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Immunoregulatory Role of Interleukin-37 in Rheumatoid Arthritis; Relation to Disease Activity and Joint Destruction

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Abstract

Background: The Interleukin (IL)-37 is a member of IL-1 cytokines and reported to down-regulate inflammation as a natural suppressor of innate immune responses. We measured serum IL-37 concentration in Rheumatoid Arthritis (RA) patients and analyzed clinical disease activity and radiographic erosion in RA.

Aim of the Study: To throw some light on Interleukin-37 (IL-37) in patients with rheumatoid arthritis and its impact on disease activity and joint damage.

Subject and Methods: 30 patients diagnosed to had Rheumatoid Arthritis (RA) selected from Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation Department, Tanta University Hospitals fulfilling the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria for diagnosis of RA, and 20 apparently healthy individuals matched in age and sex participated as controls. Patients with other autoimmune diseases, acute coronary syndrome or any current infections were excluded. Disease Activity Score in 28 joints (DAS 28) was assessed for all patients; routine laboratory investigations (rheumatoid factor RF, anti-cyclic citrullinated peptide anti CCP, complete blood count CBC, Erythrocyte Sedimentation Rate ESR & C Reactive Protein CRP) and serum level of IL 37 measured by Enzyme-Linked Immunosorbent Assay ELISA were evaluated. Degree of joint destruction was assessed by Larsen score.

Results: Serum IL-37 level was significantly higher in RA patients than control and positively correlated with level of disease activity assessed by DAS-28 score, also with clinical and laboratory indicators of disease activity as well as degree of bone erosion measured by Larsen score.

Conclusion: IL-37 was increased in RA patients and its level was increased with disease activity, so it could prove to be potential biomarker for RA diagnosis, disease activity assessment and curative effect observation.

Key Words: *Rheumatoid arthritis – Immunoregulatory IL-37 activity – Joint destruction.*

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Introduction

RHEUMATOID Arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint inflammation, synovial hyperplasia, progressive destruction of articular cartilage and bone erosion, leading to disability and substantial loss of mobility [1].

Pro-and anti-inflammatory cytokines play a major role in the initiation and perpetuation of the chronic inflammatory process in the synovial membrane of RA patients. Monokines are abundant in rheumatoid synovial tissue, whereas low amounts of lymphokines are found. The levels of pro-inflammatory cytokines, such as Interleukin-1 (IL-1), Tumor Necrotizing Factor-alpha (TNF-a) and Interleukin-23 (IL-23), are significantly increased in the peripheral blood and synovial fluid of RA patients, which contribute to the proliferation of synovial tissue and joint erosion [2].

Blocking these cytokines could partly relieve inflammatory symptoms of RA and reduce disease severity. Therefore, therapies targeting these cytokines or their receptors are recognized as effective treatments for patients with RA [3].

Interleukin-37 (IL-37) is an anti-inflammatory cytokine that inhibits both innate and adaptive immunity by down-regulating pro-inflammatory molecules and pathways. IL-37 is up-regulated as a natural defense mechanism in inflammatory states and in various autoimmune diseases including Rheumatoid Arthritis (RA), weight reduction after gastric banding surgery, Inflammatory Bowel Disease (IBD), hepatitis B and C, Systemic Lupus Erythematosus (SLE), Guillain-Barré Syndrome (GBS), psoriasis, atherosclerosis, and Acute Coronary Syndrome (ACS) [4].

In RA, the expression of IL-37 is mostly controlled by pro-inflammatory cytokines during the acute phase and the recovery phase of RA. Immunohistochemistry staining on the synovial tissue from individuals with active RA demonstrated the presence of large amounts of IL-37 in the diseased synovial lining [5].

The aim of this work is to study serum level of IL-37 in patients with newly diagnosed rheumatoid arthritis and find out its relation with disease activity and degree of bone erosion.

