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Research Article

Diagnostic and Predictive Utility of Serum Interleukin-37 in Rheumatoid Arthritis: A Case-Control Study

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Abstract

***Background*:** Rheumatoid arthritis is the most common cause of inflammatory polyarthritis. Interleukin-37 (IL-37) has been found to play an important regulatory role in the development of inflammatory diseases. ***Objectives*:** To assess serum IL-37 level in rheumatoid arthritis (RA) patients compared to controls, to evaluate its diagnostic and predictive utility in RA patients and to investigate IL-37 level correlation with demographic and clinical characteristics of RA. ***Methods*:** Eighty subjects, 40 RA patients aged between 23-63 years and 40 healthy controls aged between 28-67 years were evaluated. An enzyme-linked immunosorbent assay (ELISA) was used to analyze the serum IL-37 levels. ***Results*:** Serum IL-37 was significantly higher in RA patients compared to healthy controls. At optimum cut off value of >58.275 pg/ml, serum IL-37 had 100% accuracy, positive predictive value, negative predictive value, sensitivity, and specificity. Serum IL-37 level was not significantly related to Disease Activity Score of 28 joints-erythrocyte sedimentation rate (DAS28-ESR), also not correlated with C-reactive protein(CRP), rheumatoid factor(RF) and anti-cyclic citrullinated peptide antibody (Anti-CCP). Also there was no correlation between the level of IL-37 and treatment. ***Conclusions*:** IL-37 was significantly higher in RA patients compared to healthy controls with a high diagnostic and predictive ability, and may be a potential biomarker for diagnosis and prediction of RA.

Keywords: serum IL-37, rheumatoid arthritis, disease activity, inflammatory arthritis.

الفائدة التشخيصية والتنبؤية لمستوى الأنترلوكين-37 في مرض التهاب المفاصل الرثوي: دراسة على الحالات المرضية

الخلاصة

الخلفية: التهاب المفاصل الرثوي (RA) هو السبب الأكثر شيوعا لالتهاب المفاصل المتعدد. ثبت ان إنترلوكين-37 يلعب دور تنظيمي مهم في تطوير الأمراض الالتهابية. **الأهداف**: تقييم مستوى انترلوكين-37 في مصل مرضى (RA) مقارنة بالضوابط، لتقييم فائدته التشخيصية والتنبؤية في مرضى (RA) والتحقيق من اقترانه مع المعايير الأخرى. **الطرائق**: تم تقييم ثمانين شخصا منهم 40 مريضا و مريضا تتراوح أعمارهم بين 23-63 عاما و40 من الأصحاء الذين تتراوح أعمارهم بين 28-67 عاما. تم استخدام فحص مناعي لتحليل مستويات انترلوكين-37 في المصل. **النتائج**: مستوى انترلوكين-37 أعلى بكثير في مرضى RA مقارنة بالأصحاء. عند قيمة القطع المثلى > 58.275 بيكوغرام/مل لأنترلوكين-37 مستوى دقة وقيمة تنبؤية إيجابية، قيمة تنبؤية سلبية، حساسية، وخصوصية. تصل الى 100%، ولم يكن مستوى المصل مرتبطا بشكل كبير بنقاط نشاط المرض البالغة 28 كما أنه لا يرتبط بالبروتين التفاعلي وعامل الروماتويد و Anti-CCP كما لم يكن هناك أي ارتباط مع نوع العلاج. **الاستنتاجات**: كان انترلوكين-37 أعلى بكثير في مرضى RA مقارنة بالأصحاء وذو قدرة تشخيصية وتنبؤية عالية ، وقد يكون علامة بيولوجية محتملة لتشخيص والتنبؤ بمرض التهاب المفاصل الرثوي.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability [1]. RA affects approximately 0.5-1% of the adult population worldwide with an annual incidence of 3 per 10,000 adults. It occurs more commonly in females than in males, with a 2-3:1 ratio [2]. Some Native American populations had a remarkably high prevalence more than (5%) [3]. In Iraq, the incidence for rheumatoid arthritis was observed in 3.02% in 2011 in Babylon province [4]. The etiology of RA remains elusive; susceptibility factors are evident. The pathology of RA is characterized by the infiltration of several inflammatory cells into both the pannus and the joint fluid and by subsequent tissue destruction. Chemokines, as well as other inflammatory mediators, play key roles in the pathogenesis of RA, and the coordinated production of chemokines and pro-inflammatory cytokines is important in the orchestration of the inflammatory responses observed in patients with RA [5]. Imbalance between pro- and anti-inflammatory cytokine activities favors the induction of autoimmunity, chronic inflammation, and there by joint damage [6]. The cells of the innate immune system possess broad proinflammatory, destructive, and remodeling capacities, and considerably contribute to inflammation and joint destruction both in the acute and chronic phases of RA [7]. The immune response is characterized by the development of specific autoantibodies including rheumatoid factor which is present in approximately 70 % of patients with RA, although the specificity is low and anti-citrullinated peptide antibodies (ACPA) which is occur in approximately 50 % of patients with RA and have a specificity of 90-95% for the disease [8,9]. Interleukin-37 could suppress innate immune response and recently IL-37 has been found to play an important regulatory role in the development of a variety of inflammatory diseases, autoimmune diseases, and tumors [10-12]. Human IL-37 gene is located on chromosome 2 with a length of 3.617 kb [13]. The 6 exons encode five isoforms of IL-37 including IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e [13,14]. IL-37 has been described as an anti-inflammatory cytokine in several inflammatory diseases in addition to RA, including inflammatory bowel disease (IBD) [15], systemic lupus erythematosus (SLE) [16], graves' disease(GD) [17], and ankylosing spondylitis (AS) [18]. There is still a long way to go before the specific role of IL 37 is completely elucidated, but so far, the anti-inflammatory effect of IL 37 has been comprehensively reported. As an inhibitor of both innate and adaptive immunity and inflammatory responses, IL 37 plays a pivotal role in the antimicrobial response, including antiviral, antibacterial, neutralization of endotoxins and anti-immune and tumor regulation, mainly by changing the permeability of bacterial cells [19]. A variety of cytokines are involved in the pathogenesis of rheumatoid arthritis. Dysfunction of immune regulation is the leading cause of RA [20]. It was found that serum level of IL-37 in patients with RA were significantly higher than those in healthy controls [21-23]. Up to our knowledge there was no previous study in Iraq that assessed serum IL-37 in RA. So this study was aimed to assess serum IL-37 level in RA patients compared to controls, to evaluate IL-37 diagnostic and predictive utility in RA patients, and to investigate IL-37 level correlation with sociodemographic and clinical characteristics of Rheumatoid arthritis patients.

