHRC1 is directly implicated in disease progression. As a result, CTHRC1 is expressed in subsets of activated fibroblast-like synoviocytes (FLS) linked to RA pathogenesis [13]. Furthermore, via regulating osteoclast–osteoblast interaction, CTHRC1 acts as a crucial modulator of bone resorption and formation [14–16], supporting the idea that CTHRC1 levels may represent a more direct pathological or protective role in cartilage and bone erosion in RA by promoting Wnt/PCP signaling in the synovium, thus potentially modulating inflammatory cell migration and cell differentiation, as well as bone remodeling [16,17]. Also, CTHRC1 might act as part of either Wnt or TGF-β signalling pathways. Canonical and noncanonical branches of the Wnt signalling pathway are considered to play major roles in RA pathogenesis, in part, by modulating the activation of FLS and by promoting the production of pro-inflammatory cytokines and chemokines [16].

One means of such communication occurs via cytokines. Cytokines are molecules that are released by some cells macrophages, B lymphocytes, T lymphocytes and mast cells and affect the same or other cells via their specific receptors [18]. These molecules may have pro-inflammatory or anti-inflammatory roles. In RA, the equilibrium is shifted towards pro-inflammatory cytokines. Tumour necrosis factor alpha (TNF-α) plays a key role in organizing the cytokines cascade in several inflammatory diseases. As it functions as a "master regulator" of inflammatory cytokine production, TNF-α has been recommended as a therapeutic agent for many diseases [19]. According to past studies, interleukin 10 (IL-10), an anti-inflammatory cytokine in RA, plays a protective function in the pathogenesis of RA [20]. In this study, we estimated the validity and diagnostic role of CTHRC1 in patients with RA and associated with disease activity and cytokines levels.

Materials and Methods

The study sample involved 100 RA patients (16 males, 84 females) and 25 control groups. Age ranged from 20 to 65 years, and the average age of RA patients was 46.4 ± 12.03 years, while the average age of the control group was 41.06 ± 7.8 years. The disease duration was 1–15 years, and the subjects were successively recruited between November 2021 and March 2022 during routine visits to the rheumatology outpatient clinic of Baghdad Teaching Hospital. The 2010 ACR/EULAR criteria [21] were used in diagnosing the patients. All patients underwent a baseline of disease activity score (DAS28) to assess RA activity, the score ranged from 1 to 10 and included 28 swollen and tending joint counts, the ESR, and a visual analogue scale [21]. It measured ESR, RF, C-reactive protein (CRP), and ACPA in all patients. Based on DAS28, subjects were divided into four groups: remission < 2.6, low 2.6–3.2, moderate 3.2–5.1, and severe > 5.1.

All subjects had venous blood samples are taken, which were then allowed to clot for 15 min before being separated using centrifugation 4000 rpm/5 min. The levels of CTHRC1, IL-10, TNF-α (MyBioSource, USA), serum CRP, and ACPA (Demeditec Diagnostic GmbH, Germany) were measured via an ELSA plate reader (HumaReader HS, Human GMBh, Germany). The RF marker was estimated by using a Latex assay (SPINREACT, Spain). The ESR was evaluated using the hematology siemens system.

Statistical analysis

The statistical analysis was carried out using SPSS version 25 and MedCalc version 19.7.4 and graphic illustration using GraphPad Prism version 8. The data were obtained as the mean ± standard deviation (SD), median (interquartile range [IQR]), and frequency (percentage) for normally, not normally distributed numerical and categorical variables, respectively. Non-parametric, parametric, and chi-squared tests were used to find the significant difference between the not-normally, normally distributed numerical, and categorical variables, respectively. The level of significance was indicated

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with P < 0.05. The Spearman's rank correlation was performed to assess the significance of correlation for the relationship between the two quantitative variables. A receiver operating characteristic (ROC) curve was used to assess the validity of CTHRC1 as a diagnostic biomarker and to determine the optimum cut-off value for the serum CTHRC1 levels.

