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Interleukin-37 as an anti-inflammatory cytokine: does its relation to disease activity suggest its potential role in rheumatoid arthritis therapy?

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Abstract

Background: This study aimed to measure the serum and synovial interleukin (IL)-37 levels in rheumatoid arthritis (RA) patients compared to patients with primary knee osteoarthritis (PKOA) and healthy controls and to detect its relation to RA disease activity.

Results: This cross-sectional study included 50 RA patients with a mean age of 40.24 ± 8.62 years, 50 patients with PKOA with a mean age of 56.69 ± 4.21 , and 40 healthy controls with a mean age of 41.75 ± 7.38 years. The mean serum IL-37 level in the RA patients (382.6 ± 73.97 pg/ml) was statistically significantly ($P < 0.001$) the highest among the studied groups; however, it showed a non-significant difference between the PKOA patients (70.38 ± 27.49 pg/ml) and the healthy controls (69.97 ± 25.12 pg/ml) ($P > 0.94$). Both serum and synovial IL-37 levels were significantly positively correlated with disease activity scores ($r = 0.92$, $P < 0.001$ and $r = 0.85$, $P < 0.001$), tender joint counts ($r = 0.83$, $P < 0.001$ and $r = 0.82$, $P < 0.001$), swollen joint counts ($r = 0.72$, $P < 0.001$ and $r = 0.60$, $P < 0.001$), visual analog scale ($r = 0.82$, $P < 0.001$ and $r = 0.82$, $P < 0.001$), erythrocyte sedimentation rate ($r = 0.75$, $P < 0.001$ and $r = 0.65$, $P < 0.001$), and C-reactive protein ($r = 0.93$, $P < 0.001$ and $r = 0.79$, $P < 0.001$), respectively.

Conclusion: Serum and synovial IL-37 were significantly elevated in the RA patients, and they were closely correlated. Being less invasive, the serum IL-37 could be a marker of disease activity and could reflect the effective disease control by drugs. Having an anti-inflammatory effect could not suggest IL-37 as the key player to control inflammation alone, but its combination with other anti-proinflammatory cytokines could be investigated.

Keywords: Rheumatoid arthritis, Interleukin-37, Disease activity

Background

Rheumatoid arthritis (RA) is an autoimmune chronic systemic inflammatory disease affecting mainly the peripheral joints with a predilection to the small joints of hands and feet with finger deformities [1], marked disability, and bad quality of life [2].

The yearly rate of RA had been estimated to be around 0.5 with a prevalence of 1 to 2%, which is greatly different according to ethnic and geographic distribution [3].

The actual etiopathogenesis of RA remains unknown; however, autoimmunity and systemic inflammation are the main keys in the pathogenesis process which is ascertained by detection of auto-antibodies including rheumatoid factor (RF) and anti-cyclic citrullinated protein antibodies (Anti-CCP Abs) [4].

Immune dysregulation along with inflammatory cells attacking the synovial lining of the joints leads to thickening and hyperplasia with pannus and cartilage

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destruction; moreover, cytokines play a pivotal role in disease progression through an imbalance between pro-inflammatory and anti-inflammatory cytokines [5, 6].

One of the recently encountered cytokines in the pathogenesis of RA is interleukin-37 (IL-37) previously known as IL1F7, which is a member of the IL-1 family that includes seven agonists (IL-1 α , IL-1 β , IL-18, IL-33, IL-36 α , IL-36 β , and IL-36 γ) and four antagonists (IL-1 receptor antagonists (Ra), IL-36Ra, IL-37, and IL-38) [7].

IL-37 is expressed in several tissues as in the thymus, bone marrow, lymph nodes, liver, lung, testis, placenta, uterus, colon, and various inflammatory cells including the natural killer cells, monocytes, stimulated B cells, and keratinocytes [8], where it is induced and upregulated in response to many inflammatory stimuli such as toll-like receptors (TLRs) agonists, IL-1 β , tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), IL-18, and transforming growth factor- β 1 (TGF- β 1) and lipopolysaccharide (LPS) [9].

