Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: March 2022 **2022, 19(5): 1014-1020** **E-ISSN: 2411-7986**

DOI: http://dx.doi.org/10.21123/bsj.2022.6293

The Role of Serum Chitinase-3-Like 1 Protein (YKL-40) Level and its Correlation with Proinflammatory Cytokine in Patients with Rheumatoid Arthritis

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Received 6/5/2021, Accepted 6/7/2021, Published Online First 20/3/2022, Published 1/10/2022

Abstract:

Chitinase-3-like 1 protein (YKL-40) is a glycoprotein primarily produced in the arthritic joint and plays a crucial role in inflammatory processes. The aim of the study is to establish the role of YKL-40 as a biomarker for rheumatoid arthritis (RA) compared to proinflammatory biomarkers and disease activity. The study included 58 patients and 18 control. Diseases activity score (DAS-28) and clinical disease activity index (CDAI) were measured. Serum level of YKL-40, tumor necrosis factor-α (TNF-α), interleukin-1B (IL-1β), erythrocyte sedimentation (ESR), rheumatoid factor (RF), C-reactive protein (CRP), and anti-citrullinated protein antibody (ACPA) were assessed. The results showed that the median serum YKL-40 level which was 5.42 ng/ml, the TNF-a level which was 123.6 ng/ml, and the IL-1B level which was 204.365 pg/dl were significantly higher in patients compared to control 3.28 (1.58–4.99) ng/ml, 56.47 (9.38–77.01) ng/ml and 67.887 (15.493–122.689)pg/dl respectively. There was no correlation between serum YKL-40 and disease activity, while there were significant associations observed with TNF-α (r=0.5,p =0.0001) and IL-1β (r=0.41, p=0.001). YKL-40 indicating good levels of RA prediction at 2.47 ng/ml, sensitivity 87.9%, specificity 58.6%, accuracy 78.1%, PPV 80.9%, and NPV 70.8%. In conclusion, a higher level of serum YKL-40 is found in RA patients. The findings from our study suggest a strong association between YKL-40 and the proinflammatory biomarkers. As a result, these biomarkers together might play a role in RA pathogenesis, and YKL-40 may be used as a potential diagnostic biomarker for RA.

Keywords: CHI3L1; IL-1β; Rheumatoid arthritis; TNF-α; YKL-40

Introduction:

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affected by both genetic, epigenetic, and environmental factors. According to the World Health Organisation, RA affects 0.5-1 % of the population and contributes to functional disability [1,2]. RA is more frequent among women and can appear at any age [3]. It primarily affects the synovial lining tissue and may cause chronic impairment and socioeconomic burdens [4]. The diagnosis of RA at its initial stage remains problematic as there is no precise test to predict RA with certainty [5]. The two main remarkable auto-antibodies in RA are rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). ACPA is highly predictive for the progression and severity of RA. 20–30% does not have ACPA [6,7] or RF, and erosive RA may be present without these markers. Accordingly, the disease phenotype is classified into ACPA-positive and negative RA [8]. Despite the diagnostic value of RF and ACPA, additional biomarkers are required to enhance the early detection and treatment of patients and improve the understanding of the pathways involved in RA [9].

A protein recently found to be a potential biomarker of RA has been chitinase-3-like 1 protein, (40 KDa) also known as Human cartilage glycoprotein-39, YKL-40, and CHI3L1. It has a mammalian composition [10], and is secreted by many cell types present in the arthritic joint macrophages, neutrophils, synoviocytes, and chondrocytes [11]. However, there is evidence that YKL-40 has a specific biological role. After tissue injury, the cell-

matrix is inflamed, re-modeled, and differentiated as macrophages and dendritic cells with cell proliferation and protection against apoptotic signals via a chitinolytic-independent mechanism [12].