Results

Clinical and laboratory manifestations

The general manifestations of RA patients and the control group are shown in Table 1. The mean BMI in patients with RA was 29.2 ± 4.14 kg/m^2 and in the control group was 29.96 ± 3.7 kg/m^2. The mean disease duration of patients was 6.63 ± 3.6 years 1–15 years. The study showed no significant difference between patients and the control group in terms of age, and body mass index (BMI) P > 0.05, while significant differences were seen in terms of smoking state, ESR, RF, CRP, and ACPA P < 0.05.

Table 1. Characteristic features of patients with RA and control.

Parameters	RA patients (n = 100)	Control (n = 25)	P-value
Age (years)	45.55 ± 10.644	42.8 ± 7.141	0.229
Gender (no. [%])	-	-	
Male	16 (16)	6 (24)	0.382
Female	84 (84)	19 (76)	
BMI (Kg/m^2)	29.2 ± 4.14	29.96 ± 3.7	0.163
Smoking state (no. [%])	-	-	0.0001*
Smoker	12 (12)	10 (40.0)	
Non-smoker	88 (88)	15 (60.0)	
Disease duration (years)	6.63 ± 3.6	----	-
DAS28	4.26 ± 1.13	----	-
Therapy (no [%])	19 (19.0)	----	-
MTX			
ETC	30 (30.0)	----	-
MTXETC	51 (51.0)	----	-
ESR (mm/h)	29 (19–49)	9.00 (5.0–20.0)	0.0001*
RF (no [%])			
Positive	92 (92.0)	-	0.0001*
Negative	8 (8.0)	25 (100)	
CRP (µg/ml)	4.949 (4.359–15.021)	3.203 (2.971–3.435)	0.0001*
ACPA (U/ml)	388.69 (254.477–535.767)	68.967 (59.948–79.259)	0.0001*

-The obtained data were examined using mean ± SD, median (IQR), and frequency (percentage). MTX = methotrexate; ETC = etanercept; MTXETC = mixed methotrexate and etanercept.

CTHRC1 levels

Fig. 1 shows that a significant elevation in serum CTHRC1 level was observed in the RA group 29.367 (23.44-35.00 ng/ml) compared to control group 15.732 (13.40-18.69 ng/ml) at P < 0.05, while there was no significant difference P > 0.05 in CTHRC1 level among the groups categorized based on DAS28.

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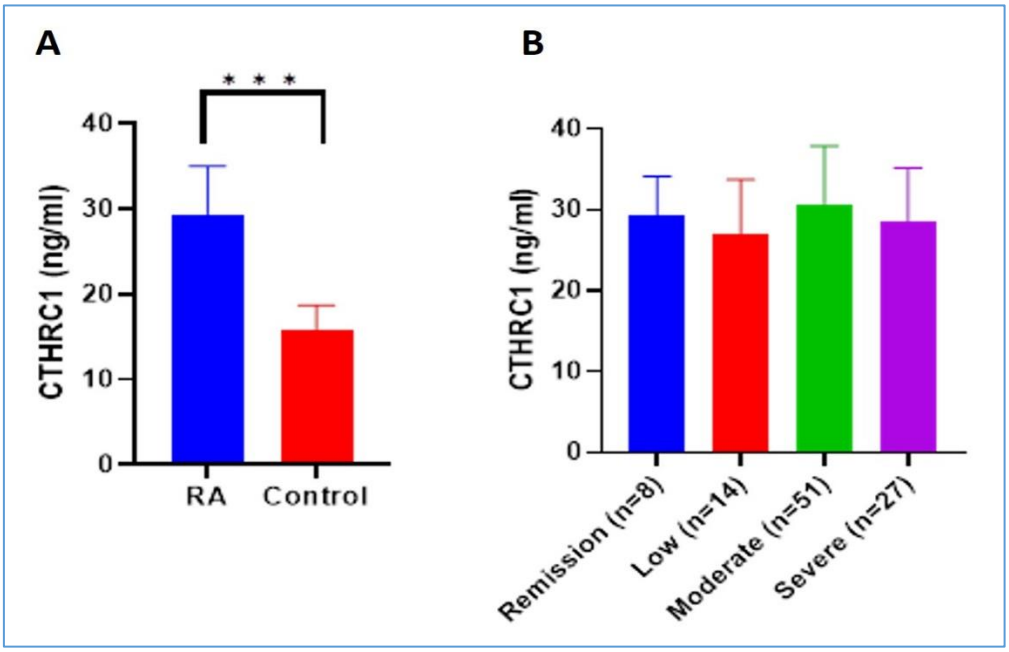