Subjects and Methods

The present study was conducted on thirty rheumatoid arthritis patients diagnosed according to the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2010 criteria for diagnosis of RA [6] on September 2017, patients were selected from outpatient clinic of Physical Medicine, Rheumatology and Rehabilitation Department of Tanta University Hospital and twenty apparently healthy individuals matched in age and sex served as control group. The study was approved by the Ethical Committee of Tanta University and written informed consents were obtained from all participants. Patients with other auto-immune diseases, acute coronary syndrome or current infection were excluded from the study. All patients and controls were subjected to:

A- Clinical assessment medical history and complete clinical examination including assessment of disease activity by Disease Activity Score 28 (DAS 28), the level of disease activity can be interpreted as remission (DAS28 >2.6), low (2.6 ≤ DAS28 >3.2), moderate (3.2 ≤DAS28 ≤5.1), or high (DAS28 <5.1) [7].

B- *Routine laboratory investigations:* Rheumatoid Factor (RF) and C-Reactive Protein (CRP) by latex agglutination method, Anti-Cyclic Citrullinated Peptide antibodies (ACCP) by ELISA, Erythrocyte Sedimentation Rate (ESR) by Westergren tube and complete blood cell count by automated counter.

C- *Specific laboratory investigations:* Measurement of serum IL-37 by quantitative sandwich Enzyme-Linked Immunosorbent Assays (ELISA).

Principle of the assay:

This kit uses ELISA to assay the level of human IL-37 in samples. The microplate in the kit is precoated with human IL-37 monoclonal antibody, add standards and sample then add IL-37 antibodies labeled with biotin and combined with streptavidin-HRP to form immune complex; then carry out incubation and washing again. Then add chromogen solution A and B. The color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of the color and the concentration of the human substance Interleukin 37 (IL-37) of sample were positively correlated. A standard curve of known concentration of IL-37 can be established and the concentration of IL-37 in the samples can be calculated accordingly.

Contents:

Standard (240pg/ml): 0.5ml, standard diluents: 3ml, Elisa strip plate: 96 wells coated with human IL-37 monoclonal antibody, Streptavidin-HRP-conjugate reagent: 6ml, Wash solution: 20ml of a 20-foldconcentrated solution, Biotin-IL-37 Ab: 1ml, Chromogen solution A: 6ml, Chromogen solution B: 6ml and Stop solution: 6ml.

Assay procedure:

1- All samples, working standards and reagents were prepared.

2- Blank well: Neither samples nor IL37 antibody labeled with biotin nor Streptavidin-HRP was added, only chromogen solution A, B and stop solution.

3- Standard wells: 50 µl of standards were added in the first five wells, Streptavidin-HRP 50 µl

4- Test wells: 40 µl of samples were added, then add both IL 37 antibody 10 µl and Streptavidin-HRP 50 µl

5- The plate was incubated 60 minutes at 37ºC, then the solution was discarded and the wells were washed 5 times with 1x wash buffer, then after the last wash, any remaining wash buffer was removed by decanting; the plate was inverted and blotted against clean paper towels.

6- 50 µl of chromogen solution A and 50 µl of chromogen solution B were added to each well. Gently mixed and incubated for 10 min at 37ºC away from light.

7- 50 µl of stop solution was added to each well to stop the reaction (the blue color changes into yellow immediately) and the absorbance was read at 450nm wave length within 15 minute after adding the stop solution.

Calculation of results:

The standard curve was drawn by plotting the mean absorbance obtained from each standard against its concentration with absorbance value on the vertical (Y) axis and concentration on the horizontal (X) axis using linear graph paper. The

concentration of the samples was read directly from this standard curve.