Upon its induction, IL-37 is secreted extracellularly and binds to IL-18 receptor α (IL-18R α) at the plasma membrane; IL-18 tends to recruit IL-18 R β chain and forms a tripartite complex; moreover, IL-37 can be translocated into the nucleus and perform regulatory functions on gene transcription upon binding to the nuclear DNA which suppresses the inflammation and decreases the production of pro-inflammatory cytokines and chemokines [9, 10].

IL-37 as an anti-inflammatory cytokine has been proposed to play a role in the pathogenesis of inflammatory, autoimmune, and metabolic disorders, and cancers, which makes it a potential target of therapy [11, 12]. This study aimed to measure the serum and synovial interleukin (IL)-37 levels in RA patients compared to PKOA patients and healthy controls and to detect its relation to RA disease activity.

Methods

Study participants

This cross-sectional study included 50 adult RA patients, fulfilling the American College of Rheumatology and European League Against Rheumatism 2010 criteria for the classification of RA [13] from those attending the outpatient clinic of the hospital in the period between March and June 2020. Fifty patients with primary degenerative knee osteoarthritis (PKOA) were diagnosed according to the ACR clinical and laboratory classification criteria [14], added to the Kellgren and Lawrence radiographic criteria for the classification of PKOA [15]. Forty healthy volunteers from the hospital workers and their relatives, who were age- and sex-matched to the RA patients and had no symptoms or signs suggestive of any connective tissue disease or radiographic OA, served as controls.

Inclusion criteria

RA patients' age should be between 18 and 50 years old. Patients with PKOA should have osteophyte-defined radiographic OA ≥ 2 according to Kellgren and Lawrence classification system and effusion in at least one knee at the time of the study.

Exclusion criteria

Patients with erosive osteoarthritis, RA patients with radiological evidence of secondary OA, intra-articular corticosteroid injection in the knee in the previous 6 months, other rheumatological diseases (e.g., systemic lupus erythematosus, systemic sclerosis, and spondyloarthropathies), chronic liver and kidney diseases, malignancy, and pregnant were excluded.

This study was approved by the local Ethics Committee of our hospital, and all subjects signed a written informed consent before participation in the study.

Clinical assessment

All RA and PKOA patients had been evaluated by full history taking and a thorough clinical examination with a special emphasis on the disease duration, duration of morning stiffness, recording the number of tender and swollen peripheral joints, the presence of knee swelling (effusion or bony enlargement), and the medical history regarding the treatment at the time of the study.

RA patients' global assessment and knee pain severity in PKOA patients were assessed with a visual analog scale (VAS) on a scale from 0 to 10, where lower scores indicate lower levels of clinical symptoms or pain [16].

Disease Activity Score with the erythrocyte sedimentation rate (DAS28-ESR) was calculated electronically (<http://www.das-score.nl>) for the RA patients, and accordingly, they were grouped into 4 groups: remission (DAS28 ≤ 2.6), mild ($2.6 < \text{DAS28} \leq 3.2$), moderate ($3.2 < \text{DAS28} \leq 5.1$), and severe ($5.1 < \text{DAS28}$).

Laboratory tests

Five milliliters of blood was collected by venipuncture from the patients on the same day of the clinical assessment.

The ESR was determined by the Westergren technique, and the value in the first hour (1st h) was saved, C-reactive protein (CRP) and rheumatoid factor (RF) were determined by immune-nephelometry assay, and anti-cyclic citrullinated peptide antibodies (CCP Abs) was measured by chemiluminescent microparticle immunoassay (CMIA) using architect I 2000 (Abbott Laboratories, Abbott Park, IL, USA).

Measurement of IL-37 level

Synovial fluid samples were withdrawn from the knee of 29 RA patients, guided by musculoskeletal ultrasonography

(MSUS) (lateral, medial joint, and supra-patellar recesses). MSUS-guided aspiration was done using a (LOGIQ e GE Healthcare, Wauwatosa, USA) machine with a multilinear high-frequency (8–13 MHz) transducer.