Figure 1. A CTHRC1 levels in RA patients and control subjects. B CTHRC1 levels in the four groups divided according to DAS28.

TNF-α and IL-10 levels

Fig. 2 shows a significant $P < 0.05$ increase in TNF-α level in the sera of patients with RA 63.48 (56.82–82.28) compared to the control group 33.78 (31.48–38.15), and a significant increase $P < 0.05$ level of IL-10 in the sera of RA patients 67.1 (49.35–79.89) compared to the control group 25.12 (22.34–29.2).

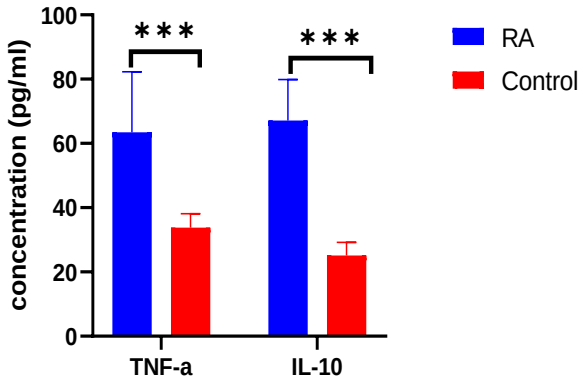

Figure 2. Levels of TNF-α and IL-10 in the sera of RA patients and control.

Comparison between CTHRC1 and other studied parameters

A comparison was carried out between the levels of CTHRC1 and RF, ACPA, CRP, ESR, TNF-α, IL-10, and DAS28 as show in Fig. 3. The results showed a positive correlation between CTHRC1 and ACPA (**r = 0.254, P = 0.011**), CRP (**r = 0.372, P = 0.0001**), TNF-α (**r = 0.202, P = 0.044**), and IL-10 (**r = 0.206 , P = 0.009**), while no correlation was observed between CTHRC1 and DAS28 (**r = 0.046, P = 0.650**), RF (**r = 0.073, P = 0.472**), and ESR (**r = 0.01, P = 0.919**).

