

# Correlation between disease activity and serum interleukin-23 in rheumatoid arthritis

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## Background

Interleukin-23 (IL-23) is a proinflammatory cytokine that is thought to be central to the development of autoimmune diseases.

This study was conducted to determine whether or not serum concentration of IL-23 is elevated in patients with rheumatoid arthritis (RA) and to determine the relationship between the IL-23 level and disease activity in patients with RA.

## Patients and methods

Serum samples were obtained from 100 patients with RA and 50 healthy controls. Clinical parameters of the disease were determined, including 28-Joint Disease Activity Score, Clinical Disease Activity Index, Health Assessment Questionnaires, C-reactive protein, rheumatoid factor levels, anti-cyclic citrullinated peptide antibodies, and degree of bony erosions based on radiographs. The levels of IL-23 were determined by enzyme-linked immunosorbent assay (ELISA). The correlations between the serum levels of IL-23 and disease activity parameters of patients with RA were determined.

## Results

Serum IL-23 level was significantly elevated in patients with RA, 0.00–49.30 pg/ml (19.12±13.45 pg/ml) compared with healthy controls, 0.00–1.40 pg/ml (0.90 ±0.63 pg/ml) ( $P=0.0001$ ). Serum IL-23 levels in patients with RA correlated with Clinical Disease Activity Index ( $r=0.952$ ,  $P=0.000$ ), Health Assessment Questionnaires ( $r=0.953$ ,  $P=0.000$ ), and 28-Joint Disease Activity Score ( $r=0.967$ ,  $P=0.000$ ). Moreover, serum IL-23 levels in patients with RA correlated with erythrocyte sedimentation rate ( $r=0.950$ ,  $P=0.000$ ), C-reactive protein ( $r=0.954$ ,  $P=0.001$ ), and rheumatoid factor ( $r=0.917$ ,  $P=0.000$ ). There was a statistically significant difference between IL-23 mean values associated with different radiograph classes in patients with RA ( $P=0.001$ ).

## Conclusion

Levels of serum IL-23 in patients with RA were significantly higher than in healthy controls. Moreover, elevated serum IL-23 levels were correlated with clinical and laboratory parameters of disease activity. It should be considered as a useful marker to detect active RA. IL-23 is involved in disease progression and bony erosions in patients with RA. Anti-IL-23 drugs could have a potential role in the treatment of RA.

## Keywords:

anti-cyclic citrullinated peptide, Clinical Disease Activity Index, enzyme-linked immunosorbent assay, interleukin-23, 28-Joint Disease Activity Score, rheumatoid arthritis

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## Introduction

Rheumatoid arthritis (RA) is a chronic immune disorder that affects synovial membrane and causes subsequent joint destruction. The chronic inflammation process is responsible for stimulating destructive mechanisms in the joint, which cause structural damage and lead to functional disability and deterioration [1]. Cytokines play a key role in the processes that cause articular destruction and extra-articular manifestations [2]. The list of potential proinflammatory cytokines important in the pathogenesis of RA and other autoimmune and inflammatory diseases has been extended to include the cytokine, interleukin (IL)-23 [3]. Functionally,

IL-23 has been classified as a proinflammatory mediator responsible for keeping balance between effectors and regulatory T-cell response, and it is a necessary factor for the development of T-cell-dependent inflammation [4]. IL-23 is one of the essential factors required for the survival and/or expansion of T helper (Th)17 cells, which produce IL-17, IL-17F, IL-6, and tumor necrosis factor- $\alpha$

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(TNF- $\alpha$ ). Th17 cells stimulated by IL-23 promote generation of osteoclast through production of IL-17, which induces receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) on mesenchymal cells. The IL-23–IL-17 axis includes Th17 cells and plays a key role in the development of autoimmune arthritis [5]. IL-23 has a role in chronic inflammation, which is a common characteristic of many autoimmune diseases. IL-23 promotes the Th17 pathway, which has been shown to be active in the pathogenesis of many chronic inflammatory diseases, including psoriasis, inflammatory bowel disease, and multiple sclerosis. In inflammatory bowel disease, stimulation of colonic leukocytes by IL-23 induced the production of IL-17 [6]. Therefore, blocking the IL-23 might be beneficial for the treatment of inflammatory bowel disease. Another example of this is with RA, IL-23 levels are significantly higher in the peripheral blood of patients with RA than in normal controls [7].