The characteristic inflammation of RA happens due to the profusion of inflammation-promoting cytokines over those of the inhibiting [13]. Among the proinflammatory cytokines, tumor necrosis factor (TNF-α) is the crucial pathogenic cytokine that regulates the formation of other inflammatory molecules in the synovial tissue. Both TNF-α and interleukin-1β (IL-1β) share proinflammatory activities, promote T cell activation and stimulate the synthesis of other proinflammatory proteins [14,15] leading to joint damage and disability [16]. As YKL-40 is expressed in cartilage remodelling or degradation, its concentration in serum may be associated with these cytokines. YKL-40 could promote the secretion of TNF-α and IL-6 by activating the signalling pathway of the nuclear factor-κB (NF-κB), thereby facilitating inflammation pathogenesis [17].

This study aims to examine the serum concentration of YKL-40 and its relation to the levels of proinflammatory cytokines in RA patients.

Materials and Methods:

Patients and control

This study included 58 RA patients (female 53/ male 5) fulfilling the 2010 American College of Rheumatology /European League Against Rheumatism (ACR/EULAR) classification criteria for RA [18]. They were recruited between November 2019 and February 2020 from the outpatients of Baghdad Teaching Hospital. Eighteen healthy individuals of matched age and gender (F: M 16/2) served as control. Informed written permission was obtained from all study subjects before including them in the study. The study was approved by the Ethics Committee of the Medical City, and the National Training and Human Development Centre.

The following laboratory tests were performed for all subjects. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and kidney function tests, complete blood count (CBC), RF and ACPA were measured. The disease activity score (DAS-28) and clinical disease activity index (CDAI) were recorded. When the diagnosis was done, all patients were on medication.

Methods

Blood was obtained from each subject and left to coagulate at room temperature for approximately 15 min. It was then separated for 5 min. by centrifugation. Sera were moved in 1-ml Eppendorf tubes, and stored at -4°C till the completion of the checks. The kits were provided as follow: Serum YKL-40 (Shanghai Yehu Biological Technology Co., Ltd.,Cat.No. YHB3317Hu), serum TNF-α (Shanghai Yehu Biological Technology Co., Ltd., Cat. No. YHB3112Hu), serum IL-1B (Shanghai Yehu Biological Technology Co., Ltd., Cat. No. YHB1720Hu), serum CRP, and serum ACPA (Demeditec Diagnostics GmbH, Germany) concentrations were assessed by the enzyme-linked immunosorbent assay according to the manufacturer's references.

Statistical analysis

SPSS version 25 was used. Quantitative variables were presented as mean± SD or median 95%CI and interquartile range (IQR: 25^{th}-75^{th} percentile), while categorical variables were presented as frequency and percentage. The normal distribution of variables was investigated through the Shapiro-Wilk test. Spearman's rank coefficient was considered. The receiver operating characteristic (ROC) curve method was applied to evaluate the cut-off value of the serumYKL-40 level. The specificity, sensitivity, negative predictive value, and positive predictive value were also computed [19]. A P-value < 0.05 was considered significant.

Result:

The mean age of the 58 patients was 43.5±10.7 years (20-65 years), and the 18 control was 43.22 ± 4.9 years (20-65 years). The mean disease duration in patients was 6.98±6.12 years (1-15 years). Characterstics of the patients compared to the control are presented in Tab.1.

The median serum YKL-40 level in RA was 5.42 ng/ml (4.28–7.16 ng/ml) significantly higher compared to that in control 3.28 ng/ml (1.58–4.99 ng/ml) (p=0.0001). The median serum TNF-α and IL-1B in patients was significantly higher (123.6 ng/ml; 97.6–147.2 ng/ml and 204.365 pg/dl; 139.749-235.55 pg/dl respectively) compared to control (56.47 ng/ml; 9.38–77.01 ng/ml and 67.887 pg/dl; 15.493–122.689 pg/dl respectively) (P=0.0001) Fig.1.

Table 1. Baseline characteristics of rheumatoid arthritis patients and control.