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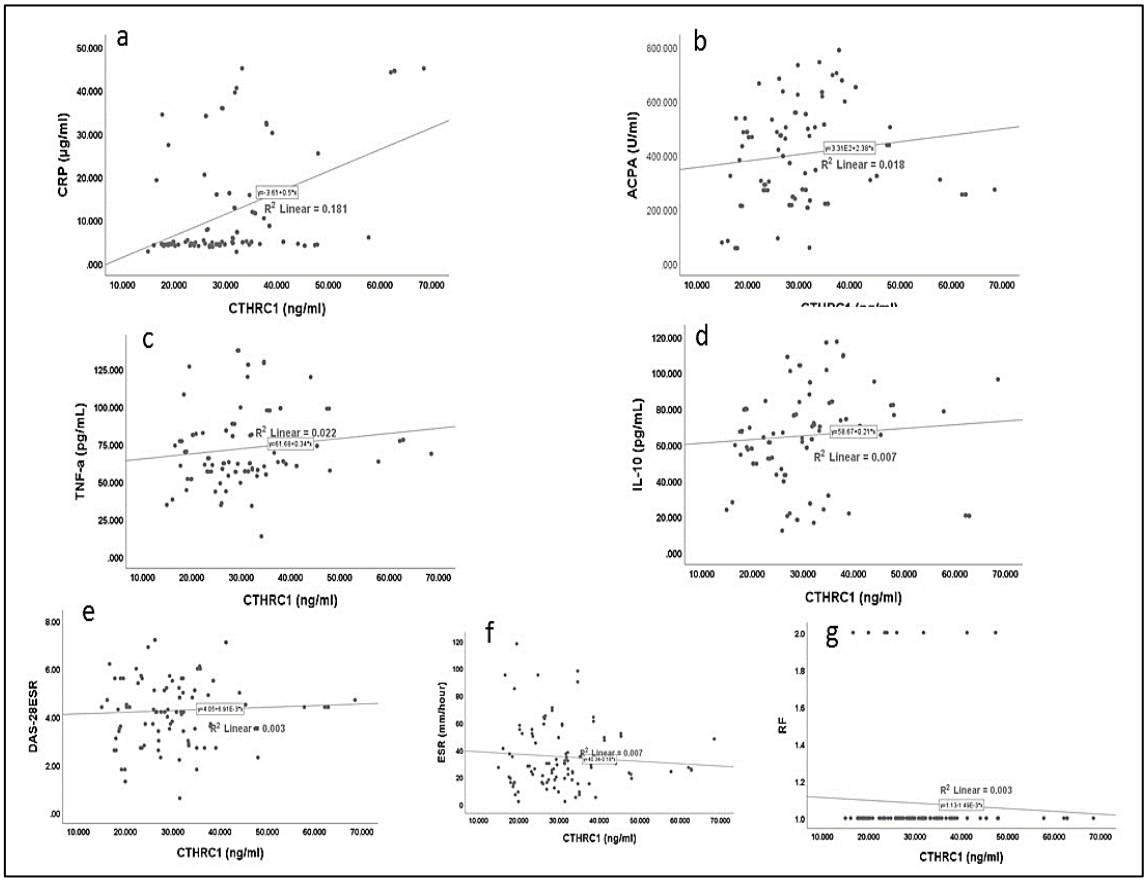

Figure 3. Correlation between CTHRC1 and (a) CRP (r = 0.372, P = 0.0001), (b) ACPA (r = 0.254, P = 0.011), (c) TNF-α (r = 0.202, P = 0.044), (d) IL-10 (r = 0.206 , P = 0.009), (e) DAS28 (r = 0.046, P = 0.650), (f) ESR (r = 0.01, P = 0.919), and (g) RF (r = 0.073, P = 0.472).

Receiver Operating Characteristic Curve (ROC)

The ROC curve analysis was used to assess the ability of serum levels of CTHRC1 to discriminate patients with RA from the control shown in Fig. 4. The area under the curve (AUC) of CTHRC1 was 0.945 ($p < 0.001$) at a Youden index of 0.71, positive predictive value (PPV) of 100, and negative predictive value (NPV) of 46.3, which is the perfect level of RA prediction.

