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Original Article

Estimation of Interleukin 32 and Interleukin 37 Serum Levels in Iraqi Patients with Rheumatoid Arthritis

Mohammed Jasim, E[1 *], Khudhur Jameel, S[1], Ihsan Awadh, N[2]

1. Medical Microbiology Department, Medical College, Al-Iraqia University, Baghdad, Iraq
2. Medical City Complex, Internal Medicine Department, Rheumatology Unit, Baghdad, Iraq

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Corresponding Author: esraa.m.jasim@students.aliraqia.edu.iq

Abstract

Rheumatoid arthritis (RA) is an autoimmune condition characterized by persistent inflammation in synovial joints. Interleukine-32 (IL32) is known to have significant pro-inflammatory effects in RA, and IL37 is an anti-inflammatory cytokine that reduces the immune response and inflammation. This study aimed to investigate serum levels of IL32 and IL73 in RA patients. The sample included 50 patients (46 females and four males) with RA and 40 healthy controls. The enzyme-linked immunosorbent assay (ELISA) detected serum levels of IL32 and IL37. The disease parameters' activity was measured by the clinical disease activity index, and the Erythrocyte sedimentation rate was measured by the Westergren method. Moreover, C-Reactive protein, Rheumatoid factor, and Anti-Cyclic Citrullinated Peptide antibodies were measured using the ELISA. The results showed elevated serum levels of IL32 and IL37 in patients with RA (P<0.05). The mean duration of RA in most patients was <12 years, and the level of disease activity among the cases group was mainly moderate (70%). There was no significant difference between the mean levels of IL32 and IL37 in patients with RA. This study showed that although IL32 and IL37 played an essential role in RA pathogenesis, there was no significant correlation between serum levels of IL32 and IL37 and disease duration or activity.

Keywords: Cytokines, IL32, IL37, Pro-inflammatory cytokine, Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, and inflammatory disorder that mainly affects flexible (synovial) joints but can also affect many other organs and tissues. The pathophysiology of this autoimmune disease is not entirely clear; however, it is known that its development is influenced by genetics. Females have a three-fold greater prevalence of RA than males. After the age of 25, there is a higher chance of getting this disease, and populations between the age of 35 and 55 are more likely to be affected. The systemic symptoms of RA, such as skeletal, pulmonary, cardiovascular, and psychological issues, include synovial inflammation, hyperplasia (swelling), the production of autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody, destruction of cartilage and bone (deformity), as well as the swelling of the synovium (1).

Pro-inflammatory and anti-inflammatory cytokines play a significant role in the initiation and continuation of the chronic inflammatory process in the synovial membrane of RA patients. Rheumatoid synovial tissue contains high concentrations of monokines but low concentrations of lymphokines. The peripheral blood and synovial fluid of RA patients have significantly higher levels of pro-inflammatory cytokines, including Interleukin-1 (IL1) and Tumor necrosis factor-alpha, which promote the growth of the synovial tissue and

joint erosion (2). Inflammation, immunological diseases, cellular differentiation, and immune response control are all mediated by cytokines. In particular, it has been established that novel inflammatory mediators, such as IL32 and IL37, and the cell-signaling events they are associated with play a part in RA and experimental arthritis (3). IL32 is induced by IL18 in natural killer (NK) cells and was previously thought to be an NK transcript (4). Many different types of cells, such as NK cells, mast cells, epithelial cells, keratinocytes, T lymphocytes, and monocytes, express IL32. Studies have demonstrated that IL32 contributes to the pathogenesis of RA due to its increased production of autoimmune-related substances, such as pro-inflammatory cytokines and chemokines (4).

IL37 was initially referred to as IL-1F7 (IL-1 Family Member 7), but its name was later altered to IL37 (5). The anti-inflammatory cytokine IL37 inhibits immune responses by reducing the production of pro-inflammatory cytokines, such as tumor necrosis factor, IL-1α, IL-1ß, and IL-6 (6). The activities of both pro-inflammatory and anti-inflammatory cytokines, which have been found in large quantities in RA patients, influence the severity of the condition. Joint injury is caused when these opposite cytokine activities are out of balance (7).

This study aims to estimate serum levels of IL32 and IL37 and their association with disease duration and activity in patients with RA.