Variable	RA patients (n=58)	Control (n=18)	P value
Age (years)	43.5±10.7	43.22 ± 4.9	-
Female:Male	53:5 (10.6:1)	16:2 (8:1)	-
BMI	28.76±3.77	28.7 ± 4.04	0.636
Disease Duration (y)	6.98±6.12	-	-
ESR (mm/hour)	20.5 (14–39.5)	9 (5–16.5)	0.0001
Positive RF	55 (94.8)	0 (0)	0.0001
CRP (µg/ml)	11.16 (3.1–63.1)	4.77 (2.23–10.95)	0.006
ACPA (U/ml)	213.2 (46.4–636.5)	23.80 (14.66–33.39)	0.0001
YKL-40 (ng/ml)	5.4 (4.3–7.2)	3.28 (1.58–4.99)	0.0001
TNF-α (ng/ml)	123.6 (97.6–147.2)	56.47 (9.38–77.01)	0.0001
IL-1β (pg/dl)	204.365 (139.749-235.55)	67.887 (15.493–122.689)	0.0001
DAS-28	4.16±1.13	-	-
CDAI	16.34±7.5	-	-
MTX	25 (43.1)	-	-
ETC	12 (20.6)	-	-
MTX, and ETC	21 (36.2)	-	-

BMI: Body mass index; ESR. Erythrocyte rate of sedimentation; RF. Rheumatoid factor; CRP. C-reactive protein; ACPA. Anti-citrullinated protein antibody; YKL-40. Chitinase-3-like 1 protein; TNF-α: Tumour necrosis factor-α; IL-1β: Interleukin-1B; DAS-28. Disease activity score 28-joints; CDAI: Clinical disease activity index; MTX. Methotrexate; ETC: Etanercept. Results are presented as mean ±SD, N (%), and median (25th-75th percentiles). Values are significant at $p<0.05$

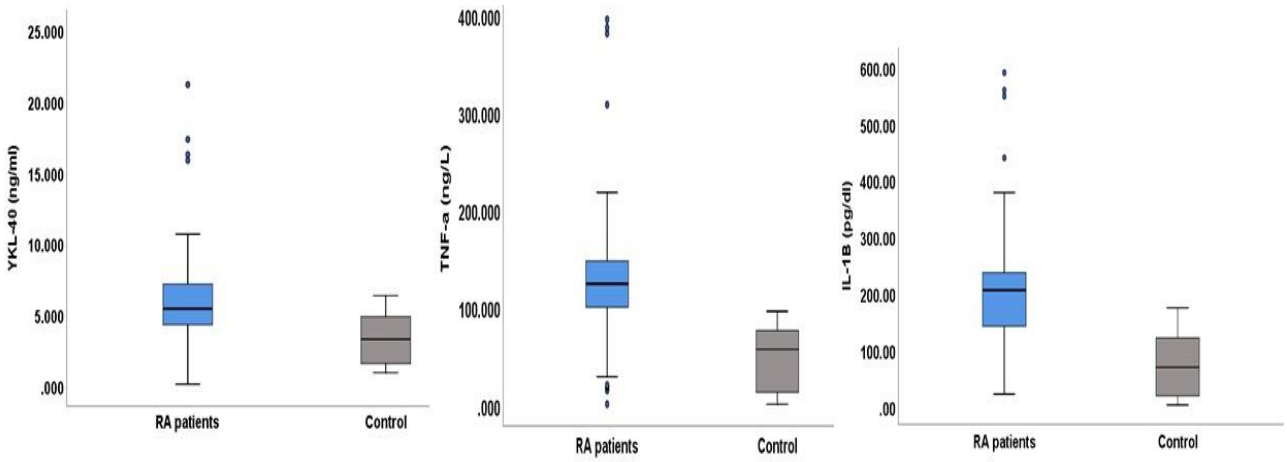

Figure 1. Serum YKL-40, TNF-α and IL-1β in rheumatoid arthritis patients and control.