About 2 ml of venous blood was obtained and allowed to clot for 30 min; then, the sera were separated. Both samples were stored at -80°C till used in the enzyme-linked immunosorbent assay (ELISA). The serum and synovial levels of IL-37 were measured using a quantitative sandwich enzyme immunoassay (EIA ab, China). The provided microplate is coated with IL-37-specific antibodies. Serial dilutions of the standard containing human IL-37 were used to get the standard curve. The samples, together with the standard dilution, were added to the microtiter plate and incubated for 2 h. After that, the liquid was removed, and the bound IL-37 was detected by adding biotin-conjugated antibodies specific for IL-37. After incubation and washing, avidin conjugated to horseradish peroxidase (HRP) was added. After second incubation and washing procedures, tetramethylbenzidine-containing substrate was added, and color developed in proportion to the amount of bound IL-37. After the specified incubation period, the color development is stopped by the addition of an acid stop solution. Then, the optical density was measured by the ELISA plate reader at 450 nm.

Radiological tests

Plain X-ray of both knees (Antero-posterior and lateral views) was done on all the patients and controls. PKOA was defined if the patients have a score of ≥ 2 according to Kellgren and Lawrence classification system [15].

Statistical methods

Data were presented as means \pm standard deviation (SD), median and interquartile range (IQR), or numbers and percentages. The significance of difference was tested using Student's *t*-test to compare the mean of two groups of parametric data and the ANOVA test to compare the mean of $>$ two groups of parametric data. For continuous non-parametric data, Mann-Whitney *U* test was used. Chi-square test was used for categorical parameters. Spearman's relationship coefficient was considered.

The cutoff levels of the serum and synovial IL-37 were tested using the receiver operating characteristic curve. A statistical significance is considered when a *P* value was ≤ 0.05 , and a *P* value < 0.001 was considered highly significant. All data were tabulated, coded, and analyzed using STATA/SE version 11.2 for Windows.

Results

This cross-sectional study included 50 RA patients with a mean age of 40.24 ± 8.62 years, 50 PKOA patients with

a mean age of 56.69 ± 4.21 , and 40 healthy controls with a mean age of 41.75 ± 7.38 years (Table 1). We aimed to include radiologically diagnosed PKOA patients to compare the synovial level of IL-37 in RA and another non-inflammatory disease as OA that is prevalent among the old people, and the patients with PKOA were statistically significantly older than the RA patients ($P < 0.001$) and the healthy controls ($P < 0.001$) while both RA patients and healthy control were matched for age ($P = 0.38$). There was no significant statistical difference ($P = 0.4$) between the studied group as regards the sex (Table 1).

The mean disease duration, as well as the median duration of morning stiffness, was statistically significantly longer in the RA patients than the patients with PKOA ($P < 0.001$) (Table 2).

The tender joint count in the RA patients ranged from 0 to 11 with a median of 1 and an IQR of 1–2, while the number of swollen joints ranged from 0 to 5 with a median of 1 and an IQR of 1–2 (Table 2).

DAS scores of the RA patients ranged from 1.6 to 6.2 with a mean of 3.37 ± 1.26 . Seven (14%) RA patients had severe disease activity, 10 (30%) were moderately active, 20 (40%) patients had mild disease activity, and 13 (26%) RA patients were in remission at the time of the study.

Clinical and laboratory features of the RA and PKOA patient groups are shown in Table 2.

The mean serum level of IL-37 in the RA patients (382.6 ± 73.97 pg/ml) was statistically significantly ($P < 0.001$) the highest among the studied groups; however, it was not statistically significantly different between the PKOA patients (70.38 ± 27.49 pg/ml) and the healthy controls (69.97 ± 25.12 pg/ml) ($P > 0.94$). Regarding the serum IL-37, at a cutoff level of 295 pg/ml, 41 RA patients had significantly elevated serum IL-37 levels with a sensitivity of 82%.