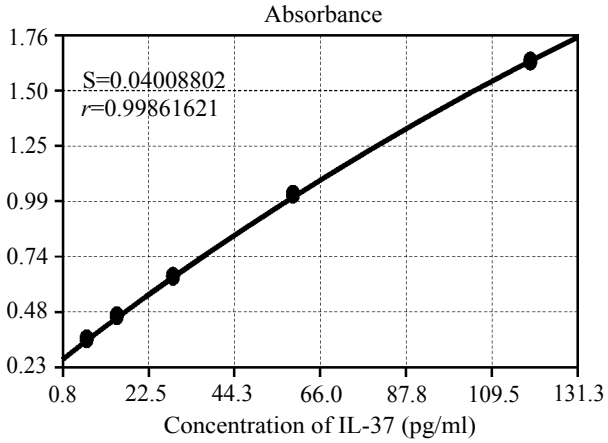

Fig. (1): Standards curve of serum Il-37.

Radiological assessment by Larsen score. The joints considered are, Proximal Interphalangeal joints (PIP) 2th to 5th, metacarpophalangeal joints (MCP) 2th to 5th in each hand, four quadrants in the wrist and metatarsophalangeal (MTP) 2 th to 5th in each foot [8]. Statistical description of the present study was conducted, using the mean value, standard deviation and standard error. Analytic statistics using student *t*-test, Mann-whitney test, Kruskal Wallis test, Pearson correlation coefficient (*r*), and chi-square test were applied by SPSS V.20. Power of significance: Probability level (*p*-value) ≥0.05=non-significant, *p*-value <0.05=significant, *p*-value <0.01=highly significant.

Results

In control group there were 5 males (25%) and 15 females (75%), the age was ranged from 25-42 year with a mean value 32.70±5.56 years, while in patient group there were 3 males (10%) and 27 females (90%), the age was ranged from 24-40 year with a mean value 33.03 ±4.08 with insignificant difference between two groups.

The patients group was subdivided into three subgroups according to disease activity score 28 (DAS-28): Subgroup I: Patients with low disease activity score ranged from (2.6 ≤DAS28 >3.2) and included 6 patients. Subgroup II: Patients with moderate disease activity score ranged from (3.2 ≤ DAS28 ≤5.1) and included 12 patients. Subgroup III: Patients with severe disease activity score, their score (>5.1) and included 12 patients.

The mean value of IL-37 levels in subgroup III was highly significantly increased when compared to subgroup I (p<0.001) and subgroup II (p=0.001), while there was no difference between subgroup I & II (p=0.078), (Table 1).

There were positive significant correlations between IL-37 serum level with clinical parameters (TJCSJC, DAS, and Morning stiffness), laboratory parameters (ESR, WBCs, CRP and RF), and degree of bone erosion assessed by Larsen Score, (Table 2).

Using the ROC curve, cutoff was estimated to be >45.8pg/ml for detection of IL-37 with sensitivity 90%, specificity 80%, positive predictive value 87.10%, negative predictive value 84.21% and accuracy 86.0%, (Table 3).

Table (1): Comparison between serum disease activity score (DAS28) and IL-37 level in patient groups.

IL-37 (pg/ml)	DAS-28			Kruskal Wallis test	
	Subgroup (I) (n=6)	Subgroup (II) (n=12)	Subgroup (III) (n=12)	H	*p*-value
Range	39.80 -66.0	48.0- 83.60	74.80- 93.70	21.745	<0.001*
Mean ± SD.	48.90 ±9.67	65.87 ±12.61	85.65 ±4.90		
	I & II		I & III	II & III	
	p=0.078		*p*<0.001 *	*p*<0.001 *	

Table (2): Correlation between IL37 and different parameters in patient group.