There was a significant positive correlation between serum YKL-40 level with TNF-α (r=0.5, P =0.0001) in patients and also with IL-1β in patients (r= 0.41, P=0.001). There were no significant associations between serum YKL-40 and the characteristic features, including DAS28, RF, ACPA, and CRP (P >0.05) as shown in tab.2, Fig.2.

Table 2. Correlation between YKL-40 and other parameters.

Parameters	R value	P value
DAS28	0.15	(0.28)
RF	0.09	(0.52)
ACPA	-0.15	(0.25)
CRP	-0.03	(0.83)
ESR	0.16	(0.23)

DAS-28: disease activity score 28-joints; RF. rheumatoid factor; ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; and ESR: erythrocyte rate of sedimentation.

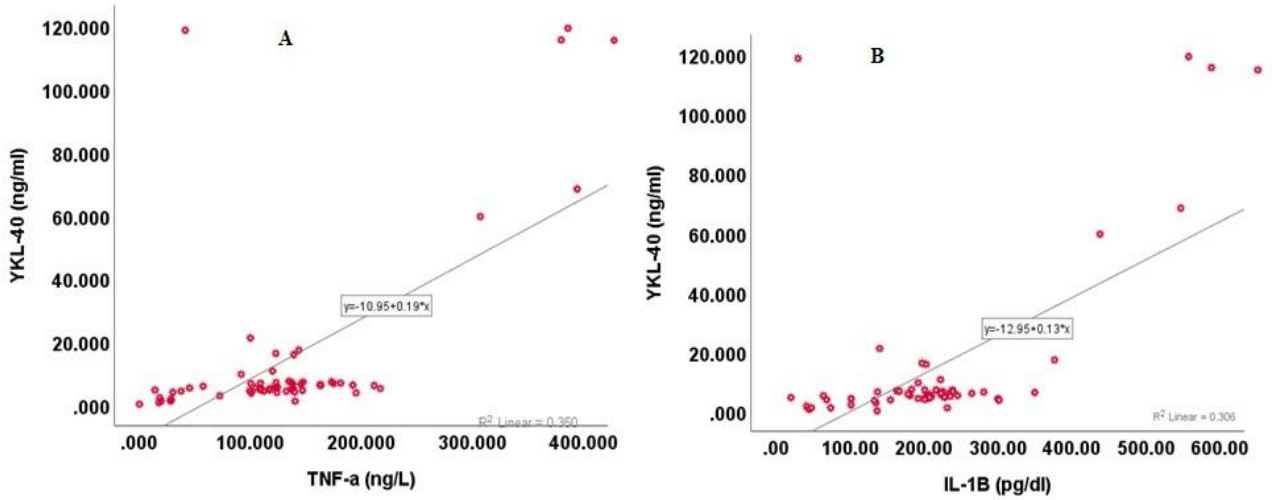

Figure 2. The correlation of YKL-40 with (A) TNF-α and with (B) IL-1β in rheumatoid arthritis patients

ROC curve analysis was performed to distinguish patients from control with regard to serum YKL-40 Fig.3. The AUC was 0.769 ($p<0.0001$) for the existence of RA diagnosis which indicates good levels of prediction at an optimal cut-off value of 2.47 ng/ml, sensitivity 87.9%, specificity 58.6%, accuracy 78.1%, PPV 80.9%, and NPV 70.8%.