Twenty-nine RA patients were presented by knee effusion at the time of the study. The mean IL-37 synovial level (625.44 ± 73.92 pg/ml) was statistically significantly higher than its serum level (382.6 ± 73.97 pg/ml) in the RA patients ($P < 0.001$) while there was no statistically significant difference between the mean synovial and serum IL-37 levels (80.8 ± 27.66 pg/ml and 70.38 ± 27.49 pg/ml,

Table 1 Descriptive demographic data of the studied groups

Variables	RA patients	PKOA	Control	<i>P</i>
Age (years)				$< 0.001^*$
Range	20–50	52–65	39–58	$P1 < 0.001^*$ $P2 = 0.38$
Mean \pm SD	40.24 ± 8.62	56.69 ± 4.21	41.75 ± 7.38	$P3 < 0.001^*$
Sex M/F	16/34	22/28	13/27	0.4

RA rheumatoid arthritis, PKOA primary knee osteoarthritis, SD standard deviation, M male, F female, $P \leq 0.05^*$ significant difference, $P > 0.05$ non-significant, $P1$ difference between RA and PKOA patients regarding the mean age, $P2$ difference between RA patients and healthy control groups regarding the mean age, $P3$ difference between PKOA patients and healthy control groups regarding the mean age

Table 2 Clinical and laboratory characteristics of the rheumatoid arthritis and primary knee osteoarthritis patients

	RA	PKOA	P
Disease duration (years)			0.005*
Range	2–17	1.5–15	
(Mean ± SD)	(6.94 ± 2.98)	(4.69 ± 3.21)	
Morning stiffness duration (min)			< 0.001*
Median (IQR)	45 (20–60)	15 (10–25)	
VAS			0.64
Range	0–9.5	0–8.5	
(Mean ± SD)	(3.85 ± 2.78)	(4.09 ± 2.35)	
ESR mm/1 st h			< 0.001*
Range	10–90	8–17	
Median (IQR)	20 (13–32.25)	12 (10–15)	
CRP mg/dl			< 0.001*
Range	2–33	2–5	
Median (IQR)	12 (5.5–15)	4(2–5)	
RF (positive)	41/50	5/50	< 0.001*
RF titer IU/ml			
Range	8–220	–	
Mean ± SD	48 (28–73.3)		
Positive Anti-CCP titer U/ml	31/50	0/50	
Anti-CCP Abs titer U/ml	5–70	–	
	29.5 (17.5–39.5)		

RA rheumatoid arthritis, PKOA primary knee osteoarthritis, SD standard deviation, IQR inter-quartile range, VAS visual analog scale, ESR mm/1st h erythrocyte sedimentation rate in the first hour in millimeter, CRP C-reactive protein, mg/dl milligram per deciliter, RF rheumatoid factor, IU international unit, CCP Abs cyclic citrullinated peptide antibodies, U/ml unit/milliliter, P > 0.05 non-significant, P ≤ 0.05*significant

respectively) in the PKOA patients, P = 0.06 (Table 3 and Fig. 1). Regarding the synovial IL-37, at a cutoff level of 559 pg/ml, 25 RA patients had significantly elevated synovial IL-37 levels with a sensitivity of 86.2%.

The mean serum and synovial levels of IL-37 were statistically significantly increased in the RA patients with severe/moderate disease activity (P < 0.001) compared to the RA patients who had mild disease activity and who were in remission (Table 4).

All RA patients were on hydroxychloroquine (200–400 mg) ± NSAIDs or corticosteroid (5–20 mg/day) as needed. Twenty-six (26) RA patients were receiving methotrexate (7.5–25 mg/week), MTX + leflunomide (10 patients), etanercept + MTX (4 patients), adalimumab (7 patients), and tocilizumab (3 patients). The RA patients who were receiving biological disease-modifying anti-rheumatic drugs (bDMARDs) had statistically significantly less active disease and significantly lower serum

Table 3 Comparison between the mean serum and synovial levels of IL-37 in the studied groups

IL-37 (Mean ± SD)	Studied groups			P
	RA patients	PKOA	Healthy control	
	Range (mean ± SD)			
Serum IL-37 pg/ml	250–550	21–122	22–110	< 0.001*
	382.6 ± 73.97	70.38 ± 27.49	69.97 ± 25.12	P1 < 0.001* P2 < 0.001* P3 = 0.94
Synovial IL-37 pg/ml	450–780	23–142	–	< 0.001*
	625.44 ± 73.92	80.8 ± 27.66		
P	< 0.001*	0.06		