METHODS

Study design

This case control study was conducted at the Rheumatology Consultation Clinic of Baghdad Teaching Hospital/Medical City from February 2020 to the end of April 2020. Ethical approval was taken from Medical City Directorate and Baghdad Teaching Hospital, Department of Medicine, College of Medicine and an informed consent was obtained from all participants after explaining the nature of the study to them.

Inclusion criteria

Patients included were 1) Males and females with age >18 years, 2) had RA diagnosed by a rheumatologist according to the American College of Rheumatology-European Alliance of Associations for Rheumatology (ACR-EULAR) 2010 Classification Criteria for diagnosis of RA [24].

Exclusion criteria

Patients were excluded due to the presence of overlapping other inflammatory arthritis with RA like seronegative arthritis or connective tissue diseases (like SLE), malignancy, thyroid disease, diabetes mellitus, pregnancy, and liver or renal diseases.

Sampling method and sample size

A total of 40 consecutive patients with RA enrolled in the study. Of those there were 5 males and 35 females aging from 23 to 63 years. Another 40 healthy subjects (7 males and 33 females) age from 28 to 67 were taken as controls matched in age and gender.

Clinical and laboratory evaluation

Full history and clinical examination were done for all participants in the study, body mass index (BMI) was calculated and the recent relevant investigations were recorded including complete blood count (CBC) and erythrocyte sedimentation rate (ESR), fasting blood sugar (FBS), renal function test (RFT) and liver function test (LFT), general urine examination (GUE). Rheumatoid factor and Anti-cyclic citrullinated peptide (Anti-CCP), C-reactive protein was done to the patients and healthy controls. We used Disease Activity Score of 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI) to evaluate disease activity, which is widely used as an indicator of RA disease activity and response to treatment [10]. The joints included in DAS28 are (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2), and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TEN28) and swelling (SW28) are counted [13].

Accordingly, the disease activity of the affected person can be classified as follows: Remission: DAS28 ≤2.6; Low disease activity: 2.6< DAS28 ≤3.2; Moderate disease activity: 3.2< DAS28≤ 5.1; High disease activity: DAS28 >5.1 [24].

Analysis of serum IL-37

Whole blood specimens were gently to avoid hemolysis. Blood was allowed to clot for two hours at room temperature. Serum was separated by centrifugation for 20 min at 1000×g. Specimens were stored at -20°C. Serum IL-37 concentrations were quantified by using a commercial human IL-37 ELISA kit (MYBIOSOURSE, USA) according to the manufacturer's protocol.

Statistical analysis

The descriptive statistical analysis was performed using mean and standard deviation (mean±SD) for numerical variables. Frequency and percentage for categorical variables. The association between socio-demographic characteristics and IL-37 was examined by chi square test, fisher exact test, Mann Whitney U test and independent *t*-test. To differentiate IL-37 between patients and control we used independent t test. validity assessment for IL-37 was measured using Receivers operating characteristics (ROC) curve. Area under the curve (AUC) was calculated using Receivers operating characteristics (ROC) Curve. A Multiple linear regression analysis was conducted to determine the factors affecting or associated with IL-37 using enter method. *P* value less than 0.05 was considered statistically significant. All analyses were performed using statistical package for social sciences (SPSS) version 24.