Studies show that increased levels of IL-23 in plasma of patients with chronic RA are associated with disease activity [6]. IL-23 has the capacity to promote the development of the proinflammatory CD4<sup>+</sup> T-cell subset Th17 and is thus believed to contribute to inflammatory conditions [8]. IL-23 can induce chronic inflammation through two independent pathways. The first pathway is by the activation of Th17 cells and the second by the induction of the secretion of IL-17 by non-T cells. Th17 cells produce cytokines such as IL-17, IL-17F, IL-6, IL-21, IL-22, and TNF- $\alpha$ , which play an important role in the RA collagen-induced arthritis [4].

Serum IL-23 levels in patients with RA are decreased after TNF blockade. These observations suggest that IL-23 could be a valuable inflammatory biomarker in RA [9].

In the current study, we determined whether or not serum levels of IL-23 are increased in patients with RA, and whether or not the increased levels of IL-23 are significantly correlated with RA disease activity. We compared the serum concentrations of IL-23 in patients with RA and healthy controls, and then determined the correlation between the serum levels of IL-23 and the parameters associated with disease activity in patients with RA.

## Patients and methods

This study was carried out on 100 patients with RA and 50 healthy volunteers as a control group. A total of 100 patients with a clinical diagnosis of RA (90 female and

10 male) were recruited from the rheumatology and rehabilitation outpatient clinic and inpatient department at Beni Suef University Hospital in the duration between January 2014 and March 2015. All participants fulfilled the ACR classification criteria for RA [10].

Informed consent was obtained from the patients and controls. The study was performed with the approval of local ethics committee.

When the serum samples were obtained, clinical assessments, such as tender joint counts, swollen joint counts, and Health Assessment Questionnaires (HAQ) score, were performed. At the same time, the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) and rheumatoid factor (RF) levels were determined using standard laboratory methods. Radiographs of hands were obtained from patients with RA and evaluated for the presence of erosions blinded to the clinical data.

Assessment of the patient clinical state was done using the following:

- (1) The 28-Joint Disease Activity Score (DAS28) [11].
- (2) Clinical Disease Activity Index (CDAI) [12].
- (3) Assessment of disability index using HAQ [13].

## Laboratory investigations

The following laboratory examinations were performed for all patients.

### Routine laboratory tests

Routine laboratory tests included the following:

Complete blood count, ESR by Westergren method taking first hour [14], CRP detection by latex slide test [15], RF positivity and its quantitative titer [16], and anti-cyclic citrullinated peptide (ACCP) antibodies [17].

### Measurement of interleukin-23 levels

Serum samples were collected intravenously and stored at  $-20^{\circ}\text{C}$  after centrifugation (3000g for 15 min at  $2^{\circ}\text{C}$ ) until analysis. The serum concentration of IL-23 was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit. The human IL-23 ELISA is an ELISA for the quantitative detection of human IL-23. The human IL-23 ELISA is for research use only and not for diagnostic or therapeutic procedures.

An anti-human IL-23 coating antibody is adsorbed onto microwells. Human IL-23 present in the sample or standard binds to antibodies adsorbed to the microwells. Following incubation, unbound biological components are removed during a wash step. A biotin-conjugated anti-human IL-23 antibody is added, and it binds to human IL-23 captured by the first antibody. A colored product is formed in proportion to the amount of human IL-23 present in the sample or standard. The reaction is terminated by the addition of acid and absorbance is measured at 450 nm. A standard curve is prepared from eight human IL-23 standard dilutions, and human IL-23 sample concentration is determined [18].