RA rheumatoid arthritis, PKOA primary knee osteoarthritis, IL-37 interleukin-37, SD standard deviation, pg/ml picogram per milliliter, P ≤ 0.05* significant difference, P > 0.05 non-significant, P1 difference between RA and POA patients regarding the mean serum IL-37 level, P2 difference between RA patients and healthy control groups regarding the mean serum IL-37 level, P3 difference between PKOA patients and healthy control groups regarding the mean serum IL-37 level

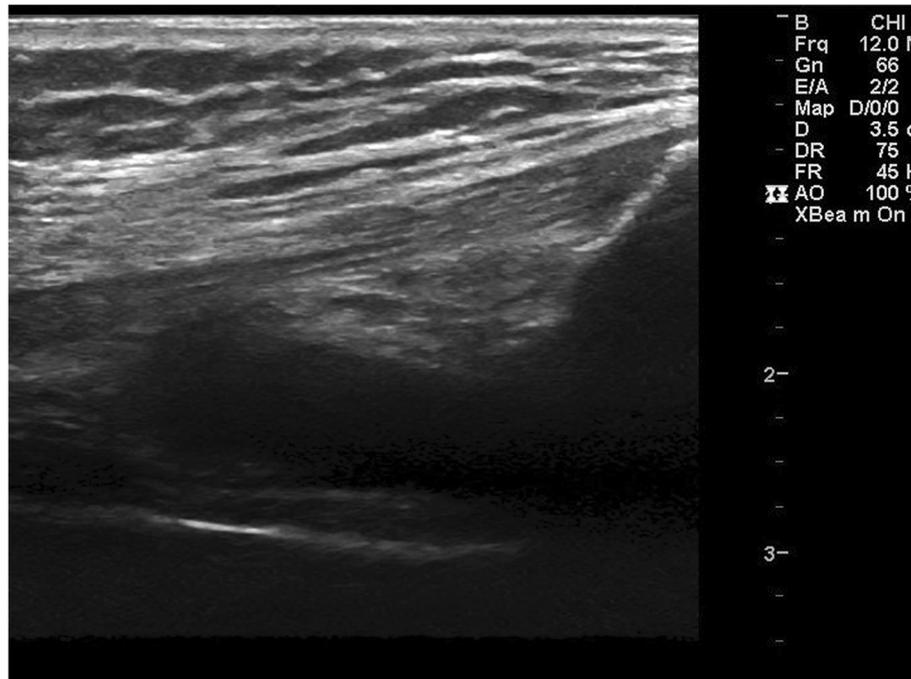


Fig. 1 Moderate right knee synovial effusion in the supra-patellar bursa of a 38-year-old female RA patient with a disease duration of 8 years and DAS-28 score of 4.5. She had combined high serum and synovial IL-37 of 440 pg/ml and 670 pg/ml respectively, and she was receiving MTX 17.5 mg/week. RA, rheumatoid arthritis; DAS, disease activity score; IL-37, interleukin 37; MTX, methotrexate. Straight arrow, quadriceps tendon; curved arrow, upper border of the patella; star, suprapatellar effusion

IL-37 levels than those who were receiving conventional synthetic DMARDs (Table 5).

The serum and synovial levels of IL-37 showed significant positive correlations with DAS scores ($r = 0.92, P < 0.001$ and $r = 0.85, P < 0.001$) as well as with the individual parameters of disease activity including tender joint counts ($r = 0.83, P < 0.001$ and $r = 0.82, P < 0.001$), swollen joint counts ($r = 0.72, P < 0.001$ and $r = 0.60, P < 0.001$), and VAS ($r = 0.82, P < 0.001$ and $r = 0.82, P < 0.001$), respectively. There were statistically significant positive correlations between the serum and synovial levels of IL-37 and the inflammatory markers including the ESR ($r = 0.75, P < 0.001$ and $r = 0.65, P < 0.001$) and CRP ($r = 0.93, P < 0.001$ and $r = 0.79, P < 0.001$) while they were not significantly correlated with RF ($r = 0.02, P = 0.38$ and $r = 0.28, P = 0.13$) or Anti-CCP Abs titers ($r = 0.23, P = 0.1$ and $r = 0.02, P =$

0.89), respectively. It was noticeable that both the serum and the synovial IL-37 levels were significantly positively correlated ($r = 0.90, P < 0.0001$) (Table 6).