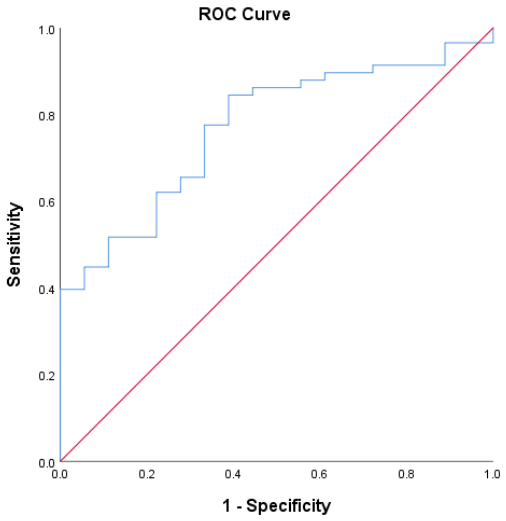

Figure 3. Receiver operating characteristic (ROC) curve of serum chitinase-3-like 1 protein (YKL-40) as a diagnostic marker in rheumatoid arthritis (RA) patients AUC: 0.769, 95% CI (0.656–0.882).

Discussion:

The literature on serum YKL-40 in RA patients provides variable findings [10,11,20,21], a negative RF and ACPA is present in a remarkable number of RA patients. Several markers were used to test the activity of RA patients [22], but the pathology of the illness and the prediction of the clinical course could not be determined by a single marker. Thus, a special new synovitis and disease activity marker is still needed. The diagnostic value of YKL-40 and proinflammatory markers combined with other biomarkers for RA were evaluated. YKL-40 could be considered as a possible novel biochemical marker. It is also considered a candidate for bone resorption, and has been proposed to take on a pathogenic function in the inflammatory process and the degradation of joints [23]. Cytokines have a potent relation to autoimmune disorders, the most prominent among others is RA, which targets synovial joints [16]. Increased production of proinflammatory cytokine could stimulate the autoimmune process [14]. These soluble factors have participated in the activation, differentiation and migration of pathogenic cells to the joints with consequent activation of osteoclasts and damage [24].

In the present work, serum YKL-40 levels were significantly higher in patients than in control; and this finding is in line with the previous studies [10,21]. Furthermore, YKL-40 can have a function in inflammation and the immune process and is also linked to cell migration and reorganization. YKL-40 secretion may regulate the stimulation of the protein kinase B, NF-κB, and other cytokines and signaling pathways that are linked to the pathogenesis of RA [25]. YKL-40 is a candidate for autoantigen in RA. Newly, a multi-biomarker disease activity (MBDA) score based on 12 serum markers was assessed as a baseline predictor for one-year radiographic progression in early RA [26]. YKL-40 was between these biomarkers.

No association was found between YKL-40 and DAS-28; this is in agreement with Narayan et al. [10] and Kazakova et al. [20] but contrary to the study of Mastsumoto and Tsurumoto's [27] that found

increased serum levels YKL-40 associated with disease activity in early RA. It also contradicts the findings of Kassem et al. [28] , Al-Sayed et al. [29], and Jafari-Nakhjavani et al. [21]. There was also no relation between YKL-40 with ESR, CRP, ACPA, and RF; this is in agreement with Jafari-Nakhjavani et al. [21] and Narayan et al. (except ACPA, RF) [10], but in disagreement with Kazakova et al. [30]. In the results of this report no correlation of serum YKL-40 with age or disease duration was present. This is in agreement with others [10,21].

In this research, the ESR, CRP and anti-CCP were higher in RA patients compared to control which are in line with previous study [31]. It has been found that RF and ACCP antibody are sensitive biomarkers for the diagnosis of RA and that ACCP antibody is more specific than RF.

Serum YKL-40 levels were found to have a link with the proinflammatory cytokines TNFα and IL-1β, and this is in harmony with Kazakova et al. [20]. YKL-40 is a transmembrane protein in which split components bind to an unidentified receptor, and its expression is controlled by different cytokines [32]. This study showed that TNF-α and other multifunctional cytokines can also activate YKL-40 secretion. Other reported that YKL-40 production increases by above 30% in osteoarthritic cartilage primary chondrocytes due to these cytokines [33].

This work has several strong points: First, the participants had no other infections. Second, the patients received just one combination of drugs.