RESULTS

Table 1 shows the socio-demographic characteristics of patients and controls. There was no statistical significant difference regarding sex, smoking, age, and BMI between patients and controls (*P*=0.531, *P*=0.676, *P*=0.647, and *P*=0.286, respectively). The majority of respondents were female in both groups. The mean age among patients was 47.88±10.68 years and the mean BMI was 30.41±5.81 kg/m^2. The mean duration of the disease among the patients was 9.48±7.28 years. The CDAI mean value was 30.28±7.81 and DAS28 was 5.76±0.69. The majority of patients were with severe RA condition (87.5%), not on NSAID (72.5%) and almost half of patients on steroid (47.5%). Almost 85% of the patients were maintained on methotrexate and only 7.5% on etanercept. The mean value of ESR was 45.63±30.01 mm/hr, High hsCRP was present in 29 patients (72.5%), and positive RF in 35(87.5%), and the median (interquartile range) was 34.03 (0.85-111.84) for patients. The mean IL-37 among patients (699±635.29 pg/ml) was statistically significantly higher compared with controls (34.18±12.67 pg/ml) (*P*<0.001), and the effect size was 1.48) (Figure 1).

Table 1: Sociodemographic and clinical characteristics of RA patients and controls.

Variables	RA Patients (*n*=40)	Controls (*n*=40)	*P*-value
Age, mean ±SD (year)	47.88±10.68	49.05±11.89	0.647
Female *n*(%)	35(51.5)	33(48.5)	0.531
BMI, mean±SD, kg/m^2	30.41±5.81	29.18±4.39	0.286
Smoking status positive	3(42.9)	4(57.1)	0.676
Disease duration Median (IQR) (year)	7(3-15)		
Disease activity n(%)			
Mild	5(12.5)		
Moderate	35(87.5)		
Severe	0(0)		
CDAI (mean±SD)	30.28±7.81		
DAS 28 (Mean±SD)	5.76±0.69		
ESR mm/hr (mean±SD)	45.63±30.01		
hsCRP	29(72.5)		
Positive RF	35(87.5)		
ACPA, Median (IQR)	34.03 (0.85-111.84)		
Medications n(%)			
NSAIDs	11(27.5)		
Steroids	19(47.5)		
Methotrexate	34(85)		
Etanercept	3(7.5)		

SD, standard deviation, BMI, Body mass index; IQR, interquartile range; CDAI, Clinical disease activity index; ESR, Erythrocyte sedimentation rate; DAS28, Disease activity score 28; CRP, C-reactive protein; ACPA, anti-citrullinated peptide antibody; NSAIDs, Non-steroidal anti-inflammatory drugs.

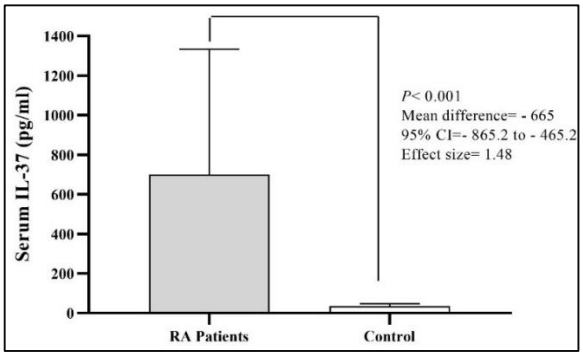

Figure1: Serum IL-37 levels in RA patients and controls.

The area under the curve (AUC= 1) with an optimum cut-off value for IL-37 >58.275 to differentiate between patients and controls. Sensitivity, specificity, and accuracy, positive predictive value (PPV), and negative predictive value (NPV) of IL-37 in identifying patients from controls were 100%. (Table 2). Using multiple linear regression analysis to predict the impact of sociodemographic and clinical characteristic factors on IL-37, we found no significant association between these factors and IL-37 (*P*>0.05).

Table 2: Validity parameters of IL-37 level to differentiate RA patients from healthy controls.

Variable	AUC	Optimum cut-off value	Sensitivity	specificity	Accuracy	PPV	NPV
IL-37	1.000	>58.275	100%	100%	100%	100%	100%

IL-37: interleukin-37; AUC: Area Under Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

The R square value was 0.704. That means the model's success in explaining 70% of the factors related to IL-37 as shown in Table 3.

Table 3: Multiple Linear Regression analysis to predict the effect of sociodemographic and clinical characteristics of RA patients on IL-37.