Discussion

Rheumatoid arthritis (RA) is a prevalent autoimmune inflammatory arthritis obviously affecting the quality of life [17], with a complex affection of different body organs and extra-articular manifestation causing real disability [18].

The exact etiology of RA remains uncertain, where it targets primarily the synovium causing synovial hypertrophy with bone erosions, cartilage destruction, and subsequent progressive joint damage and deformity [18]. Understanding the mechanisms and mediators that are engaged in the RA pathogenesis is ultimate [19]. All the components of the innate and

Table 4 Comparison between the mean serum and synovial IL-37 levels in the RA group in respect to the disease activity (DAS-28)

IL-37 (Mean ± SD)	DAS-28 (50, 100%)		P
	Severe/moderate (17, 44%) (Mean ± SD)	Mild/remission (33, 56%)	
Serum IL 37 pg/ml	457.94 ± 48.96	341.77 ± 52.09	< 0.001*
Synovial IL 37 pg/ml	672.64 ± 50.03	556.63 ± 46.61	< 0.001*

RA rheumatoid arthritis, DAS Disease Activity Score, IL-37 interleukin-37, pg/ml picogram per milliliter, $P \leq 0.05$ * significant

Table 5 Comparison between the mean serum and synovial IL-37 levels in the RA group according to the medications

IL-37 (mean ± SD)	RA patients on DMARDs (50, 100%)		P
	RA patient on bDMARDs (14, 28%)	RA patients on csDMARDs (36, 72%)	
Serum IL-37 pg/ml	309.64 ± 45.76	410.97 ± 62.53	< 0.001*
Synovial IL-37 pg/ml	568.33 ± 8.49	632.03 ± 75.28	0.16
DAS-28 score	2.48 ± 0.53	3.95 ± 1.25	0.0001*

RA rheumatoid arthritis, IL-37 interleukin-37, SD standard deviation, bDMARD biological disease-modifying anti-rheumatic drugs, cs conventional synthetic, P ≤ 0.05* significant difference, P > 0.05 non-significant, DAS Disease Activity Score

adaptive immune system were claimed, and various abnormal cellular and humoral immune responses are still under investigation [20, 21].

The innate immune system in RA is persistently activated, and this was confirmed by continued expression of macrophage-derived cytokines such as TNF- α , IL-1, and IL-6 [22] which are claimed to play a role in the osteoclast-induced bone resorption and expansion of the synoviocytes [23, 24]. This is why the biological medications targeting TNF- α and IL-6 are to ameliorate the disease activity and induce remission in active RA patients [25].

Many cytokines orchestrate the process of inflammation and could be divided into inflammatory and anti-inflammatory cytokines and natural cytokine antagonists [20, 21], and any disturbed balance between those pro- and anti-inflammatory cytokines is the cornerstone in inducing the inflammatory response that uniquely characterizes RA pathogenesis [26].

One of the newly recognized cytokines is IL-37, which was initially distinguished as IL-1 family member 7 (IL1F7); however, unlike most of the pro-inflammatory

IL family members, IL-37 has been speculated as a fundamental inhibitor of innate immunity [27, 28].

IL-37 has been reported in previous studies as an anti-inflammatory cytokine in different inflammatory diseases including RA [29], ankylosing spondylitis [30], Graves' disease [31], systemic lupus erythematosus [32], adult Still disease [33], and erosive osteoarthritis [34].

In this current study, we aimed to measure the serum and synovial interleukin (IL)-37 levels in the RA patients compared to patients with PKOA and healthy controls and to detect its relation to RA disease activity.