	IL37	
	r	*p*-value
TJC	0.929	<0.001*
SJC	0.934	<0.001*
DAS-28	0.934	<0.001*
Larsen score	0.929	<0.001*
Morning stiffness	0.792	<0.001*
ESR (mm/h)	0.729	<0.001*
Platelets ($X10^3$/µl)	0.137	0.471
WBCs ($X10^3$/µl)	0.879	<0.001*
Hb (g/dl)	–0.004	0.985
CRP (mg/L)	0.814	<0.001*
RF (U/mL)	0.726	<0.001*
ACCP (U/mL)	0.292	0.117

TJC : Tender Joint Count.
SJC : Swollen Joint Count.
DAS-28 : Disease Activity Score-28.
ESR : Erythrocyte Sedimentation Rate.
WBCs : White Blood Cells.
Hb : Hemoglobin.
CRP : C Reactive Protein.
RF : Rheumatoid Factor.
ACCP : Anti-Cyclic Citrullinate Peptide.

Table (3): ROC curve between controls and patients as regard IL-37.

	IL37				
Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
>45.8	90.0	80.0	87.10	84.21	86.0

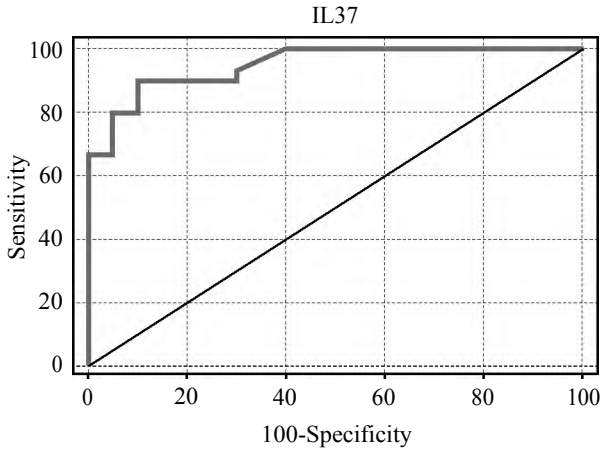

Fig. (2): ROC curve between controls and patients as regard IL-37.

Discussion

Rheumatoid arthritis is an autoimmune disorder where the immune system attacks body's own tissues and causes pain, swelling, stiffness and loss of function of joints. It affects females more than males and can affect any joint but is common in the wrist and fingers. It often starts in middle age and is most common in older people. The disease may occur for only a short time, or symptoms might come and go. The severe form can last a lifetime [6].

Genes, environment, and hormones may be risk factors for rheumatoid arthritis. The morbidity and mortality caused by RA are a consequence of local and inflammatory processes that damage cartilage, bone, soft tissue, blood vessels and viscera [6].

Cytokines are proteins with growth, differentiation and activation functions that regulate and determine the nature of immune responses and the cellular arrangement of immune organs, this immune response may be cytotoxic, humoral, cell-mediated or allergic. Each cytokine may have a different function depending on the cellular source, target and the specific phase of the immune response during which it is presented. Numerous cytokines have both pro-inflammatory and anti-inflammatory function [9].

Most members of IL-1 family are pro-inflammatory except IL-37 which is anti-inflammatory. It suppresses immune response by shifting the cytokines equilibrium away from excessive inflammation. This function is achieved at least in part by inhibition of dendritic cell activation on the cellular level and by interaction with Smad3 and modulation of kinase checkpoints on the molecular level [10].

The aim of this work is to investigate serum level of IL-37 in patients with newly diagnosed rheumatoid arthritis and find out its relation with disease activity and degree of bone erosion.

In this study, there was no significant statistical difference between the two studied groups regarding age and sex.

The results of this work indicated that there was statistical significant difference between the two studied groups regarding platelets count, WBCs and Hb. These results are in agreement with the results of Yazici et al., [11] who found that White Blood Cell (WBC), platelets count and Mean Platelet Volume (MPV) were significantly higher in patients with RA when compared to controls and these platelets indices were substantially decreased after therapy, while Yang et al., 2015 [12] found that there was no significant difference in platelets count between RA patients and controls which disagreed with the results of the present study.