### Radiographs

They provide a permanent measure of damage in RA. Plain radiographs of hands are important in the evaluation of the RA disease course and its possible modification over years [19].

Larsen score is the most widely used measure of radiograph that provides a continuous quantitative scale of more than 100 U, rather than a limited qualitative measure of radiographic damage [20].

### Statistical analysis

Data analyses were performed with statistical package for the social sciences software version 20 (IBM, Chicago, USA). All of the descriptive variables were expressed as mean±SD. Cross-tabulation test was used for comparison between percentage values, Student's *t*-test for comparison between means of two groups with a normal distribution, and Mann-Whitney *U* or Kruskal-Wallis tests to compare the means of variables that did not have a normal distribution. Pearson's correlation test was done to detect if change in one variable is accompanied by a corresponding change in the other variable.

## Results

### Demographic data of patients with rheumatoid arthritis and controls included in the study

A total of 100 adult patients with RA according to the 2010 ACR/EULAR classification criteria were the participants of this study. They were 10 (10%) male and 90 (90%) female patients; their age ranged from 25.00 to 55.00 years, with a mean of 45.40±8.48 years, and their disease duration ranged from 25.00 to 31.00 months, with a mean of 7.16±7.29 months. Moreover, 50 healthy controls, including 10 (20%) males and 40 (80%) females, with a mean age of 41.30±7.04 years, were also included (Table 1).

**Table 1 Demographic data of patients with rheumatoid arthritis and controls included in the study**

	N	Range	Mean±SD
Age of patients (years)	100	25.00–55.00	45.40±8.48
Disease duration (months)	100	25.00–31.00	7.16±7.29
Sex of patients [N (%)]			
Female	80 (80)		
Male	20 (20)		
Age of controls (years)	50	21–51	41.30±7.04
Sex of controls [N (%)]			
Female	40 (80)		
Male	10 (20)		

### Clinical and laboratory data of patients with rheumatoid arthritis included in the study

Examination of patients with RA revealed that morning stiffness duration ranged from 0.00 to 120 min, with a mean of 0.56±0.105 min; tender joint count ranged from 0.00 to 20.00, with a mean of 9.08±5.45 min; swollen joint count ranged from 0.00 to 18.00, with a mean of 7.61±5.15; DAS28 ranged from 1.00 to 6.20, with a mean of 3.37±1.57; CDAI ranged from 1.00 to 29.00, with a mean of 12.52±9.56; and HAQ ranged from 0.00 to 51.00, with a mean of 21.13±14.51.

Testing of the serum hemoglobin level revealed that it ranged from 8.80 to 14.00 g/dl, with a mean of 10.71±1.24 g/dl; ESR ranged from 9.00 to 90.00 mm<sup>3</sup>/first hour, with a mean of 39.45±24.85 mm<sup>3</sup>/first hour; CRP ranged from 1.0 to 45.00 mg/l, with a mean of 18.23±13.30 mg/l; and RF titer ranged from 2.00 to 42.00 IU/ml, with a mean of 20.85±10.46 IU/ml (Table 2).

### Comparison between patients and controls according to serum levels of interleukin-23

Testing the level of serum IL-23 in our patients with RA, it ranged from 0.00 to 49.30 pg/ml, with a mean of 19.12±13.45 pg/ml. On the contrary, the levels of IL-23 in the sera of normal controls ranged from 0.00 to 1.40 pg/ml, with a mean of 0.90±0.63 pg/ml. The mean serum level of IL-23 in patients with RA was significantly higher than those in healthy control ( $P=0.0001$ ) (Fig. 1). Comparison of serum interleukin-23 levels according to sex, age, and disease duration

There was no significant difference between IL-23 mean levels in male patients (22.70±16.30 pg/ml) compared with female patients (18.22±12.68 pg/ml) ( $P=0.31$ ).