IL-37 could be detected in a little amount in the sera of the healthy population; our results were similar to previous studies that reported increased serum level of IL-37 in RA patients in comparison to healthy individuals [5, 31, 32, 35].

What's more, this finding is compatible with Nold et al., who have reported greater amounts of IL-37 by immunohistochemical staining of synovial lining from RA patients compared to that of healthy controls [10].

IL-37 acts as a natural suppressor of innate inflammation [12–29]. It has a dual action. Upon its expression in the macrophages and epithelial cells, IL-37 is secreted into the extracellular space and either inhibits the actions of pro-inflammatory cytokines mainly TNF and IL-1 or their receptors [5]. Alternatively, it could be translocated to the nucleus to interrupt the responsible transcription genes and almost completely inhibits the synthesis of the pro-inflammatory cytokines [36].

Taking into account that primary OA and RA are common musculoskeletal disorders and both primarily involve the joints, however, the underlying pathophysiology of each condition is distinct. Typically, RA is an autoimmune condition with subsequent characteristic inflammation while OA differs in the way that a combination of mechanical, cellular, and biochemical processes alters the normal cartilage remodeling process that is magnified by joint movement excessive use leading to abnormal cartilage repair and increased cartilage degradation [37].

In our study, we compared the serum and synovial IL-37 levels in the RA patients and those with PKOA as a prototypic degenerative disease. IL-37 levels were significantly higher in the RA patients than in the patients

Table 6 Correlations of the serum and synovial IL-37 levels with clinical and laboratory characteristics of the RA patients

	Serum IL-37		Synovial IL-37	
	r	P	r	P
Age	- 0.13	0.34	- 0.06	0.72
Disease duration	0.25	0.06	0.34	0.06
Tender joint count	0.83	< 0.001*	0.82	< 0.001*
Swollen joint count	0.72	< 0.001*	0.60	0.0004*
VAS	0.82	< 0.001*	0.82	< 0.001*
ESR (mm/1 st h)	0.75	< 0.001*	0.65	< 0.001*
CRP (mg/dl)	0.93	< 0.001*	0.79	< 0.001*
RF (IU/ml)	0.02	0.38	0.28	0.13
Anti-CCP Abs (U/ml)	0.23	0.1	0.02	0.89
DAS-28	0.92	< 0.001*	0.85	< 0.001*
Serum IL-37 (pg/ml)	-	-	0.90	< 0.001*
Synovial IL-37 (pg/ml)	0.90	< 0.001*	-	-

IL-37 interleukin-37, VAS visual analog scale, ESR mm/1st h erythrocyte sedimentation rate of the first hour in milliliter, CRP C-reactive protein, mg/dl milligram per deciliter, RF rheumatoid factor, IU international unit, CCP Abs cyclic citrullinated peptide antibodies, U/ml unit/milliliter, DAS Disease Activity Score, IL-37 interleukin 37, P > 0.05 non-significant, P ≤ 0.05* significant

with PKOA. We could not detect a significant difference between the PKOA patients and healthy controls regarding the serum IL-37 levels, ensuring that there is no inflammatory process in both groups. These results are in accordance with others who found no significant differences in the IL-37 mRNA and protein levels between the OA patients and the healthy controls [34]. Serum protein and mRNA level of IL-37 were notably elevated in the patients with erosive inflammatory OA compared with PKOA patients as reported by Ding et al. [34]. Erosive OA is a distinct clinical type of OA that is regulated by many pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 and anti-inflammatory cytokines as IL-4, IL-10, and TGF- β . It is frequently misdiagnosed as many inflammatory arthropathies [38–40].

In our study, serum and synovial levels of IL-37 in RA patients were significantly positively correlated with ESR and CRP which are known markers of acute inflammation, in agreement with others [5–32] who showed the same significant correlation.