Regarding Hb, Wilson et al., [13] demonstrated that anemia is a common comorbidity in individuals with rheumatoid arthritis. Vatutin et al., [14] indicated that anemia develops in 36-65% of cases of RA and explained the pathogenic mechanisms of an anemia in RA which is change of a metabolism of iron, life shortening of erythrocytes, or their inadequate production a bone marrow.

As regard ESR, this study showed that the mean value of ESR level was significantly increased in RA patients when compared to control group as in inflammatory disorders, RBCs tend to form rouleoux that partly results from increased levels of fibrinogen and thus form sediment more rapidly.

These results are in agreement with the results of Cynthia et al., [15] and Liang et al., [16] who found that ESR level was significantly increased in RA patients compared to control group and it was a significant predictors of swollen joint count in rheumatic patients.

Yazici et al., [11] found that ESR was significantly higher in patients with RA and pointed to that inflammatory marker to be substantially decreased after therapy with both anti-TNF-alpha and conservative therapy.

Normal ESR value tends to exclude active inflammatory disorders including RA and it can be used to monitor the inflammatory activity during therapy Elkon, [17].

This study showed that there was statistical significant difference between the studied groups as regard CRP with increase in its positive percent in patients. CRP is an acute-phase reactant serum protein that is present in low concentration in normal serum. It is produced during periods of inflammation and is detectable in the serum of patients with various infectious and inflammatory diseases [17].

Yazici et al., [11] found that CRP was significantly high in patients with RA and that inflammatory marker was significantly decreased after therapy with both anti-TNF-alpha and conservative therapy.

Nielen et al., [18] showed that approximately half of patients with RA have specific serologic abnormalities several years before the onset of symptoms. An elevated serum level of RF or anti-CCP in a healthy individual suggests a high risk for the development of RA, so RF and anti-CCP testing assist in the early detection of RA in high-risk populations.

The results of this study showed that serum IL-37 levels in RA patients were significantly increased in RA patients compared to controls. Concomitant with these results, Yang et al., [12] found that significantly higher levels of plasma IL-37 were detected in RA patients as serum levels of IL-37 were dramatically higher in RA patients compared to healthy controls.

Ting et al., [19], found that the plasma concentration of IL-37 was undetectable in the healthy controls, while it was elevated markedly in the RA patients. Also, IL-37 levels in patients with active RA were significantly enhanced when compared with those in patients of remission. They hypothesized that IL-37 may be a potential biomarker for RA diagnosis, disease activity assessment, or curative effect observation.

Ye et al., [20], demonstrated that active RA patients showed higher IL-37 levels than patients with inactive RA and explained that IL-37 alleviates rheumatoid arthritis by suppressing production of IL-17 and its triggering cytokine, and limiting Th17 cell proliferation. Their findings revealed an anti-inflammatory effect of IL-37 in human RA.

Zhao et al., [21] showed that plasma levels of IL-37 were significantly higher in active RA patients compared to healthy controls. This suggests that IL-37 may be activated by pro-inflammatory cytokines or other unknown factors in the acute phase of RA.

This study illustrated the relation between disease activity (DAS28) and ACCP in RA patients and there was statistical significant increase between the three subgroups regarding ACCP as the mean value of ACCP was low in patients with low disease activity than those with moderate and those with severe disease activity, and that was agreed with Papadopoulos et al., [22], who revealed that ACCP-positive patients displayed more active disease with higher DAS-28, and more severe disease indicated by the higher radiological Larsen score and that the serum levels of ACCP were not found to be associated with disease activity and severity. In early RA, the presence of ACCP is associated with increased disease activity and severity, this was found to be independent of circulating levels of ACCP.

Miriovsky et al., [23], demonstrated that higher ACCP concentrations (particularly in RF-positive patients) were associated with increased disease activity in United States veterans with RA, indicating that ACCP concentration is predictive of future disease outcomes in men.

The present study showed the relationship between disease activity and serum IL-37 levels; mean value of IL37 was significantly lower in patients with low disease activity than those with moderate and severe disease activity (DAS28).