2. Materials and Methods

2.1. Sampling

A case-control study was conducted in the Rheumatology Consultation Clinic of Baghdad Teaching Hospital /Medical City Complex, Baghdad, Iraq, on RA clinical examinations diagnosed according to the American College of Rheumatology/European League against Rheumatism ACR/EULAR 2010 criteria. A total of 50 RA patients (46 females and four males) and 40 healthy participants were included in the study, which was performed from November 2021 to March 2022.

2.2. Clinical Examination

Clinical examination, including the assessment of the disease activity by the clinical disease activity index (CDAI), was conducted on all patients. The disease activity was interpreted as either remission (CDAI<2.8), low (CDAI=2.8-10), moderate (CDAI=10-22), or high (CDAI>22) (8). All patients and controls were subjected to routine laboratory investigations, including the Erythrocyte sedimentation rate (ESR) by the Westergren tube, C-Reactive protein (CRP), Rheumatoid factor (RF), and Anti-Cyclic Citrullinated Peptide antibodies (ACPA), by the enzyme-linked immunosorbent assay (ELISA).

2.3. Measurement of Serum Levels of IL32 and IL37

Specific laboratory investigations were performed according to the manufacturer's protocol to measure serum levels of IL32 and IL37 by the sandwich ELISA (MyBioSource, USA). The optical density was measured at 450 nm in a microplate reader, and the concentration of IL32 and IL37 was calculated**.**

2.4. Statistical Analysis

Data were entered, checked, and analyzed using the SPSS (version 26) and STATISTICA (version 9). Descriptive statistics were used in the form of frequency distribution tables, numbers, and percentages for qualitative data and mean, standard deviation, and range for quantitative data. Unpaired t-test, One-Way ANOVA test, and the Chi-squared test (alternative Likelihood ratio) were used to identify significant differences between the cases and controls regarding different quantitative and categorical parameters. A *P*-value of <0.05 was used to determine statistical significance throughout the study.

3. Results

A total of 90 samples were investigated, including cases and the control group. The study samples were aged 23 to 72 years, and most of them were in the age group of 51-60 (34.4%). The mean age of the cases group was 48.92±10.700 years, and they were mainly

in the age group of 51-60 (36%). On the other hand, the mean of the controls was 46.0±11.944, and they were mainly in the age group of 51-60 (32.5%) with no significant differences among them (*t*=-1.222, df: 88, *P*=0.225), which reflects the matching purpose of sample selection. Moreover, the entire study sample was female-dominant (cases=92.2% and the control=92.5%) (Table 1).

In addition, the mean duration of RA was 8.42±5.466, with most of the patients suffering being <12 years (80%) (Figure 1).

The level of disease activity among the cases group was mainly moderate (70%), followed by low and high (20% and 10%) (Figure 2).

For blood parameters among the study groups, it has been found that the mean level of ESR was significantly higher in the cases group than in the control group (42.52±21.205 vs. 12.18±5.310, respectively; *P*<0.05). Similarly, the mean level of CRP was significantly higher in the cases group than in the control group (2.77484±1.438752 vs. 1.17528±0.502372, respectively; *P*<0.05). The mean levels of ACPA and RF were also significantly higher in the cases group of RA than in the RA control group (0.36290±0.120678 vs. 0.23463±0.029051 and 0.29276±0.144911 vs. 0.19488±0.25063, respectively; *P*<0.05) (Table 2).

Table 1. The characteristics of the cases and control groups (n=90)

Characteristics	Study groups Rheumatoid arthritis			
	Cases (n=50)	Control (n=40)		Significance
		Age (years)		
Mean ± SD	48.92 ± 10.700	46.0 ± 11.944	47.62 ± 11.299	*t*= -1.222, df: 88, *P*= 0.255[a]
Range (min-max)	47 (25- 71)	41 (23- 64)	49 (23- 72)	
		Age (In groups)		
<31	4 (8)	6 (15)	10 (11.2)	x^2: 3.379, df: 4, *P* = 0.496 [b]
31-40	8 (16)	10 (25)	18 (20)	
41-50	15 (30)	7 (17.5)	22 (24.4)	
51-60	18 (36)	13 (32.5)	31 (34.4)	
≥ 61	5 (10)	4 (10)	9 (10)	
		Gender		
Female	46 (92)	37 (92.5)	83 (92.2)	Likelihood Ratio: 0.008, df: 1, *P* = 0.930 [b]
Male	4 (8)	3 (7.5)	7 (7.8)	