RF has been the most common serological marker for the diagnosis of RA for a long time; however, it is not specific and can be associated with many other autoimmune or infectious diseases and even in healthy elderly people. On the contrary, anti-CCP Abs reported higher specificity of about 98% in RA diagnosis and strongly can predict the development of RA early before disease onset by more than 20 years and parallel the disease severity in established RA disease [41, 42].

We could not find a significant relationship between the serum or synovial IL-37 and either the RF or Anti-CCP Abs titers which were consistent with a previous study [32]. It was observed that IL-37 expression increased in the CD3+ and CD4+ T cells due to activation of T cells not the B lymphocytes [43]. Considering that RF and anti-CCP could be detected in the RA disease as being an autoimmune disease, however, they are not sufficient to distinguish the active RA patients [32].

In this current study, IL-37 levels were strongly associated with disease activity in the RA patients, which is in agreement with others [31, 35]. Owing to it is anti-inflammatory action, IL-37 was reported to be protective against septic shock [10, 44], DSS-induced colitis [45], concanavalin A-induced hepatitis [46], and in an experimental model of ischemia/reperfusion-induced hepatitis [47]. Experimental studies on the collagen-induced arthritis model of mice revealed that intra-articular injection with IL-37 significantly reduced the severity of knee arthritis [8].

Certainly, RA patients with high disease activity have increased expression levels of circulating pro-inflammatory cytokines that mediate the inflammation and their subsequent joint damage effect; these inflammatory signals and cytokines stimulate IL-37 expression

to suppress the inflammation and ameliorate disease severity as being anti-inflammatory cytokine.

The subsequent release of IL-37 is expected to exert negative feedback control to suppress excessive pro-inflammatory cytokines in RA patients. Unfortunately, this does not occur as the levels of IL-37 remain low in comparison to the levels of inflammatory cytokines and cannot antagonize or suppress their destructive effect with subsequent imbalance between the anti-inflammatory and pro-inflammatory cytokines which promote the ongoing inflammation and disease progression [48–50]. This explained the close association between increased IL-37 levels and RA disease activity. This why in our study, RA patients who had mild disease activity and who were in remission in response to bDMARDs had decreased serum IL-37 levels compared with those patients who were still active.

We could not correlate the IL-37 levels with other inflammatory markers as TNF and IL-6 in RA patients is considered a limitation of our study.

Conclusion

Serum and synovial IL-37 were significantly elevated in the RA patients, and they were closely correlated. Being less invasive, the serum IL-37 could be a marker of disease activity and could reflect the effective disease control by drugs. Having an anti-inflammatory effect could not suggest IL37 as the key player to control inflammation alone, but its combination with other anti-proinflammatory cytokines could be investigated.

Abbreviations

RA: Rheumatoid arthritis; PKO: Primary knee osteoarthritis; IL: Interleukin; DAS: Disease activity score; VAS: Visual analog scale; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ACR/EULAR: American College of Rheumatology and European League Against Rheumatism; RF: Rheumatoid factor; CCP abs: Cyclic citrullinated peptides antibodies; MSUS: Musculoskeletal ultrasonography; MTX: Methotrexate

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Authors' contributions

All authors chose and accepted the concepts of the article. E.B was responsible for manuscript preparation, follow-up data and statistical analysis, and musculoskeletal ultrasonographic-guided aspiration of knee effusion, and is the corresponding author. E.E. was responsible for literature research, case and data collection regarding the patients with rheumatoid arthritis, and manuscript revision. M.B. was responsible for literature research, case and data collection regarding the OA patients, and manuscript editing. S.A and A.K were responsible for the laboratory tests and analysis. The manuscript has been read and approved by all the authors.

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Availability of data and materials

All are available

Ethics approval and consent to participate

The study scheme was reviewed and approved by the ethical committee of scientific research of the Care National Hospital, Riyadh, KSA, according to

the statement of the Helsinki Declaration of 1983. Reference number: CNH_023.

For more information, please contact Dr/M. Kattan (the committee chairman). Tel: 00966507908566.

The study was clarified to all participants who signed an informed written consent before participation according to the ethical committee of scientific research of the Care National Hospital.

Consent for publication

Not applicable.

Competing interests

All authors declare competing interest.

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