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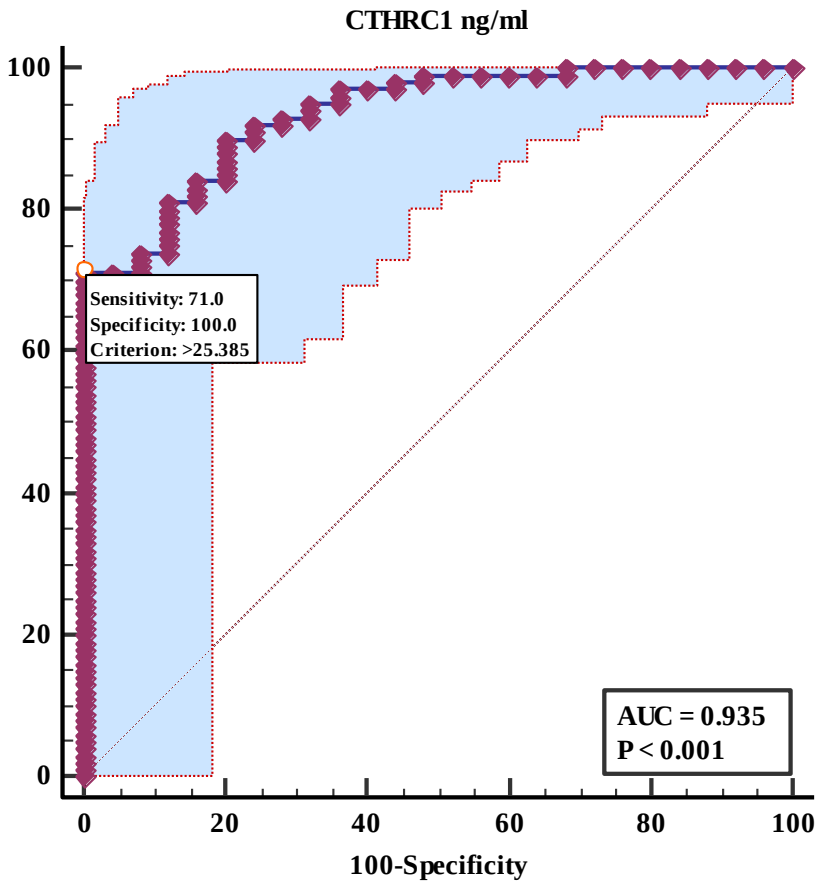

Figure 4. ROC curve of CTHRC1 levels in patients with RA.

Discussion

Rheumatoid Arthritis is a multifactorial disease with significant contributions from genetic and epigenetic factors. Therefore, it has a complex pathology, resulting in difficulty when diagnosing. The traditional serological biomarkers used in diagnosis are absent in one-third of RA patients and even more in early disease stages. In the early stages of RA, 61.6% showed to be positive for ACPA. Both sensitivity and specificity of the ACPA are significantly higher than the RF test [1]. In addition, RF is used to diagnose other inflammatory diseases as well [22]. Therefore, it is important to find a biomarker that has high sensitivity and high specificity as early diagnosis and therapy of RA can slow the progression of joint damage in 90% of patients [23].

In this study, we found a promising biomarker, with high sensitivity and high specificity, for the diagnosis of RA by combining CTHRC1 with traditional biomarkers of RA. It was found that serum CTHRC1 levels were significantly higher in patients with RA compared to that in the control. A cut off value of > 25.385 ng/ml of CTHRC1 provided a significant indication to differentiate between RA patients and control, with a sensitivity of 71%, specificity of 100%, and AUC of 0.935. This finding is in line with the findings of Myngby *et al.* [10] and Hu *et al.* [11], who published that CTRHC1 was able to distinguish between RA and control groups with sensitivity values of 62% and 84.5% and specificity values of 86%and 75.6%, respectively.

This study is novel research as it shows the correlation between CTHRC1 and cytokines – TNF-α and IL-10 highlighting the potential significance of CTHRC1 in arthritis pathogenesis. Of the two, TNF-α is one of the main pro-inflammatory cytokines that is involved in the pathogenesis of RA [18], whereas IL-10 is an anti-inflammatory mediator of cytokines secreted in active stages of RA [20]. A previous study

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P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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showed a positive association between CTHRC1 and IL-1β and IL-6 in a mouse model of arthritis [10].

This research has also shown significant associations between serum CTHRC1 levels and CRP and ACPA levels. These findings are compatible with Selim *et al.* [9], who found higher CTRHC1 levels with increased ACPA and CRP levels. Myngby *et al.* [10] also showed that CTHRC1 levels in RA were not significantly elevated in patients with OA or ReA, as did another study [8]. The present study showed no significant correlation between CTRHC1 and RF, ESR, and DAS28; this differs from other studies due to many factors such as sample size, population studies, and kinds of kits used in the study.