[a]: Unpaired T-Test, [b]: Likelihood Ratio (alternative to Chi-Square Test)

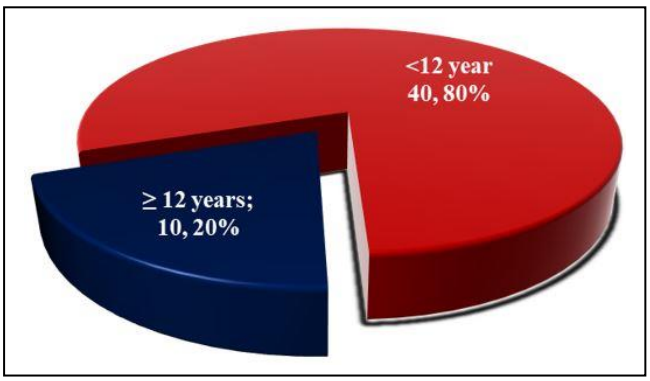

Figure 1. Distribution of duration of Rheumatoid arthritis among cases group (n= 50)

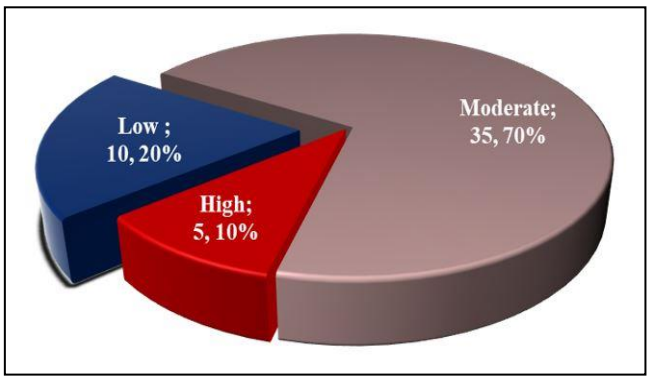

Figure 2. Distribution of activity level of Rheumatoid arthritis among cases group (n= 50)

Table 2. Mean comparison of blood parameters among study groups (n=90)

Blood Parameters (Mean ± SD)	Study groups (n=90)		Mean differences	Significance [a]
	Cases (n=50)	Control (n=40)		
(ESR)	42.52 ± 21.205	12.18 ± 5.310	-30.345	*t*= -8.823, df:88, *P*= 0.000
(CRP)	2.77484 ± 1.438752	1.17528 ± 0.502372	-1.599565	*t*= -6.706, df:88, *P*= 0.000
ACPA	0.36290 ± 0.120678	0.23463 ± 0.029051	-0.128275	*t*= -6.565, df:88, *P*= 0.000
RF	0.29276 ± 0.144911	0.19488 ± 0.25063	-0.097885	t= -4.217, df:88, P= 0.000

a: Unpaired T-Test

Significant differences were identified between the study groups regarding the immunological parameters of IL32 and IL37. The mean level of IL32 was significantly higher in the cases group than in the control group (145.54624±21.572666 vs. 88.35078±12.593109, respectively; $P<0.05$). Furthermore, the mean level of IL37 was significantly higher in the cases group than in the control group (337.19326±80.576575 vs. 165.06718±30.727720, respectively; $P<0.05$) (Table 3).

Regarding the association between immunological parameters and disease duration in the cases group, no significant differences were identified between the mean levels of IL32 and IL37 in patients with RA with a duration of either less or more than 12 years ($P>0.05$) (Table 4).

Regarding the association between immunological parameters and disease activity in the cases group, no significant differences were identified between the mean levels of IL32 and IL37 among patients with RA with low, moderate, and high disease activity scores (Table 5).