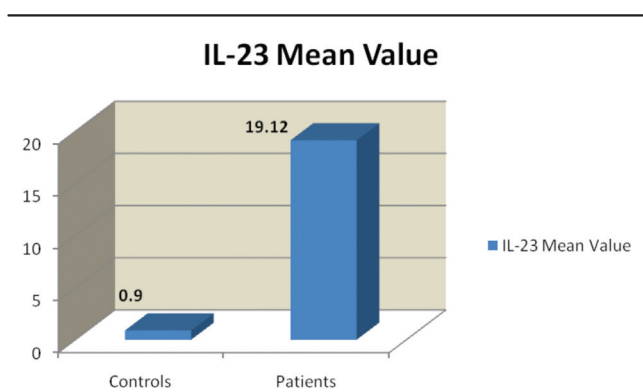
There was a positive correlation between IL-23 levels and age of patients with RA ( $r=0.129$ ), but it was statistically nonsignificant ( $P=0.326$ ).

**Table 2 Clinical and laboratory data of patients with rheumatoid arthritis**

Variables	Range	Mean±SD
Morning stiffness duration (min)	0.00–120	0.56±0.105
DAS28	1.00–6.20	3.37±1.57
CDAI	1.00–29.00	12.52±9.56
ESR (mm <sup>3</sup> /first hour)	9.00–90.00	39.45±24.85
RF titer (IU/ml)	2.00–42.00	20.85±10.46
HAQ	0.00–51.00	21.13±14.51
IL-23 (pg/ml)	0.00–49.30	19.12±13.45
Tender joint count	0.00–20.00	9.08±5.45
Swollen joint count	0.00–18.00	7.61±5.15
Hemoglobin level (g/dl)	8.80–14.00	10.71±1.24
CRP (mg/l)	1.0–45.00	18.23±13.30

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, 28-Joint Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IL-23, interleukin-23; RF, rheumatoid factor.

**Figure 1**



Comparison of patients and controls according to mean serum level of IL-23

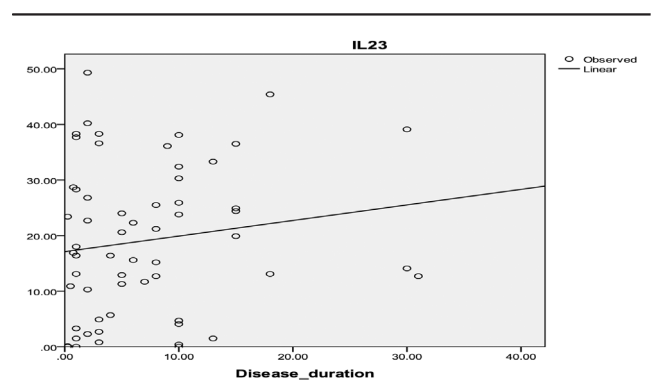
There was a positive correlation between IL-23 levels and disease duration of patients with RA ( $r=0.152$ ) but was statistically nonsignificant ( $P=0.247$ ) (Fig. 2).

**Comparison of serum interleukin-23 according to C-reactive protein, rheumatoid factor, and anti-cyclic citrullinated peptide positive and negative groups**

The IL-23 mean in patients with positive RF (26.39 ±11.00 pg/ml) was higher than those with negative RF (6.55±5.81 pg/ml), and the difference between both means was statistically significant ( $P=0.001$ ).

- (1) A comparison of the mean values of IL-23 levels between the ACCP-positive (22.77±12.01 pg/ml) and ACCP-negative (2.89±4.47 pg/ml) patients revealed highly significant difference between the two groups ( $P=0.001$ ).
- (2) The mean of IL-23 level of patients with positive CRP (30.39±8.99 pg/ml) was about three times higher than the patients with negative CRP (9.26 ±7.67 pg/ml), and the difference between both means was statistically significant ( $P=0.001$ ) (Table 3).