As an anti-inflammatory cytokine, IL-37 could be up regulated by inflammatory stimuli and cytokines (Toll like receptor agonists, IL-1 β, IL-18, TNF-α, and IFN-γ). Thus, the pro-inflammatory cytokines in RA patients stimulate IL-37 expression then IL-37 mediates a negative feedback mechanism to suppress excessive pro-inflammatory cytokines in RA patients. The elevation of anti-inflammatory cytokines including IL-37 may be an underlying mechanism to relieve joint inflammation and disease severity. However, these anti-inflammatory cytokines may still be too low to neutralize the deleterious effects of pro-inflammatory cytokines in progressive RA. The uncontrolled inflammation might be due to the inadequate antagonism of anti-inflammatory cytokines against pro-inflammatory cytokines. This may be the reason why the anti-inflammatory cytokines including IL-37 only correlate with disease activity rather than with disease remission [24].

These results were agreed with Yang et al., [12], who analyzed the relationship between serum IL-37 levels and disease activity in RA patients and found that serum levels of IL-37 were significantly

lower in patients with low disease activity than those with moderate and severe disease activity.

Zhao et al., [21], evaluated the relationship between IL-37 and disease activity in RA patients, and found that plasma IL-37 was positively correlated the DAS28 score in RA patients and reported that plasma IL-37 levels were decreased in patients who treated with disease-modifying anti-rheumatic drugs (DMARDs).

The results of this study indicated that IL-37 level was positively correlated with Tender Joint Count (TJC), Swollen Joint Count (SJC) and morning stiffness. IL-37 level was significantly correlated with degree of bone erosion assessed by Larsen Score. It was also positively correlated with ESR, CRP, RF and WBCs, this was matched with Liang et al., [16] and Yang et al., [12] who found that higher levels of IL-37 levels were positively correlated with increased disease activity (DAS28) score, SJC, TJC and morning stiffness. They also found that IL-37 is positively associated with ESR, CRP, RF, IL-17 and IL-23, suggesting that IL-37 may play a critical role in the pathogenesis of RA.

Ting et al., [19], found that no significant correlation between IL-37 level and CRP concentration and that was disagreed with our results.

Ye et al., [20], found that serum IL-37 correlated closely with DAS28 and CRP and ESR, but it lacked an association with other laboratory values as RF and anti-CCP and explained that IL-17 and IL-17-driving cytokines enhance the acute-phase response, as well as stimulate anti-inflammatory cytokine IL-37 expression to down-regulate excessive inflammation during the pathogenic process of RA. Furthermore, found that there was no association between IL-37 and RF/anti-CCP, indicating the greater role of T cells in the pathogenesis of RA, because RF and anti-CCP antibodies production were mainly derived from plasma cells and B lymphocytes.

Ting et al., [19], found that IL-37 showed a significant correlation with disease activity (DAS28) and IL-4, IL-7, IL-10, IL-12, and IL-13 concentrations in RA patients. These findings suggest that IL-37 plays an important role in the pathogenesis of RA and may prove to be a potential biomarker of active RA.

The results of this study showed that there was no statistically significant correlation between IL-37 and platelets count, and ACCP. These results are in accordance with that of Liang et al., [16] and Yang et al., [12] who found that no significant correlation was observed between serum levels of IL-37 and platelets or anti-CCPs.

Thus, both pro inflammatory and anti-inflammatory cytokines are highly produced in RA patients, especially in those with active RA. Interleukin-1 family members are highly inflammatory but IL-37 is a unique member that broadly suppresses inflammation and innate immunity, Pico molar concentrations of the IL-37 precursor optimally suppress pro-inflammatory cytokines production such as IL-1 β, IL-6, and TNF α from human blood macrophages. IL-37 can be elevated in humans with inflammatory and autoimmune diseases where it functions to limit inflammation Dinarello et al., [25].