There are a few limitations including: the size of the population was small, that there is no synovial fluid level of YKL-40 for a proper overview of its state and the cross-sectional study design. A longitudinal study is warranted to follow-up the relation to treatment and to understand the role of YKL-40 and the possibility of it being a diagnostic tool or therapeutic target.

Conclusion:

The level of Serum YKL-40 is significantly positively correlated with the proinflammatory cytokines (TNF-α and IL1-β). This may suggest a possible potential role in the pathogenesis of RA and subsequently might help in the treatment of RA. In addition, S.YKL-40 has a very good diagnostic performance with high accuracy to differentiate RA from healthy individuals. This may indicate a possible biomarker that can help in the diagnosis of RA.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' contributions statement:

A.B., B.C., and C.D. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript

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Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: March 2022 **2022, 19(5): 1014-1020** **E-ISSN: 2411-7986**

دور مستوى مصل بروتين-1 شبيه الكيتيناز-3 (YKL-40) وارتباطه بالسيتوكين المنبه للالتهابات في مرضى التهاب المفاصل الروماتويدي

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الخلاصة:

بروتين-1 شبيه الكيتيناز-3 (YKL-40) هو بروتين سكري ينتج بشكل أساسي في المفصل الملتهب ويلعب دورًا مهمًا في العمليات الالتهابية. الهدف من البحث هو دراسة دور YKL-40 كمعلم حيوي لالتهاب المفاصل الروماتويدي (RA) مقارنة بالواسمات المسببة للالتهابات ونشاط المرض. شملت الدراسة 58 مريضا و18 شخص سليم كمجموعة تحكم. تم قياس درجة نشاط المرض (DAS-28) ومؤشر نشاط المرض السريري (CDAI). مستوى مصل YKL-40، عامل نخر الورم-الفا (TNF-α)، إنترلوكين-1بيتا (IL-1β)، سرعة ترسب الدم (ESR)، عامل الروماتويد (RF)، البروتين المتفاعل C (CRP)، وتم تقييم الأجسام المضادة للبروتين السيترولييني (ACPA). أظهرت النتيجة أن متوسط مستوى YKL-40 في المصل كان 5.42 نانوغرام / مل، ومستوى TNF-a كان 123.6 نانوغرام / مل، ومستوى IL-1B 204.365 بيكوغرام / ديسيلتر أعلى بشكل ملحوظ في المرضى مقارنة بمجموعة التحكم 3.28 نانوغرام / مل ، 56.47 نانوغرام / مل و 67.887 بيكوغرام / ديسيلتر على التوالي. لم يكن هناك ارتباط بين YKL-40 في المصل ونشاط المرض، بالرغم من وجود ارتباطات مع TNF-α وIL-1β. كما اظهر تحليل خصائص المستقبل التشغيلية باحتلال YKL-40 مساحة تحت المنحنى قدرها 0.769 في مرضى RA. يشير YKL-40 إلى مستويات جيدة لتنبؤ RA عند 2.47 نانوغرام / مل، والحساسية 87.9٪، والنوعية 58.6٪، والدقة 78.1٪، و PPV80.9٪، وNPV 70,8٪. في الختام، تم العثور على مستوى أعلى من مصل YKL-40 في مرضى RA. أشارت نتائج دراستنا إلى وجود ارتباط قوي بين YKL-40 والعلامات الحيوية المسببة للالتهابات. نتيجة لذلك، قد تلعب هذه المؤشرات الحيوية معًا دورًا في التسبب في مرض التهاب المفاصل الروماتويدي ، ويمكن استخدام YKL-40 كمؤشر بيولوجي تشخيصي محتمل لـ التهاب المفاصل الروماتويدي.

الكلمات المفتاحية: بروتين-1 شبيه الكايتينز-3، YKL-40 ،التهاب المفاصل الروماتويدي، انترلوكين-1 بيتا، عامل نخر الورم-الفا.