**Figure 2**



Serum IL-23 levels and disease duration

**Table 3 Serum interleukin-23 in C-reactive protein, rheumatoid factor, and anti-cyclic citrullinated peptide positive and negative groups**

	Serum IL-23 (pg/ml) (mean±SD)	P-value
CRP		
Negative	9.26±7.67	0.001*
Positive	30.39±8.99	
RF		
Negative	6.55±5.81	0.001*
Positive	26.39±11	
ACCP		
Negative	2.89±4.47	0.001*
Positive	22.77±12.01	

ACCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; IL-23, interleukin-23; RF, rheumatoid factor. \*The correlation is statistically significant.

**Comparison of serum interleukin-23 in patients with rheumatoid arthritis according to different radiological classes**

By studying the IL-23serum level for patients with different RA radiological classes (Larsen score), we found that patients with radiograph class 4 have IL-23 mean value (45.40±8.89 pg/ml) that is higher than those with class 3 (29.84±8.87 pg/ml), class 2 (32.20 ±8.74 pg/ml), and class 1 (13.42±8 pg/ml). There was a statistical significant difference between IL-23 mean value associated with the different radiograph classes ( $P=0.001$ ) (Table 4).

**Correlation between interleukin-23 and general clinical variables**

- (1) IL-23 was positively correlated with morning stiffness duration ( $r=0.907$ ); moreover, there was a positive correlation between IL-23 levels and both DAS28 ( $r=0.967$ ) and CDAI scores ( $r=0.952$ ), and both correlations were statistically significant ( $P=0.000$ ).
- (2) IL-23 serum levels were highly significantly correlated with swollen joint count ( $r=0.970$ ,  $P=0.000$ ).



**Table 4 Relation between interleukin-23 and radiograph classification**

Radiograph classes	IL-23 (pg/ml)		P-value
	Range	Mean±SD	
Class 0	0.00–4.9	1.70±2.04	0.001*
Class 1	0.00–28.30	13.42±80.00	
Class 2	20.60–49.30	32.20±8.74	
Class 3	12.70–39.10	29.84±8.87	
Class 4	45.40–45.40	45.40±8.89	

IL-23, interleukin-23. \*The correlation is statistically significant.

- (3) Moreover, there was significant positive correlation between IL-23 serum levels and tender joint count ( $r=0.719$ ,  $P=0.000$ ).
- (4) IL-23 was positively correlated with HAQ ( $r=0.953$ ), and the correlation was statistically significant ( $P=0.000$ ) (Table 5 and Fig. 3).

#### Correlation between serum levels of interleukin-23 and laboratory disease parameters

- (1) There was a positive correlation between IL-23 and both RF titer ( $r=0.917$ ) and ESR ( $r=0.950$ ). Both correlations were statistically significant ( $P=0.000$ ).
- (2) There was a negative correlation between IL-23 and hemoglobin concentration ( $r=-0.642$ ), and it was statistically significant ( $P=0.000$ ).
- (3) There was a positive correlation between IL-23 and CRP ( $r=0.954$ ), and the correlation was statistically significant ( $P=0.001$ ) (Table 6).

About the drug treatment, all patients were under disease-modifying antirheumatic drugs. None of them was receiving biologics.