In some humans with inflammatory diseases, high levels of endogenous IL- 37 may be protective. In others, levels of IL-37 may be insufficient and inflammation may be greater. IL-37 emerges as a possible therapeutic agent to suppress inflammatory or autoimmune diseases Dinarello et al., [25].

Conclusion:

IL-37 as an anti-inflammatory cytokine could be considered as an important biomarker for diagnosis as well as assessment of activity and joint destruction in patients with rheumatoid arthritis. Also IL-37 may be a possible target in the future therapy to control the process of inflammation and suppress autoimmune diseases.

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تقييم مستوى الإنترلوكين ٣٧ فى المصل فى مرضى الرثيان المفصلى

يعد إلتهاب الرثيانى مرض مناعى مزمن يصيب الغشاء الزلالى للمفصل مما يؤدى إلى تدمير الغضروف وتآكل العظام والإعاقة. ينتمى الإنترلوكين–٣٧ لعائلة الإنترلوكين 1 التى تنمع المناعة الفطرية والتكيفية ويزداد تركيزه كآلية دفاع طبيعى فى الحالات الإلتهابية وفى آمراض المناعة الذاتية بما فى ذلك إلتهاب المفاصل الرثيانى، الذئبة الحمراء، الصدفية، وغيره من الآمراض المتعلقة بالإلتهاب.

يهدف البحث إلى: تحديد مستوى تركيز الإنترلوكين–٣٧ فى مصل مرضى الرثيان المفصلى وعلاقته بنشاط المرض ومدى تآكل العظام، وقد ضمت هذه الدراسة ٢٠ شخصا آصحاء كمجموعة ضابطة و٣٠ مريضا بالرثيان المفصلى حديثى التشخيص تم إختيارهم من العيادة الخارجية لقسم الطب الطبيعى والروماتيزم والتآهيل. كلية الطب جامعة طنطا منهم ٣ ذكور و٢٧ إناث وتتراوح آعمارهم من (٢٥–٤٠) عام، وتم تقسيمهم إلى ٣ مجموعات فرعية طبقا لدرجات نشاط المرض. كذلك تم إختيار ٢٠ شخصا آصحاء كمجموعة مقارنة منهم ٥ ذكور و٥ إناث من نفس الفئة العمرية، وتم عمل الآتى: آخذ التاريخ المرضى بالكامل مصحوبا بالفحص الإكلينيكى، تقييم نشاط المرض بإستخدام (معدل نشاط المرض ٢٨)، صورة دم كاملة، قياس سرعة الترسيب، بروتين سى التفاعلى، معامل الروماتويد، الآجسام المضادة للسترولين، قياس نسبة مصل الإنترلوكين–٣٧ بطريقة الإليزا وتقييم درجة تآكل العظام بإستخدام معدل لارسن، ولوحظ زيادة نسبة الإنترلوكين ٣٧ فى مصل المرضى ذوى آعلى درجة نشاط للمرض مقارنة مع المجموعة الضابطة، ووجد إرتباط إيجابى بين مستوى الإنترلوكين–٣٧ ودرجة تآكل العظام، وعدد المفاصل المتورمة، درجة التبيس الصباحى، سرعة الترسيب، عدد كرات الدم البيضاء، بروتين سى التفاعلى، الآجسام المضادة للسترولين ومعامل الروماتويد ولم يوجد إرتباط بينه مستوى الإنترلوكين–٣٧ والصفائح الدموية ونسبة الهيموجلوبين.

ونستنتج من هذا: زيادة مستوى الإنترلوكين–٣٧ فى مرضى الرثيان المفصلى حديثى التشخيص، لذلك يمكن إستخدامه كعلامة بيولوجية لتشخيص هذا المرض وتقييم نشاطه ومتابعة التآثير العلاجى، وقد يكون هدفا محتملا فى المستقبل العلاجى للسيطرة على عملية الإلتهاب وقمع آمراض المناعة الذاتية.