Variables	β	*P*-value	95%CI
Age (years)	-0.427	0.277	-73.7-22.9
BMI (kg/m2)	-0.308	0.344	-107.4-40.2
Gender	-0.204	0.657	-2228.1-1452.9
Smoking	-0.022	0.951	-709.6-669.7
Duration of disease	0.277	0.361	-30.9-79.3
CDAI	0.000	1.000	-90.2-90.2
DAS28	0.069	0.898	-980.7-1106.8
Disease activity	0.548	0.200	-625.2-2704.8
NSAID	0.083	0.758	-681.4-913.9
Steroids	0.403	0.203	-310.1-1321.9
Methotrexate	-0.010	0.973	-1158.3-1121.8
Etanercept	0.174	0.460	-760.6-1588.9
Anti-CCP	-0.130	0.740	-1.3-0.9
ESR (mm/hr)	-0.016	0.962	-15.1-14.4
hsCRP	0.125	0.720	-859.4-1210.4
RF	0.418	0.172	-390.7-1975.4

* Multiple linear regression analysis was performed using enter method. Significant level at $P < 0.05$. $r^2 = 0.704$. β: Regression coefficient; NSAID: nonsteroidal anti-inflammatory drugs; RF: Rheumatic Factor; hsCRP: high sensitivity C Reactive protein; ESR: Erythrocyte Sedimentation Rate; CDAI: clinical disease activity index; DAS28: disease activity score28; Anti-CCP: anti cyclic citrullinated peptide antibody; BMI: body mass index.

DISCUSSION

The exact pathogenesis of RA is unknown; though strong evidence suggests that cytokines play a role in disease progression [25]. To the best of our knowledge, this is the first study in Iraq which assessed serum IL-37 in RA patients compared to healthy controls, its diagnostic and predictive utility, and its correlation with baseline characteristics of the patients. In this study, the mean serum level of IL-37 was significantly higher in patients with RA than healthy controls, and this result was in agreement with Xia *et al*. (2015) [25], Yang *et al*. (2015) [22], Zhao *et al*. 2014 [21], and Yuan *et al*. (2019) [23], who demonstrated that serum levels of IL-37 were higher in patients with RA than controls. Serum IL-37 level cannot be used to differentiate between patients with RA and healthy controls with 100% accuracy, 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV at an optimum cut off value of >58.275 pg/ml. No previous study available to compare with it.

and disease activity score (DAS 28), CRP and ESR, and this agreed with another study [23], which showed that there was no significant correlation between IL-37 and other clinical parameters that indicated disease activity, including DAS28, CRP and ESR. However, our finding contrasted with other studies which showed that the higher the DAS 28 level and ESR, the higher the serum IL-37 level [22,25]. The lack of a significant association may be attributed to the imbalance between IL-37 and pro-inflammatory cytokines in the initiation and progression of RA. Additionally, the modest sample size and the restriction on the disease activity measurement may also have contributed to this difference. Also it may be due to the difference in the involvement of IL-37 in the local and systemic reactions, in the synovium and serum. A previous study has shown that the concentrations of IL-37 can be measured in both the serum and synovium of patients with RA. The synovial fluid IL-37 levels were much higher than those in the serum [23,11] and in the systemic circulation; this may be the reason that increased serum concentrations of cytokines do not significantly correlate with disease activity. In addition, in the current study we found that no significant correlation between IL-37 and RF. This result agreed with Xia et al, who reported that there were no significant differences in plasma IL-37 levels in RA patients with positive RF when compared to the patients with negative RF (P=0.062) and not agreed with other studies [25], which mentioned that IL-37 was significantly higher in the RF-positive RA group compared with the RF-negative group. We found in the present study a non-significant correlation between serum IL-37 and Anti-CCP which agreed with another study [11], and not agreed with Yang *et al*. [22]. In a study performed by Zhao *et al*. [21], the levels of plasma IL-37 were evaluated in RA patients before and after treatment with disease modifying antirheumatic drugs (DMARDs) and in comparison to healthy controls. The plasma levels of IL-37 in the RA patients before treatment were significantly higher compared to levels in healthy controls. However, there was no statistically significant difference between IL-37 levels before and after three months of DMARD treatment for the RA patient. As in this study, there was no significant difference between who took DMARD and who did not. This study has some limitations: small sample size with short period of time, no follow up, and single center study.

Conclusion

The serum level of IL-37 was significantly higher in patients with RA than in healthy controls, and may play an important role in the pathogenesis of RA and can be used to differentiate between RA patients and healthy individuals. Also, we reported no significant correlation between serum IL-37 levels with sociodemographic and clinical

characteristics of the patients. Larger scale studies with longer follow up multi-centric approaches are recommended to validate the results of the present study.

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Conflicting interests

The authors declared no conflicts of interest

Data sharing statement

The datasets analyzed during the current study will be available from the corresponding author on a reasonable request.

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