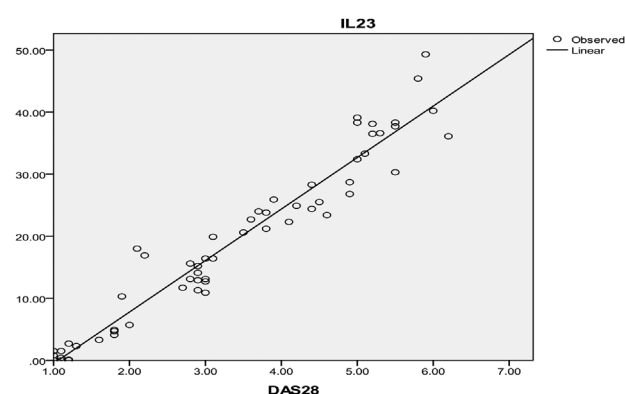
#### Discussion

RA is a chronic inflammatory disorder that is characterized by polyarthritis with often progressive joint damage and disability, immunological abnormalities, systemic inflammation, increased comorbidity, and premature mortality [21]. The pathogenesis of RA is mediated by an interdependent network of cytokines, prostanoids, and proteolytic enzymes. The levels of representative proinflammatory cytokines are increased in patients with RA compared with other forms of arthritis [22]. Cytokines play a key role in the processes that cause articular destruction and extra-articular manifestations [2]. The list of potential proinflammatory cytokines important in the pathogenesis of RA and other autoimmune and inflammatory diseases has been extended to include the cytokine, IL-23 [3]. IL-23, a novel member of the IL-12 cytokine family, is a

**Table 5 Serum interleukin-23 and clinical variables in patients with rheumatoid arthritis**

	Pearson's correlation (r)	P-value
Morning stiffness duration	0.907**	0.000
DAS28	0.967**	0.000
CDAI	0.952**	0.000
Tender joint count	0.719**	0.000
Swollen joint count	0.970**	0.000
HAQ	0.953	0.000

CDAI, Clinical Disease Activity Index; DAS28, 28-Joint disease activity score; HAQ, Health Assessment Questionnaire. \*\*The correlation is highly statistically significant.

**Figure 3**

Correlation between serum levels of IL-23 and DAS-28

**Table 6 Serum levels of interleukin-23 and laboratory disease parameters**

	Pearson's correlation (r)	P-value
RF	0.917**	0.000
ESR	0.950**	0.000
Hemoglobin level	-0.642**	0.000
CRP	0.954*	0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. \*The correlation is statistically significant. \*\*The correlation is highly statistically significant.

heterodimeric cytokine. Although it shares the common p40 subunit with IL-12, its role is different from that of IL-12 in autoimmune diseases. IL-12 induces the differentiation of naive CD4<sup>+</sup> T cells into IFN- $\gamma$ -producing Th1 cells, composed of a p19 subunit and a common p40 subunit, whereas IL-23 drives autoantigen-specific IL-17-producing T cells [23].

Izcue *et al.* [4] reported that IL-23 has been classified as a proinflammatory mediator responsible for keeping a balance between effectors and regulatory T-cell response, and it is a necessary factor for the development of T-cell-dependent inflammation. Melis *et al.* [6] found that IL-23 levels tended to be slightly higher in patients with RA, serum IL-23 levels in RA, but not in spondyloarthritis, and are strongly correlated with swollen joint count ( $r=0.697$ ,  $P=0.004$ ), ESR ( $r=0.665$ ,

$P=0.013$ ), serum CRP levels ( $r=0.578$ ,  $P=0.030$ ). One of the main findings of our study is the significant positive correlation between serum IL-23 levels and DAS28 ( $r=0.627$ ,  $P=0.039$ ). Thus, higher serum IL-23 levels indicate higher disease activity in patients with RA. Melis *et al.* [24] founded that the degree of intimal lining layer hyperplasia in patients with RA was strongly associated with IL-23 levels in the joints. Rasmussen *et al.* [25] who obtained findings consistent with our study results, demonstrated that IL-23 levels were significantly associated with DAS28 score and ESR. The production of IL-23 is initiated by several factors including the innate immune receptors such as Toll-like receptor, dectin-142, and the CD40 ligand [26]. In agreement with our results, Zaky and El-Naherty [27] who measured the level of IL-23 in patients with RA as well as the correlation between the IL-23 level and disease activity, had reported that serum level of IL-23 was significantly elevated in patients with RA ( $78.92\pm 52.47$ ) compared with control group ( $33.34\pm 3.99$ ) ( $P<0.001$ ); they concluded that IL-23 may potentially play a role in the pathogenesis of RA and may be a useful biomarker for the diagnosis of this disease. Targeting the IL-23 cytokine may provide a new therapeutic approach in the treatment of RA. In keeping with the proinflammatory properties of this cytokine, serum IL-23 levels in patients with RA showed a decreasing trend after TNF blockade [28].