Table 3. Mean comparison of immunological parameters among study groups (n=90)

Immunological Parameters (Mean ± SD)	Study groups (n=90)		Mean differences	Significance [a]
	Cases (n=50)	Control (n=40)		
Interleukin-32 (IL-32)	145.54624 ± 21.572666	88.35078 ± 12.593109	-57.195465	*t*= -14.855, df:88, *P*= 0.000
Interleukin-37 (IL-37)	337.19326 ± 80.576575	165.06718 ± 30.727720	-172.126085	*t*= -12.776, df:88, *P*= 0.000

a: Unpaired T-Test

Table 4. Mean comparison of immunological parameters among cases groups' disease duration (n=50)

Immunological Parameters (Mean ± SD)	Disease duration (n=50)		Mean differences	Significance [a]
	< 12 years (n=40)	≥ 12 years (n=10)		
Interleukin-32 (IL-32)	146.10505 ± 21.729485	143.31100 ± 21.925408	2.794050	*t*= 0.363, df:48, *P*= 0.718
Interleukin-37 (IL-37)	331.03683 ± 80.590110	361.81900 ± 79.763840	-30.782175	*t*= -1.082, df:48, *P*= 0.284

a: Unpaired T-Test

Table 5. Mean comparison of immunological parameters among cases groups' disease duration (n=50)

Immunological Parameters (Mean ± SD)	Disease activity (n=50)			Significance [a]
	Low (n=10)	Moderate (n=35)	High(n=5)	
Interlukin-32 (IL-32)	145.20000±18.022893	145.93460±22.753103	143.52020±23.723755	*F*= 0.028, df: (2,47), *P*= 0.973
Interlukin-37 (IL-37)	356.48060±117.291741	332.76269±73.601397	329.63260±36.891568	*F*= 0.353, df: (2,47), *P*= 0.705

a: One-way ANOVA Test

4. Discussion

Rheumatoid arthritis is a disorder that affects the immune system, and there is no specific age for the disease to occur (9). This study showed the distribution of rheumatism based on age in patients 25-71, with an average age of 48.92±10.700 years. Al-Rubaye, Kadhim (10) showed that the average age of onset was between 30 and 70 years, while the results of the study by Alwan, Abdul-Ridha (11) showed the mean age of patients was 42.22±11.23 years. The current results revealed that the rate of RA was higher in female patients (92%) than in males (8%). Ibrahem M. Siam and Monir (12), (13) also showed that RA is more common in women than men. Hormonal changes during puberty, pregnancy, hormone replacement therapy, and menopause, hormonal differences, as well as genetic and environmental factors, may play a complex role in promoting the immune system dysfunction toward an autoimmune process, as evidenced by autoimmune disease onsets and fluctuations (9).

According to a study conducted in Egypt by Gamal, Mahran (14), RA significantly affects patients' quality of life in terms of their health. The disease duration was the most critical element affecting both physical and mental functions. The findings of the study by Vazquez-Del Mercado, Gomez-Banuelos (15) suggested that the duration of an RA patient's condition is a predictor of vascular stiffness. Arterial stiffness caused by vascular remodeling and the loss of arterial elasticity is becoming more widely recognized as a cardiovascular disease surrogate sign. The measurement of vascular stiffness could be used to help RA patients stratify the cardiovascular risk.

The study results by Salaffi, Di Carlo (16) showed that CDAI has the advantage of excluding acute phase reactants, which is determined by adding the Swollen Joint Count, Tender Joint Count, Patient Global Health Assessment, and PhGA together in an algebraic sum. It is very useful in daily clinical practice and can be estimated at any time; therefore, according to this perspective, Gorial showed that the ability to predict the outcome and effectiveness of therapeutic interventions during the follow-up depends on assessing RA disease activity (17). The CDAI is an easy-to-use instrument for assessing disease activity. Compared to Disease Activity Score 28, the CDAI is a relevant and practical assessment tool for Iraqi patients with active RA.

The present findings demonstrated increased ESR levels in RA patients, compared to the control group. An increase in inflammatory activity caused by one or more illnesses, such as autoimmune diseases, infections, or malignancies, may be detected and tracked by ESR, as a routine hematology test. To identify the presence of elevated inflammatory activity, the ESR is utilized in conjunction with other tests and is not specific for other conditions (18). The findings of the study by Subhi, Zgair (19) in Iraq showed a significant difference in ESR levels between patients and the healthy controls. Another study by Abd El-Aziz and Mohamed (20) demonstrated that in Egyptian patients with RA, the ESR level increased, compared to the control group. CRP was critical for the inflammatory response and the host defense system against pathogens (21). In the present study, CRP was reported at a significantly higher level in RA patients, compared to the healthy controls. The results of the study by Ahmad and Zgair (22) showed a significant elevation in the CRP level in patients, compared to the healthy control group. Additionally, the results of the study by Abdulrazzaq and Hadi (23) revealed that CRP levels were significantly higher in patients than in the control group. These findings are consistent with the present results. The present study showed that the level of ACPA was significantly higher in patients than in the healthy controls, which was consistent with the findings of the study by Salama, El-Ragehy (1), demonstrating that anti-CCP antibodies were significantly higher in the RA group than in the control group. Another study by Alwan, Abdul-Ridha (11) showed that the difference between patients and the