However, we also noticed several limitations. First, the study was cross-sectional with different types of treatment (MTX, ETC) involved. Second, there was a positive or negative bias in the vital parameters as a result of the therapeutic intervention. Third, because of the sample size, the statistical analysis was limited to comparison and correlation, such as regression and cluster analysis, which require a large number of subjects.

Conclusion

The study concludes that a correlation between CTHRC1 and traditional diagnostic markers and inflammatory and anti-inflammatory mediators. This correlation proves the role of CTHRC1 in the pathogenesis of RA. Moreover, it also proves that measuring CTHRC1 levels in combination with some inflammatory factors may provide a good marker in patients suffering from RA.

Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been included with the necessary permission for re-publication, which is attached to the manuscript. The author has signed an animal welfare statement.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad, Baghdad (Reference number: CSEC/1021/0062; Date: 15/10/2021).

Author's Contribution Statement

This work is carried out in collaboration between all authors. A. R. O., conceptualisation, analysis, Visualization, curation of data, study, writing – original draft. A. K. Z., Conceptualization, Analysis, Resources, Visualization, Editing Writing. All authors read and approved the final manuscript.

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2023, 20(3 Suppl.): 928-936
https://dx.doi.org/10.21123/bsj.2023.8036
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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تقدير مستويات CTHRC1 وبعض السيتوكينات في المرضى العراقيين المصابين بالتهاب المفاصل الرثوي

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الخلاصة

بروتين الكولاجين الثلاثي الحلزوني المتكرر المحتوي على 1 (CTHRC1) هو علامة أساسية لالتهاب المفاصل الرثوي، ولكن علاقته بالعلامات المؤيدة للالتهابات والمضادة للالتهابات قد تمت تغطيتها بشكل قليل في البحوث. لتقييم مستوى بروتين CTHRC1 في مصل 100 مريض مصاب بالتهاب المفاصل الرثوي و 25 شخصًا من الأصحاء. حيث تم مقارنة مستوياته بمستويات عامل نخر الورم ألفا (TNF-α)، والبين الابيضاضي-10 (IL-10) ، ونشاط مرض التهاب المفاصل الرثوي ، والعوامل الالتهابية الاخرى. تم العثور على ارتفاع كبير في مستويات مصل CTHRC1 (29.367 ng/ml) و TNF-α (63.488 pg/ml) و IL-10 (67.1 pg/ml) في مصل المريض بالمقارنة مع تلك الموجودة في مصل الأصحاء CTHRC1 (15.732 ng/ml) ، TNF-α (33.788 pg/ml) ،و IL-10 (25.122 pg/ml) على التوالي في (P <0.05). لم يكن هناك ارتباط معنوي بين مستوى CTHRC1 و DAS28 في الدم (r= 0.046, P=0.650))، بينما كانت هناك ارتباطات طردية معنوية بين مستويات CTHRC1 و CRP في الدم (r= 0.372, P=0.0001)، ، ACPA (r = 0.254, P=0.0001) ، TNF-α (r = 0.202 ،P = 0.01) و (P = 0.044 ،r = IL-10). 0.260قدم مستوى CTHRC1 (> 25.385 ng/ml) بالاشتراك مع مستويات CRP و ACPA مؤشرًا جيدًا لتنبؤ التهاب المفاصل الرثوي مع الحساسية = 71.0 % ، النوعية = 100.0 % ، الدقة =0.71 % ، القيمة التنبؤية الإيجابية= 100.0 % ، والقيمة التنبؤية السلبية =46.3 %. أظهرت الدراسة وجود ارتباط كبير بين مستويات CTHRC1 و TNF-α و IL-10. هذه الجزيئات قد تلعب دورًا بارزًا في مسببات وتشخيص التهاب المفاصل الرثوي.

الكلمات المفتاحية: ACPA، CTHRC1، IL-10، التهاب المفاصل الرثوي، TNF-α.