Moreover, Rasmussen *et al.* [25] investigated the levels of the Th17-related cytokines (IL-17A, IL-21 and IL-23) and their association with disease activity in RA, showing that IL-23 plasma levels correlated well with DAS28 ( $P<0.01$ ), CRP ( $P<0.0050$ ), ESR ( $P<0.0023$ ) and total sharp score ( $P<0.0050$ ). Plasma levels of IL-21 and IL-23 in RA showed strong correlations, and both correlated with disease activity measured by the CRP, ESR, total sharp score, and DAS28 scores. It has been suggested that IL-23 function is not restricted to the expansion of Th17 cells. The interplay between IL-23 and IL-17 may have a significant role in the pathogenesis of RA. IL-23 stimulates IL-17 production from Th17 cells; then IL-17 induces TNF- $\alpha$ , RANKL, and IL-1 production, causing aggravation of the osteoclast differentiation leading to joint destruction, bone erosions, and synovial inflammation [29]. In agreement with Elhewala *et al.* [30] who assessed the level of IL-17A in the serum and synovial fluid in patients with RA and its correlation to disease activity, there was an increase in serum IL-17A with increased synovial hypertrophy of the knee ( $P=6.39$ ), wrist ( $P=12.23$ ), and second metacarpophalangeal joint (MCP) ( $P=53.34$ ). Finally, there was an increase in the blood IL-17A level, dryness of the eye ( $P=3.8$ ), dryness of the mouth ( $P=3.2$ ), and number of subcutaneous

nodules ( $P=2.5$ ). Moreover, Chen *et al.* [31] had found that IL-23 can stimulate osteoclast formation in two independent pathways as follows: first, by upregulating RANKL expression in osteoblasts, and second, by acting on myeloid precursors inducing the RANKL expression. They have also shown that IL-23 alone can promote osteoblast differentiation in the presence of macrophage colony stimulating factor and RANKL from murine spleen cells and bone marrow macrophages. Siti Dalila *et al.* [32] measured the serum IL-23 levels in patients with RA and healthy controls and determined the correlation of IL-23 levels with disease activity, joint damage, and functional disability in RA. They reported that the mean serum IL-23 level was much higher among patients with RA ( $24.50\pm 13.98$  pg/ml) compared with the controls ( $5.98\pm 3.40$  pg/ml;  $P<0.01$ ). There was a significant positive relationship between IL-23 levels and disease activity and questionnaire scores ( $P=0.003$  and  $0.020$ , respectively). In our study, patients with RA have significantly higher levels of serum IL-23. The IL-23 levels correlate well with disease activity, functional disability, and radiographic joint damage. These results are complemented in studies by Guo *et al.* [33] who demonstrated a positive correlation between IL-23 levels and knee joint erosions. Contradicting our findings are the results by Siti Dalila *et al.* [32] and Rasmussen *et al.* [25], which detected no association between radiographic joint damage and IL-23 levels.

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## Conclusion

The circulating IL-23 concentrations were significantly high in patients with RA compared with controls. There was a significant positive correlation between serum IL-23 levels in patients with RA and individual disease activity parameters, functional disability, and radiographic joint damage. Therefore, elevated serum IL-23 level may be a useful marker to detect active RA and disease progression in patients with RA. Our study detects that anti-IL-23 could have a potential therapeutic role in the treatment of RA and evaluates the role of ustekinumab (anti-IL-23 drug) in patients with RA.

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Nil.

## Conflicts of interest

There are no conflict of interest.

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