controls was highly significant as most RA patients had a positive Anti-CCP (91.3%). The 1987 ACR categorization criteria for RA employed RFs, antibodies that recognize the Fc-tail of immunoglobulin (Ig)-Gs, as the initial type of autoantibodies found in RA. The Fc-part of IgG, which serves as the antigen binding site for RF, has supported the idea that RA is an infection-related disease (24).

The present study showed that patients with rheumatoid had significantly high levels of RF when compared to the healthy controls. This result is consistent with other studies reporting that RF showed significantly higher levels in RA patients than in healthy individuals (25, 26). In the current study, IL32 showed a higher level in RA patients than in healthy subjects. The results showed no significant differences between IL32 concentration and the duration of RA disease. On the other hand, the study demonstrated no significant differences between serum levels of IL32 and the activity of the disease measured by CDAI as low, moderate, or high activity. The study results by Damen, Schraa (27) showed significantly higher IL32 levels in RA patients than in healthy individuals, which is consistent with the results of the current study. Another study by Gualberto Cardoso, Diniz Lopes Marques (28) reported that IL32 levels were significantly higher in Brazilian RA patients than in the controls. The reduction of IL32 activity may be helpful for RA patients, and the level of cytokines is crucial in the pathophysiology of the disease (29). Gui, Zhang (30) discovered associations between IL32 concentrations and disease activity. The mean serum levels of IL37 showed a significant increase in RA patients, compared to the healthy controls. The treatment used for RA patients could not lower the level of IL37 to a level comparable to that of healthy people. The current study showed no significant differences regarding the association between the levels of IL37 and disease duration, whether it was <12 years or >12 years. Furthermore, based on the current study results, there are no significant differences concerning the association between the levels of IL37 and low, moderate, and high disease activity evaluated by the CDAI. The study results of Mohammad *et al.* in Iraq showed a significant difference between patients and the controls by increasing the level of IL37 in patients with RA (31). The increasing level of IL37 in RA can be interpreted as the underlying mechanism for reducing joint inflammation and the severity of the disease. However, it is still insufficient to counteract the adverse effects of the RA's progressing pro-inflammatory cytokines (32). Another study by Cao, Shi (33) revealed elevated serum IL37 concentrations in Chinese RA patients, and the level of IL37 was strongly linked with RA disease activity.

The findings of the study by Baraka, Balata (34) showed that the serum levels of IL37 significantly increased in RA patients, compared to the healthy controls, and the mean serum levels of IL37 increased in RA patients with severe/moderate compared to mild disease activity. Furthermore, the RA patients treated with bDMARDs had significantly lower disease activity and significantly lower serum IL37 levels than those treated with DMARDs. IL37, which is closely associated with disease activities and may have a protective role in RA, increases along with the inflammatory response and the pro-inflammatory cytokine TNF-α, which is a significant factor in the onset of RA (35).

In conclusion, serum IL32 and IL37 levels increased in patients with RA, and there were no significant differences regarding the association between the levels of IL32 and IL37 and disease duration, as well as disease activity.

Authors' Contribution

Study concept and design: E. M. J.
Acquisition of data: S. K. J.
Analysis and interpretation of data: N. I. A.
Drafting of the manuscript: E. M. J.
Critical revision of the manuscript for important intellectual content: S. K. J.
Statistical analysis: N. I. A.
Administrative, technical, and material support: E. M. J.

Ethics

Approval of this study was obtained from the Medical College of Al-Iraqi University and the Ministry of Health. Consent was also obtained from all participants.

Conflict of Interest

The authors declare that they have no conflict of interest.

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